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Sugammadex for the reversal of muscle relaxation in general anaesthesia: a systematic review and economic assessment

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Abstract

Sugammadex for the reversal of muscle relaxation in general anaesthesia: a systematic review and economic assessment

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Background: Sugammadex (Bridion®) is a newly developed agent for the reversal of neuromuscular blockade (NMB) induced by rocuronium or vecuronium. Sugammadex can reverse profound blockade and can be given for immediate reversal and its use would avoid the potentially serious adverse effects of the currently used agent, succinylcholine. Also, sugammadex can reverse NMB more quickly and predictably than existing agents.
Objectives: To determine the clinical effectiveness and cost-effectiveness of sugammadex for the reversal of muscle relaxation after general anaesthesia in UK practice following routine or rapid induction of NMB.
Data sources: Medical databases [including MEDLINE, EMBASE, CINAHL, Science Citation Index, BIOSIS and Cochrane Central Register of Controlled Trials (CENTRAL), conference proceedings, internet sites and clinical trials registers] were searched to identify published and unpublished studies. The main searches were carried out in May 2008 and supplemented by current awareness updates up until November 2008.
Review methods: For the clinical effectiveness review, randomised controlled trials of sugammadex against placebo or an active comparator (neostigmine + glycopyrrolate) for the reversal of moderate or profound NMB and for immediate reversal (spontaneous recovery from succinylcholine-induced blockade) were included. The primary effectiveness outcome was speed of recovery from NMB, as measured by objective monitoring of neuromuscular function. For the cost-effectiveness review, a de novo economic assessment considered the routine induction of NMB and the rapid induction and/or reversal of NMB, and threshold analyses were carried out on a series of pairwise comparisons to establish how effective sugammadex needs to be to justify its cost.
Results: The review of clinical effectiveness included four randomised active-control trials of sugammadex, nine randomised placebo-controlled trials and five studies in special populations. A total of 2132 titles and abstracts and 265 full-text publications were screened. The included trials indicated that sugammadex produces more rapid recovery from moderate or profound NMB than placebo or neostigmine. Median time to recovery from moderate blockade was 1.3–1.7 minutes for rocuronium + sugammadex, 21–86 minutes for rocuronium + placebo and 17.6 minutes for rocuronium + neostigmine. In profound blockade, median time to recovery was 2.7 minutes for rocuronium + sugammadex, 30 to > 90 minutes for rocuronium + placebo, and 49 minutes for rocuronium + neostigmine. Results for vecuronium were similar. In addition, recovery from NMB was faster with rocuronium reversed by sugammadex 16 mg/kg after 3 minutes (immediate reversal) than with succinylcholine followed by spontaneous recovery (median time to primary outcome 4.2 versus 7.1 minutes). The evidence base for modelling cost-effectiveness is very limited. However, assuming that the reductions in recovery times seen in the trials can be achieved in routine practice and can be used productively, sugammadex [2 mg/kg (4 mg/kg)] is potentially cost-effective at its current list price for the routine reversal of rocuronium-induced moderate (profound) blockade, if each minute of recovery time saved can be valued at approximately £2.40 (£1.75) or more. This is more likely to be achieved if any reductions in recovery time are in the operating room (estimated value of £4.44 per minute saved) rather than the recovery room (estimated value of £0.33 per

minute saved). The results were broadly similar for rocuronium- and vecuronium-induced blockade. For rapid reversal of NMB it appeared that any reduction in morbidity from adopting sugammadex is unlikely to result in significant cost savings.

Limitations: The evidence base was not large and many of the published trials were dose-finding and safety studies with very small sample sizes. Also, some relevant outcomes, in particular patient experience/quality of life and resources/costs used, were either not investigated or not reported. In addition, it is likely that the patients included in the efficacy trials were relatively young and in good general health compared with the overall surgical population. Regarding the economic evaluation, there appears to be no evidence linking measures of clinical efficacy to patients' health-related quality of life and mortality risks.

Conclusions: Sugammadex may be a cost-effective option compared with neostigmine + glycopyrrolate for reversal of moderate NMB and also provides the facility to recover patients from profound blockade. Rocuronium + sugammadex could be considered as a replacement for succinylcholine for rapid induction (and reversal) of NMB, although this may not be a cost-effective option in some types of patient at current list prices for sugammadex. Considerable uncertainties remain about whether the full benefits of sugammadex can be realised in clinical practice.

Contents

Glossary and list of abbreviations

Glossary

Adverse effect An undesirable and unintended effect of an intervention.

Adverse effects and complications Includes recurarisation or reparalysis, residual blockade or paralysis. Each of the neuromuscular blocking agents (NMBAs) and reversal agents presents a particular set of potential adverse effects.

Adverse event Any noxious, pathological or unintended change in anatomical, physical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of a clinical study, whether or not considered treatment related. It includes exacerbation of pre-existing conditions or events, intercurrent illnesses, accidents, drug interaction or the significant worsening of disease.

ASA Physical Status American Society of Anesthesiologists (ASA) Physical Status grading system, which rates patients between I and VI. I = normal, healthy patient; II = patient with mild systemic disease; III = patient with severe systemic disease; IV = patient with severe systemic disease that is a constant threat to life; V = moribund patient, not expected to survive without the operation; and VI = brain-dead patient from whom organs are being removed for donor purposes.

Cannot intubate–cannot ventilate An emergency situation where neuromuscular block(ade) (NMB) has been induced but intubation is difficult or impossible requiring manual ventilation and reversal of the NMB. This situation is relatively rare but life-threatening when it occurs.

Complications See **Adverse effects and complications.**

Cost-effectiveness acceptability curves A graphical representation of the probability of an intervention being cost-effective over a range of monetary values for the health system's cost-effectiveness threshold.

Cost-effectiveness analysis The estimation of the costs and health benefits of mutually exclusive treatment strategies, where the consequences are measured in natural units, such as years of life gained.

Neuromuscular block(ade) Neuromuscular block(ade) (NMB) is used as an adjunct to anaesthesia to induce paralysis, so that surgery, especially intra-abdominal and intrathoracic surgeries, can be carried out with fewer complications. Because NMB may paralyse muscles required for breathing, mechanical ventilation must be available to maintain adequate respiration.

Neuromuscular blocking agents Neuromuscular blocking agents (NMBAs) are drugs that produce muscle relaxation, classified either as depolarising (succinylcholine) or non-depolarising (atracurium, cisatracurium, mivacurium, vecuronium and rocuronium among others). These drugs are routinely used in anaesthesia. *Levels of NMB*: Depth of block is defined by monitoring the neuromuscular response to stimulation using electromyography, mechanomyography or acceleromyography. '*Moderate NMB*' – represents the level of recovery from block at which it is possible to administer neostigmine to achieve reversal [return of second twitch (T2) when monitoring the train-of-four (TOF) response]. This is also sometimes referred to as 'shallow' block. '*Profound NMB*' – a post-tetanic count (PTC) of 1–2 represents profound NMB. This is also sometimes referred to as 'deep' block.

continued

Post-tetanic count A method of measuring the depth of neuromuscular block (NMB). A motor nerve is stimulated at 50 times per second (50 Hz), followed 3 seconds later by stimulation once per second (1 Hz), and the number of twitches counted to give the post-tetanic count (PTC). The PTC varies between 1 and 12, and a PTC of 1–2 represents profound NMB.

QTc A corrected QT interval, which represents the time from the start of ventricular depolarisation to the start of ventricular repolarisation in the beating cycle of the heart. Anaesthetic drugs have adverse effects on the QTc, with some prolonging it, some shortening it and others having no effect. A prolonged QTc is associated with arrhythmias and ventricular fibrillation.

Quality-adjusted life-year A measure of health-care outcomes that adjusts gains (or losses) in years of life subsequent to a health-care intervention by the quality of life (QoL) during those years. Quality-adjusted life-years (QALYs) can provide a common unit for comparing cost–utility across different interventions and health problems.

TOF Train-of-four (TOF) stimulation is a measure of the depth of neuromuscular blockade (NMB) and involves stimulation of a peripheral motor nerve with a sequence of four electrical impulses delivered at a rate of 2 Hz over 2 seconds. The number and height of the muscle twitches in response to the stimulation is recorded during NMB. Four twitches (T4) are recorded in the absence of NMB but the response is reduced or abolished during blockade. As recovery from blockade occurs, four twitches are again seen; the ratio of the height of the fourth to first twitches (TOF ratio) increases towards 1.0 and can be used to monitor the degree of recovery and occurrence of residual blockade.

List of abbreviations

AE	adverse event
ASA	American Society of Anesthesiologists
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CR_{CL}	creatinine clearance
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstract of Reviews of Effectiveness
EMEA	European Medicines Agency
FDA	US Food and Drug Administration
HEED	Health Economic Evaluations Database
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ICTRP	International Clinical Trials Registry Platform
ITT	intention to treat
MeSH	medical subject headings in the MEDLINE thesaurus
mRCT	metaRegister of Current Controlled Trials
MTC	mixed-treatment comparison
N&G	neostigmine with glycopyrrolate
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NLH	National Library for Health
NMB	neuromuscular block(ade)
NMBA	neuromuscular blocking agent
PTC	post-tetanic count
QALY	quality-adjusted life-year
QoL	quality of life
QTc	corrected QT interval
RCT	randomised controlled trial
RSI	rapid sequence induction
SAE	serious adverse event
SD	standard deviation
TOF	train of four

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Sugammadex (Bridion®) is a newly developed agent for the reversal of neuromuscular blockade (NMB) induced by rocuronium or vecuronium. Unlike current reversal agents (acetylcholinesterase inhibitors, e.g. neostigmine), sugammadex can reverse profound blockade and can be given for immediate reversal without the need to wait for partial recovery. Sugammadex has no effect on acetylcholinesterase, eliminating the need for concomitant anticholinergic drugs (e.g. glycopyrrolate), which must be administered with acetylcholinesterase inhibitors. For patients requiring rapid sequence induction of anaesthesia for endotracheal intubation, the immediate reversal possible with sugammadex could enable large doses of rocuronium to be used in the knowledge that should a 'cannot intubate–cannot ventilate' situation occur, then the blockade will be reversible. Use of sugammadex in this setting would avoid the potentially serious adverse effects of the currently used agent, succinylcholine, including anaphylactic/allergic reactions, cardiac arrest, myalgia and inducing malignant hyperthermia. Potential clinical benefits for the use of sugammadex include increased patient safety and reduced incidence of residual blockade on recovery. There are also possible benefits associated with the ability to reverse NMB more quickly and predictably from any level of blockade with sugammadex compared with existing agents, which could potentially result in increased efficiency in the health-care system.

Objectives

To determine the clinical effectiveness and cost-effectiveness of sugammadex for the reversal of muscle relaxation after general anaesthesia in UK practice following routine or rapid induction of NMB.

Methods

Review of clinical effectiveness

The systematic review of effectiveness included randomised controlled trials of sugammadex against placebo or an active comparator for the reversal of moderate or profound NMB and for immediate reversal (sugammadex administered shortly after high-dose rocuronium as could be required in the event of an emergency). Active comparators were neostigmine + glycopyrrolate (N&G) for reversal of moderate or profound blockade and spontaneous recovery from succinylcholine-induced blockade for immediate reversal. We also included trials of other neuromuscular blocking agent (NMBA)–reversal agent combinations compared with each other in moderate block. The primary effectiveness outcome was speed of recovery from NMB as measured by objective monitoring of neuromuscular function. We searched medical databases [including MEDLINE, EMBASE, CINAHL, Science Citation Index, BIOSIS and Cochrane Central Register of Controlled Trials (CENTRAL), conference proceedings, internet sites and clinical trials registers] to identify published and unpublished studies. The main searches were carried out in May 2008 and supplemented by current awareness updates up until November 2008. Separate searches were carried out for summary data on adverse effects of sugammadex, NMBAs and N&G. Included studies were synthesised as appropriate.

Assessment of cost-effectiveness

Owing to the lack of published evidence concerning the cost-effectiveness of sugammadex, a de novo economic assessment was carried out into strategies for the induction and subsequent reversal of NMB. The assessment separately considered two scenarios: the routine induction of NMB and the rapid induction and/or reversal of NMB.

The economic assessment was severely hindered by the lack of suitable evidence needed to inform many of the parameters. As such, threshold analyses were carried out on a series of pairwise comparisons.

In the routine setting, the analyses effectively simplified to ones of cost minimisation; the critical variables in this analysis were the reduction in recovery time by using sugammadex and the value of each minute of recovery time saved.

The threshold analysis sought to derive the minimum value of each minute of recovery time saved for sugammadex to be cost-effective (i.e. cost saving with assumed equal health outcomes) at the current list price for any given (absolute) reduction in the recovery time associated with sugammadex.

In the rapid induction and/or reversal setting, the strategies were assumed to have generally different expected costs and health outcomes, so cost-effectiveness analyses were carried out; critical variables included the probability of a 'cannot intubate–cannot ventilate' event occurring, the baseline probability of mortality of succinylcholine, the relative risk of mortality of adopting sugammadex, the age of the patient [and hence the quality-adjusted life-years (QALYs) forgone in the case of death] and (where a 'cannot intubate–cannot ventilate' event does not occur) the number of minutes of recovery time saved by adopting sugammadex and the value of each minute saved.

The analysis sought to derive the minimum baseline probability of death directly due to succinylcholine for sugammadex to be considered cost-effective (i.e. costing less than £20,000 per QALY gained) for any given probability of a 'cannot intubate–cannot ventilate' event.

Results

Number and quality of studies

The review of clinical effectiveness included four randomised active-control trials of sugammadex, nine randomised placebo-controlled trials and five studies in special populations. A total of 2132 titles and abstracts and 265 full-text publications were screened. Data on adverse effects were obtained from 18 references (from 703 titles and abstracts and 84 full-text publications screened), which were not assessed for quality because of the diverse range of sources included. Seven trials without a sugammadex arm were eligible for a review of other NMBAs/reversal agents.

No published full economic evaluations of either NMBAs or reversal strategies were located.

Summary of benefits and risks

The included trials indicated that sugammadex produces more rapid recovery from moderate or profound NMB than placebo or neostigmine. Median time to recovery from moderate blockade was 1.3–1.7 minutes for rocuronium + sugammadex, 21–86 minutes for rocuronium + placebo and 17.6 minutes for rocuronium + neostigmine. In profound blockade, median time to recovery was 2.7 minutes for rocuronium + sugammadex, 30 to > 90 minutes for rocuronium + placebo, and 49 minutes for rocuronium + neostigmine. Results for vecuronium were similar. In addition, recovery from NMB was faster with rocuronium reversed by sugammadex 16 mg/kg after 3 minutes (immediate reversal) than with succinylcholine followed by spontaneous recovery (median time to primary outcome 4.2 versus 7.1 minutes). The tentative conclusion from a synthesis of all relevant trials (including trials without a sugammadex arm) was that use of rocuronium or vecuronium + sugammadex would result in shorter recovery times than the use of these agents with neostigmine, and use of sugammadex with rocuronium or vecuronium may be shorter than cisatracurium/atracurium + neostigmine combinations.

In phase I–III trials ($n = 1926$ patients treated with sugammadex), rates of adverse events were similar between sugammadex administered after rocuronium or vecuronium and comparators (neostigmine or placebo). The most significant adverse events following treatment with sugammadex appear to be anaesthetic complications (up to 3%), and allergic reactions.

Summary of cost-effectiveness

In the routine setting, under the base-case assumptions, 2 mg/kg (4 mg/kg) sugammadex appears cost-effective for the routine reversal of rocuronium-induced moderate (profound) blockade at the current list price (2 ml × 10 vials, £596.40; 5 ml × 10 vials, £1491.00; 100 mg of sugammadex per millilitre) if all reductions in recovery time associated with sugammadex are achieved in the operating room, but does not appear cost-effective if all reductions in recovery time are achieved in the recovery room. Where savings in recovery time are achieved in both the operating room and the recovery room, or where there is additional value in reducing recovery times (for example in preventing operations from being delayed or forgone), the cost-effectiveness of sugammadex is highly dependent on the setting in which it is administered. The results are broadly similar for rocuronium- and vecuronium-induced blockade.

In the context of rapid reversal of NMB, where sugammadex is assumed to be associated with a

reduced risk of mortality, the decision over whether or not sugammadex is cost-effective depends upon the baseline probability of death from succinylcholine, the relative risk of mortality due to sugammadex compared with succinylcholine, the probability of a 'cannot intubate–cannot ventilate' event, the value of each minute of recovery time saved due to sugammadex (should the procedure go ahead), whether sugammadex is required to reverse moderate or profound blockade and the age of the patient (and hence the discounted QALYs forgone in the case of mortality). It would appear that any reduction in morbidity from adopting sugammadex is unlikely to result in significant cost savings for the UK NHS.

Limitations

The evidence base for the effectiveness of sugammadex is not large. Many of the published trials are dose-finding and safety studies with very small sample sizes. An additional limitation is that some relevant outcomes, in particular patient experience/quality of life and resources/costs used, were either not investigated or not reported. The patients included in the efficacy trials were probably relatively young and in good general health compared with the surgical population as a whole, but sugammadex has also been tested in various high-risk populations, increasing the potential generalisability of the trial findings.

Regarding the economic evaluation, there appears to be no evidence linking measures of clinical efficacy such as time to train-of-four (TOF) 0.9 to patients' health-related quality of life and mortality risks. As a result, direct cost-effectiveness modelling was not considered feasible. Rather, a series of threshold analyses was undertaken, which essentially establish how effective sugammadex needs to be, relative to existing practice, to justify its acquisition cost.

Conclusions

Implications for service provision

As sugammadex may be a cost-effective option compared with N&G for reversal of moderate NMB, then the use of rocuronium + sugammadex appears to be a realistic option for clinical practice. The choice of this combination of NMBA–reversal agent is further supported by the facility to recover patients from profound blockade, a facility not available with any other combination except, to a lesser extent, vecuronium + sugammadex.

The availability of sugammadex 16 mg/kg to reverse immediately block induced with high-dose rocuronium means that rocuronium + sugammadex could be considered as a replacement for succinylcholine for rapid induction (and reversal) of NMB. This would avoid the morbidity associated with succinylcholine, although the economic assessment suggests that the cost-effectiveness of sugammadex will be highly sensitive to a given patient's underlying mortality risk during the procedure, so this may not be a cost-effective option in some types of patient at the current list prices for sugammadex. This option could be considered if a price reduction for sugammadex could be negotiated, or in the context of a clinical study at a limited range of centres.

The adverse effect profile of sugammadex indicates that it is well tolerated. However, the number of patients exposed to sugammadex is relatively small and further monitoring is required as the exposed patient population expands.

There are potential benefits of sugammadex in terms of increased patient safety, increased predictability of recovery from NMB, and more efficient use of theatre time and staff, but these have yet to be explored in clinical practice. New practices in anaesthesia may have to be adopted before the full benefits of sugammadex can be realised.

Suggested research priorities

- Evaluate the effects of replacing succinylcholine with rocuronium + sugammadex for rapid induction and reversal of NMB on morbidity, mortality, patient-reported outcomes and resource use.
- Collect data on the use of sugammadex in clinical practice to obtain better estimates of the incidence and implications of rare major adverse events, for example allergic/anaphylactic reactions.
- Evaluate outcomes of sugammadex use in routine surgery for which there is little information to date, for example patient-reported outcomes, clinical signs of recovery, resource use and costs.
- Evaluate the use of sugammadex in paediatric and obstetric practice.
- The need for further randomised trials of sugammadex should be evaluated following

full publication of the trials considered in this report and in the light of trials currently in progress.
- Evaluate the use of a 4-mg/kg dose of sugammadex for immediate reversal of blockade induced by low-dose (0.6-mg/kg) rocuronium in the routine setting.
- Evaluate new theatre practices that could potentially make optimum use of the timesavings afforded through the use of sugammadex. This would ideally involve a nationwide prospective study.
- Evaluate the effects of using different combinations of anaesthesia and analgesia with sugammadex, specifically in situations where potent inhalational agents have been used but discontinued.
- Further research is needed to quantify the mortality risk of patients with different clinical characteristics in the setting of rapid induction of NMB.

Chapter 1
Background

Description of health problem

Neuromuscular blocking agents (NMBAs) are routinely used for muscle relaxation in anaesthesia. NMBAs enable relaxation of the vocal cords for the passage of a tracheal tube, and adequate relaxation of the muscles of the abdomen and diaphragm for surgical access. Prior to the use of NMBAs, muscle relaxation could only be achieved by deepening anaesthesia excessively, with consequent increased risk of delaying awakening along with respiratory and cardiac complications.[1] Properties of an ideal muscle relaxant for ambulatory anaesthesia include: rapid onset with short duration of action, predictable redistribution and elimination, absence of cumulative effects with repetitive dosing, minimal to no side effects, easy reversibility and administration, low cost and long shelf-life.[2]

All NMBAs contain at least one quaternary ammonium group, as does acetylcholine, the neurotransmitter that initiates muscle contraction, and, like acetylcholine, they act at the postjunctional nicotinic receptor of the neuromuscular junction. NMBAs may be depolarising, such as succinylcholine (suxamethonium), or non-depolarising, such as rocuronium or vecuronium (*Table 1*).[1]

Depolarising agents depolarise the muscle fibre membrane by opening ion channels in the same way as acetylcholine, but, unlike acetylcholine, they are not hydrolysed by acetylcholinesterase and remain longer at the neuromuscular junction. Thus, depolarisation lasts longer, which results in a brief period of repetitive excitation that may bring about transient muscle fasciculations (twitches) before the muscle relaxation.[3] Succinylcholine is the only depolarising NMBA in clinical use, and is the one most frequently used in emergency situations for tracheal intubation due to its rapid onset of action – neuromuscular blockade (NMB) with succinylcholine is achieved in 40–60 seconds – and short duration.[4] However, succinylcholine has a number of potentially serious adverse effects, including anaphylactic/allergic reactions, cardiac arrest and inducing malignant hyperthermia. Myalgia following administration of succinylcholine is common and can last for several days. Furthermore, there are many (albeit uncommon) conditions in which succinylcholine is contraindicated, including major burns (beyond 48 hours) and major nerve or spinal cord injuries, due to the risk of hyperkalaemia (excessive levels of potassium), possibly leading to fatal cardiac arrhythmias.[4] A small proportion of patients have an inability to break down succinylcholine in the plasma, due to a genetic abnormality in their plasma cholinesterase, and its duration of action is then prolonged: by about 30 minutes if the gene abnormality is heterozygous or by 2 hours if the abnormality is homozygous.[1] This plasma cholinesterase deficiency can also be acquired through a wide range of diseases, physiological states (e.g. pregnancy), drugs or interventions such as dialysis.[5]

Non-depolarising agents compete with acetylcholine at the binding site, limiting or preventing depolarisation.[1] There are a number of non-depolarising agents in use in clinical practice in the UK: aminosteroidal agents (pancuronium, rocuronium and vecuronium) and benzylisoquinoliniums (atracurium, cisatracurium and mivacurium). Pancuronium was the first aminosteroidal NMBA introduced into clinical practice in the 1960s, but, due to its vagolytic and sympathomimetic effects and long duration of action, it is now only used occasionally and mainly in cardiac surgery.[1] Benzylisoquinoliniums have the advantage that they degrade in the plasma and, as such, atracurium, cisatracurium and mivacurium are suitable for use in patients with poor renal function.[1]

Once surgery is complete, the patient must start breathing again, and regain muscle strength and protective laryngeal reflexes before removal of the endotracheal tube, i.e. they must have recovered from the NMB. Spontaneous recovery from succinylcholine-induced NMB occurs rapidly enough to be clinically useful (6–10 minutes),[4] but, with non-depolarising agents, reversal agents are often administered to hasten recovery and reduce the risk of postoperative complications from residual blockade. The reversal agents in current use are acetylcholinesterase inhibitors, which act

TABLE I *Classification of NMBAs*[a]

Class	Duration of action
Depolarising NMBAs	
Succinylcholine	Short acting
Non-depolarising NMBAs	
Benzylisoquinoliniums	
Atracurium	Intermediate acting
Cisatracurium	Intermediate acting
Mivacurium	Short acting
Non-depolarising NMBAs	
Steroid derivatives (aminosteroidal agents)	
Pancuronium	Long acting
Vecuronium	Intermediate acting
Rocuronium	Intermediate acting

a Adapted from Steele *et al.*[2]

by slowing the metabolism of acetylcholine at the neuromuscular junction and thereby increasing the amount of the transmitter available to compete with residual NMBA for occupancy of the nicotinic receptor. In current clinical practice, neostigmine is the most commonly used acetylcholinesterase inhibitor.

Acetylcholinesterase inhibitors are ineffective in reversing deep blockade and cannot be used to effect immediate reversal of block, as a period of recovery from block is required before they can be administered. The duration of action of the inhibitor may be shorter than the length of action of the NMBA, leading to reappearance of block or residual blockade. Residual blockade has been associated with serious adverse events, including respiratory depression, pharyngeal dysfunction, hypoxaemia and prolonged length of stay in the recovery room.[6] The acetylcholinesterase inhibitors also have their own side effects, which additional drugs are required to counteract. Muscarinic receptor antagonists (e.g. glycopyrrolate or atropine) are administered with acetylcholinesterase inhibitors to minimise the adverse effects resulting from increased acetylcholine concentrations produced by the inhibitor at muscarinic nerve endings. There are also clinical implications for their use in special patient populations. Neostigmine, for example, has been associated with cardiovascular adverse effects and should be used with caution in patients with cardiac arrhythmias.[7]

The issues arising from use of NMBAs and reversal agents are well known, and are allowed for in current patient management. For example, the effects of NMBAs are influenced by several factors, including age, medical condition [American Society of Anesthesiologists (ASA) Physical Status], gender, body weight, anaesthetic technique and the method of monitoring.[8] However, there is a potential benefit from new treatments, which could reduce the risk of complications (e.g. residual blockade) or provide benefits not available with current NMBA–reversal agent combinations (e.g. reversal of profound NMB or rapid reversal of NMB in an emergency situation as discussed in the following section).

Current service provision

It is estimated that approximately 3.6 million general anaesthetic procedures with mechanical ventilation (requiring muscle relaxation) are carried out each year in the UK. Rocuronium or vecuronium are used in approximately 0.8 million of these anaesthetic procedures for muscle relaxation, and an estimated 66% of these patients will require reversal (currently 528,000 procedures),[9] although the true figure may well be higher.

There are two main scenarios where NMB is used:

1. *'Routine' intubation for major surgery* Patients will have fasted in preparation for elective surgery and the stomach will be empty, to reduce the risk of aspiration of stomach contents into the lungs on induction of anaesthesia. NMB can be moderate (shallow) or profound (deep), depending on the type of surgery needed, but the majority of surgical procedures do not require profound block.[10] While allowing spontaneous recovery from moderate or profound block is an option, it usually takes too long and blockade is reversed with an appropriate pharmacological agent. In UK clinical practice the anticholinesterase-antimuscarinic combination used most commonly is neostigmine in combination with glycopyrrolate, but these agents are limited in their ability to reverse deep levels of blockade.
2. *Rapid sequence induction for emergency surgery or when the stomach is thought to be full* Tracheal intubation, and therefore the onset of NMB, must be as rapid as possible to minimise the risk of aspiration of gastric contents. The standard drug used for this is succinylcholine,

which has the most rapid onset of action (1 minute). Larger than standard doses of rocuronium can also be used to achieve rapid onset of blockade (within 1 minute in most patients) without the adverse effects of succinylcholine.[11]

There is the possibility in both scenarios that a 'cannot intubate–cannot ventilate' emergency can occur, requiring immediate action if the patient is to survive without hypoxic brain damage. Where non-depolarising NMBAs have been used, there is at present an unavoidable delay before reversal agents, such as neostigmine, can be administered if they are to be effective. This is of particular concern in rapid sequence induction if a large dose of rocuronium has been used. In higher doses, rocuronium has a duration of action of at least 90 minutes, but acetylcholinesterase inhibitors are unable to antagonise deep NMB and are, therefore, ineffective as rescue drugs. In circumstances where succinylcholine is used, and a 'cannot intubate–cannot ventilate' situation develops, there is no reversal agent available.[12]

Description of technology under assessment

Sugammadex (Bridion®) is a newly developed agent for the reversal of both moderate and profound NMB induced by rocuronium or vecuronium. The depth of block is determined by monitoring the neuromuscular response to stimulation using electromyography, mechanomyography or acceleromyography. Although acceleromyography is used in most clinical trials of sugammadex to define incomplete neuromuscular recovery, subjective monitoring (clinical evaluation) of NMB (e.g. testing for sustained head-lift, leg-lift or hand-grip for more than 5 seconds) remains the most widely used method for measuring NMB in clinical practice. Although clinical evaluation can be reliable, these measures are reliant upon the patient's level of consciousness and ability to cooperate.[13] Thus objective neuromuscular monitoring is recommended when muscle relaxants have been administered.[13] Methods of stimulation include post-tetanic count (PTC) and train-of-four (TOF) stimulation. To measure the PTC, a motor nerve is stimulated at 50 times per second (50 Hz), followed 3 seconds later by stimulation once per second (1 Hz) and the number of twitches counted to give the PTC. The PTC varies between 1 and 12 and a PTC of 1–2 represents profound NMB.

Train-of-four monitoring involves stimulation of a peripheral motor nerve with a sequence of four electrical impulses delivered at a rate of 2 Hz over 2 seconds. The number and height of muscle twitches in response to the stimulation is recorded during NMB. Four twitches of equal height (T1–4) are recorded if NMB has not occurred or is insufficient; 0 or 1 twitches (T0 or T1) indicates adequate NMB for surgery. The ratio of the height of the fourth to first twitches is used to monitor the decline in blockade once four twitches are seen – as recovery from NMB occurs, the TOF ratio increases towards 1.0.[9] While a TOF of 0.7 was regarded as adequate recovery when it was first described in the early 1970s, more recent studies indicate that TOF ratios of 0.7–0.9 are associated with impaired pharyngeal function with the risk of aspiration of stomach contents. In addition, a TOF ratio of less than 0.7 indicates that patients will additionally have an impaired hypoxic ventilatory response.[14]

Sugammadex, a large carbohydrate molecule, forms very tight one-to-one complexes with rocuronium or vecuronium, encapsulating these drugs and hence reducing the concentration of NMBA at the neuromuscular junction and rapidly terminating the block.[15] Sugammadex is not metabolised or broken down in the body and therefore does not affect blood sugar levels, and is excreted intact via the kidney.[16] Unlike acetylcholinesterase inhibitors, sugammadex can reverse profound blockade if an appropriate dose is used and can be given for immediate reversal of block without the need to wait for partial recovery.[17] However, it is only effective with two aminosteroidal NMBAs: rocuronium and, to a lesser degree, vecuronium.

Sugammadex is intended for administration at different doses for the reversal of different levels of NMB, as determined by objective monitoring. Moderate NMB as defined here corresponds to the terminology of Fuchs-Buder *et al*.[8] and corresponds to the level of block at which it is first possible to obtain an efficient effect with neostigmine. In many surgical procedures where complete immobilisation of the patient is not required, this level of block may have been reached by, or shortly after, the end of surgery. For reversal of moderate block, as defined in the proposed indications for sugammadex, a dose of 2 mg/kg is administered on reappearance of the second twitch (T2) in response to TOF stimulation.

Profound block refers to the level of block at which there is response to PTC stimulation

but not to TOF stimulation. Sugammadex to reverse profound block will be useful when the reversal of blockade is required very shortly after administration of rocuronium or vecuronium, or in procedures where profound block is required until the very end of surgery. Sugammadex will allow rapid recovery from profound block without having to wait for some degree of spontaneous recovery. For reversal of profound NMB, a single intravenous injection of 4-mg/kg sugammadex is administered at a PTC of 1–2. A further proposed indication for sugammadex is for immediate reversal of rocuronium-induced NMB, using a dose of 16 mg/kg administered 3 minutes after rocuronium.

Sugammadex has no effect on acetylcholinesterase, eliminating the need for concomitant anticholinergic drugs.[15] For patients requiring rapid-sequence induction of anaesthesia for endotracheal intubation, the immediate reversal possible with sugammadex could enable large doses of rocuronium to be used in the knowledge that should a 'cannot intubate–cannot ventilate' situation occur the blockade will be reversible.[17] The rocuronium + sugammadex combination may provide an onset of effect and rapid reversal at least equal to succinylcholine, but with a better safety profile, resulting in benefits in terms of avoidance of adverse events, and a lower morbidity and mortality. Overall, potential clinical benefits for the use of sugammadex include increased patient safety, improved surgical conditions and reduced incidence of residual blockade on recovery.[15,18] There are also possible benefits associated with the ability to reverse NMB more quickly and predictably from any level of blockade, with sugammadex than existing agents, which could result in increased efficiency in the health-care system.

Chapter 2
Definition of decision problem

Decision problem

The problem addressed in this report is whether any morbidity, mortality or inefficient resource use arising from the reversal of NMB in patients who have undergone general anaesthesia can be ameliorated by the use of sugammadex as a reversal agent.

Although the technology under assessment is sugammadex, the benefits of any reversal agent are interwoven with that of the NMBA used. Thus any assessment of a reversal agent has to consider it in combination with the agent or agents whose action it reverses. Similarly, all comparators will also be combinations of NMBA plus reversal agent.

In the main scenarios for the use of NMB the decision problems relating to the use of sugammadex are:

- Routine reversal of moderate NMB induced by rocuronium or vecuronium (doses of 2 mg/kg). The options for NMBA–reversal agent combinations in this indication are as listed in *Table 2*. Relevant outcomes are time to recovery, reduced risk of adverse effects for patients, and benefits in terms of improved theatre efficiency.
- Immediate reversal of profound blockade either when profound blockade has been maintained until the end of surgery (routine reversal of profound blockade), or when reversal is needed shortly after administration of rocuronium or vecuronium, for example when a 'cannot intubate–cannot ventilate' situation arises during routine intubation. There are currently no comparators for this scenario as N&G cannot be used due to the period of spontaneous recovery required before these agents can be administered. The relevant outcome is time to recovery.
- Emergency (rapid) intubation when the onset of NMB must be rapid. The intervention under assessment in this scenario is rocuronium plus sugammadex versus succinylcholine. The availability of sugammadex 16 mg/kg would allow high-dose rocuronium to be used for rapid intubation in the knowledge that the blockade could be quickly reversed if necessary. In most cases, following rapid intubation, patients would proceed through surgery and their NMB would be reversed as in the routine scenarios, i.e. the 16-mg/kg dose of sugammadex would only be used in the rare cases when the immediate reversal of the rapidly induced block was required. Relevant outcomes are time to recovery and reduced risk of adverse effects for patients.

Overall aims and objectives of assessment

The aim of this assessment is to determine the clinical effectiveness and cost-effectiveness of sugammadex for the reversal of muscle relaxation during general anaesthesia in UK practice. The assessment will examine the available evidence regarding the clinical effectiveness and cost-effectiveness of sugammadex compared with relevant comparators.

Ideally, the evidence reviewed would be from randomised controlled trials (RCTs) directly comparing reversal of NMB using rocuronium/vecuronium + sugammadex with different combinations of other

TABLE 2 *Comparators for routine reversal of NMB*

NMBA	Reversal agent
Rocuronium	Neostigmine + glycopyrrolate
Vecuronium	Neostigmine + glycopyrrolate
Atracurium	Neostigmine + glycopyrrolate
Cisatracurium	Neostigmine + glycopyrrolate
Mivacurium	Neostigmine + glycopyrrolate
Rocuronium	Sugammadex (2 or 4 mg/kg)
Vecuronium	Sugammadex (2 or 4 mg/kg)
Rocuronium	Spontaneous recovery or placebo
Vecuronium	Spontaneous recovery or placebo
Atracurium	Spontaneous recovery or placebo
Cisatracurium	Spontaneous recovery or placebo
Mivacurium	Spontaneous recovery or placebo

NMBAs + acetylcholinesterase inhibitors, or with succinylcholine in the immediate reversal situation. Where this is not available, attempts will be made to include RCTs comparing different NMBAs and reversal agents in an indirect analysis using mixed-treatment comparison (MTC), using similar techniques to, for example, Lu and Ades[19] and Higgins *et al.*[20]

Outcome measures will include the time to recovery measured by TOF stimulation with neuromuscular monitoring, plus occurrence of residual blockade and mortality. The adverse event profile of NMBA + sugammadex will be compared with that of NMBA + neostigmine–glycopyrrolate, or succinylcholine. Attempts will be made to value and compare the increased margin of control and safety that is anticipated with sugammadex combinations. Outcomes measuring patient experience, such as quality of recovery, will also be sought.

An economic evaluation is also required to consider the cost and quality-of-life (QoL) implications associated with changing from succinylcholine or NMBA + current reversal agents to NMBA + sugammadex. The specific objectives of the cost-effectiveness analysis are to: (1) identify evidence for estimating QoL and resource use (costs); (2) examine any existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models; (3) structure an appropriate decision model to characterise patients' care and subsequent prognoses and the impacts of alternative therapies, in a way that is clinically acceptable; (4) populate this model using the most appropriate data identified systematically from published literature and routine data sources; (5) relate intermediate outcomes (e.g. TOF, adverse events) to final health outcomes, expressed in terms of quality-adjusted life-years (QALYs); (6) estimate the mean cost-effectiveness of sugammadex against other comparators, based on an assessment of long-term UK NHS and Personal Social Service costs and quality-adjusted survival; (7) report cost-effectiveness of alternative treatments for specific subgroups of patient, consistent with available evidence; (8) characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision-makers; and (9) inform future research priorities in the NHS, using the model to undertake analyses of the expected value of perfect information.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

Search strategy

Searches were undertaken to identify studies specifically about sugammadex. Studies were identified by searching the following databases: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Science Citation Index, BIOSIS, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effectiveness (DARE) and Health Technology Assessment (HTA) Database. TOXLINE was searched for studies with adverse event data. In addition, information on studies in progress, unpublished research or research reported in the grey literature was identified by searching ISI Proceedings Science & Technology, Inside Conferences, ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org, Clinical Trial Results and World Health Organization International Clinical Trials Registry Platform (ICTRP). All resources were searched from their inception to the most recent date available. There was no restriction by study design, country of origin, language or publication date.

Internet searches were carried out using the specialist search gateways Intute (www.intute.ac.uk) and MedlinePlus (www.nlm.nih.gov/medlineplus/) to identify relevant resources. Potentially relevant websites identified during the initial internet gateway searches were then searched and browsed. The organisation websites searched were the Royal College of Anaesthetists, the Association of Anaesthetists of Great Britain & Ireland, the Anaesthesia Research Trust, ASA, the European Society of Anaesthesiology (ESA), the World Federation of Societies of Anaesthesiologists, and the National Library for Health (NLH) Surgery, Theatres & Anaesthesia Specialist Library.

The following conference proceedings were searched: Annual Meeting of the European Society of Anaesthesiology (2004–2008), ASA Annual Meeting (2001–2008), Association of Anaesthetists of Great Britain & Ireland Annual Congress (2004–2007), and the World Federation of Societies of Anaesthesiologists Congress (2008).

Search alerts (details of newly published articles retrieved using a saved search sent by e-mail) were set up in a number of journals: *Anaesthesia*, *British Journal of Anaesthesia*, *European Journal of Anaesthesiology* and *Anesthesia & Analgesia*. Search alerts were also set up to run weekly in MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and EMBASE.

Additional searches were undertaken to identify studies about NMBAs and other reversal agents. These searches were carried out in the following databases: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, CINAHL, Science Citation Index, BIOSIS, CDSR, CENTRAL, DARE and HTA. For these searches there were no restrictions by country of origin, language or publication date. However, a methodological search filter devised to identify RCTs was used. Adverse event information relating to NMBAs, neostigmine and glycopyrrolate was identified from the following sources: US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER); European Medicines Agency (EMEA); *British National Formulary*; Medicines Compendium; *Meyler's Side Effects of Drugs*; *Meyler's Side Effects of Drugs Used in Anesthesia*; Martindale *The Complete Drug Reference*; and AHFS (American Hospital Formulary Service) Drug Information. The following trials registers were also searched: ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org, Clinical Trial Results, and World Health Organization ICTRP. A database search for adverse events studies was undertaken in MEDLINE, EMBASE and TOXLINE. This set of searches used only the title field in TOXLINE, subject heading indexing and the subheadings 'adverse effects/adverse drug reaction' in MEDLINE and EMBASE, and was limited by date range (1998–2008) and English-language studies.

The search strategies, dates and results of all searches are listed in Appendix 1.

Inclusion and exclusion criteria

Studies were assessed for inclusion by two reviewers independently; disagreements were resolved by discussion with reference to a third reviewer if necessary. Full reports were ordered and evaluated for studies that appeared potentially relevant, based on reading the title and abstract. The first stage of screening was performed in a reference management database (ENDNOTE X1) and screening of full reports against inclusion and exclusion criteria was performed in a review specific database in Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI)-Reviewer (EPPI-Centre, Social Science Research Unit, Institute of Education, University of London).

Clinical efficacy

Studies were eligible for inclusion in the review of clinical efficacy if they met the criteria shown below.

Population

Human patients of any age and health status, undergoing in-hospital surgery involving general anaesthesia and requiring NMB.

Intervention and comparators

The intervention and comparators were different for routine and rapid intubation.

Routine intubation In routine intubation the intervention is sugammadex 2 or 4 mg/kg for reversal of moderate or profound NMB, respectively, induced by rocuronium or vecuronium.

For routine intubation, trials comparing any of the following NMBAs + reversal agent combinations were eligible for inclusion:

- rocuronium or vecuronium + sugammadex
- rocuronium, vecuronium, atracurium, cisatracurium or mivacurium + neostigmine–glycopyrrolate
- rocuronium, vecuronium, atracurium, cisatracurium or mivacurium + no reversal (i.e. spontaneous recovery) or placebo.

To be eligible, sugammadex studies were required to compare rocuronium or vecuronium + sugammadex with each other, with any listed NMBA + neostigmine and glycopyrrolate or with any listed NMBA + no reversal agent (placebo or spontaneous recovery). Comparisons not involving sugammadex were included to develop a network of evidence related to the reversal of moderate NMB in elective surgery. To be eligible, studies had to administer a reversal agent (neostigmine or placebo) at the return of T2 (second twitch of the TOF – the point at which sugammadex was given in studies of moderate block) or at an alternative point (T1 20% or 25%) based on TOF monitoring and considered to represent an equivalent degree of recovery. Studies in which no placebo was given in the 'no-reversal-agent' arm (i.e. spontaneous recovery) were included, provided that TOF outcomes were measured from one of the appropriate time points.

Rapid intubation For rapid intubation and immediate reversal of NMB, trials of rocuronium + sugammadex compared with spontaneous recovery from succinylcholine-induced NMB, or with rocuronium + placebo, were eligible for the review.

Outcomes

Studies reporting the following outcomes were eligible for the review: speed of reversal of NMB as measured by TOF monitoring (e.g. recovery of the T4/T1 ratio, i.e. ratio of the height of the fourth twitch to that of the first, to 0.9) and clinical signs of recovery (e.g. able to perform the 5 s head-lift test[21,22]); occurrence of residual blockade; adverse event profile of intervention and comparators; and mortality, if reported. Studies reporting outcomes relating to the patient's experience of recovery and any outcomes relating to improved control of anaesthesia or resource use were also included.

The primary outcome used in the review was time from administration of a reversal agent to recovery of the T4/T1 ratio to 0.9 (90% of baseline value); secondary outcomes based on TOF monitoring included recovery of the TOF ratio to 0.7 and 0.8 and, for comparing sugammadex with succinylcholine, recovery of T1 (first twitch of the TOF) to 0.1 and 0.9 in rapid intubation and immediate reversal of NMB.

Study designs

For the assessment of the clinical efficacy of sugammadex, only parallel-group RCTs were included.

Exclusion criteria

Animal models, preclinical and biological studies, case reports, studies of healthy volunteers, reviews, editorials and opinions were excluded.

Safety and adverse effects

Sugammadex

In addition to studies included in the main clinical effectiveness review, safety data included in manufacturer submissions to regulatory authorities and in reports by regulatory authorities were eligible for the review. These included pooled analyses of safety data from studies that were not otherwise eligible for the review.

NMBAs, neostigmine and glycopyrrolate

We reviewed summary sources of data (see Chapter 3, Methods for reviewing clinical effectiveness, Search strategy) on these agents, with the objective of identifying the most important adverse effects and quantifying their incidence in surgical patients. Further database searches were performed to search for studies of any design reporting specific rates of adverse effects associated with NMBAs and the combination of neostigmine and glycopyrrolate. Preference was given to primary reports with a rate estimate based on a large sample with a known denominator.

Data extraction strategy

All data extraction was performed by one reviewer and checked by another. Discrepancies were resolved by discussion, with recourse to a third reviewer if necessary. Data on study, patient, intervention and surgery characteristics, outcomes reported and study quality were extracted using a standardised data extraction form in Eppi-Reviewer 3.0. Data were extracted from only sugammadex dose-finding studies if they related to one of the proposed licensed doses of sugammadex (2, 4 or 16 mg/kg) used in the appropriate indication and compared rocuronium or vecuronium + sugammadex with each other, or included a placebo arm. For studies not published in full, any relevant data were extracted from the Organon/Schering-Plough FDA submission,[23] the FDA Advisory Committee's own briefing document[12] and the EMEA assessment report for sugammadex.[10] A separate data extraction form was designed for the review of safety and adverse effects. For the numerical analysis of primary outcome data, data were extracted into a Microsoft EXCEL spreadsheet or a WORD document.

Quality assessment strategy

The quality of RCTs was assessed using a checklist based on the Centre for Reviews and Dissemination (CRD) recommendations[24] covering randomisation, allocation concealment, blinding of outcome assessors, comparability of treatment groups and reporting of withdrawals/dropouts. The quality of the individual studies was assessed by one reviewer and checked by a second. Disagreements were resolved through consensus and a third reviewer was consulted where necessary. Studies included in the review for adverse effects only were not formally assessed for quality because of the diversity of study designs eligible for inclusion.

Data analysis

Data from the individual studies of sugammadex were tabulated and discussed in a narrative review by indication (reversal of moderate block, reversal of profound block and immediate/rapid reversal). Although we had planned to perform quantitative analyses of the results, including meta-analysis where appropriate, this was not possible because of the nature of the available data. The primary studies elected to report outcomes using a mix of arithmetic mean, geometric mean and median. Of those studies that reported the arithmetic mean, it is difficult to ascertain, without access to the primary data, that this was an appropriate statistic. The validity of the statistic hinges on the distribution of the data – only if it is normally distributed will the arithmetic mean be appropriate. The standard deviations (SDs) are presented alongside the arithmetic means for each arm of the studies; in many instances this parameter raised doubt over the normality of the data. While we are aware that techniques are available to allow confidence intervals (CIs) to be calculated adjusting for the different variances, in this instance we believe that adjustment might be inappropriate given that although the majority of the studies have different variances the treatment groups have equal, although small, sample sizes. We have elected instead to present the data as given by the primary authors, with emphasis on median and ranges where available.

Mixed-treatment comparison

In order to facilitate decision-making, we believe it is important to derive results for the relative effectiveness of all of the relevant comparator treatments. As it was anticipated that there would be no head-to-head trials comparing all the treatments, an analysis using the methods of MTCs was planned.[19,25] The purpose of a MTC is to bring together the clinical evidence regarding the efficacy of all treatments for a

specified indication. In general terms, this consists of identifying a 'network of evidence' between the treatments. In the context of the present review this would mean that, for example, although the vecuronium + sugammadex combination has not been directly compared with cisatracurium + neostigmine in a trial, they can be compared *indirectly*, as both have been assessed against a common comparator (rocuronium + sugammadex). Similarly, other treatments that have been compared with a common comparator can also be included in the analysis and compared with each other. The common comparator need not be placebo and, within a MTC, there can be more than one common comparator. Within a MTC *all* of the available trials data on a treatment for the specified indication should be included.

It was planned that the MTC would use the outcome of time to recovery, specifically time to TOF 0.9. The ability to conduct such an analysis is of course dictated by the available data and further details are given in the relevant results section (see Non-sugammadex studies for reversal of moderate NMB).

Results of review of clinical effectiveness

Quantity and quality of research available

Sugammadex efficacy trials

Searches of bibliographic databases and websites as described in Search strategy, together with the manufacturer's submission to the FDA,[23] identified 18 trials considered to meet the inclusion criteria for the review (*Figure 1*). There was good agreement between reviewers on selection of trials for the review.

Three trials of sugammadex that were ongoing or recently completed were identified: a comparison of sugammadex administered at PTC 1–2 with neostigmine administered at reappearance of T2 in patients undergoing laparoscopic cholecystotomy or appendectomy;[26] a comparison of 4-mg/kg sugammadex administered at PTC 1–2 in renal patients and control patients;[27] and a comparison of sugammadex administered at PTC 1–2, with neostigmine administered as per standard of care to reverse rocuronium-induced block in patients undergoing open abdominal surgery.[28] No further

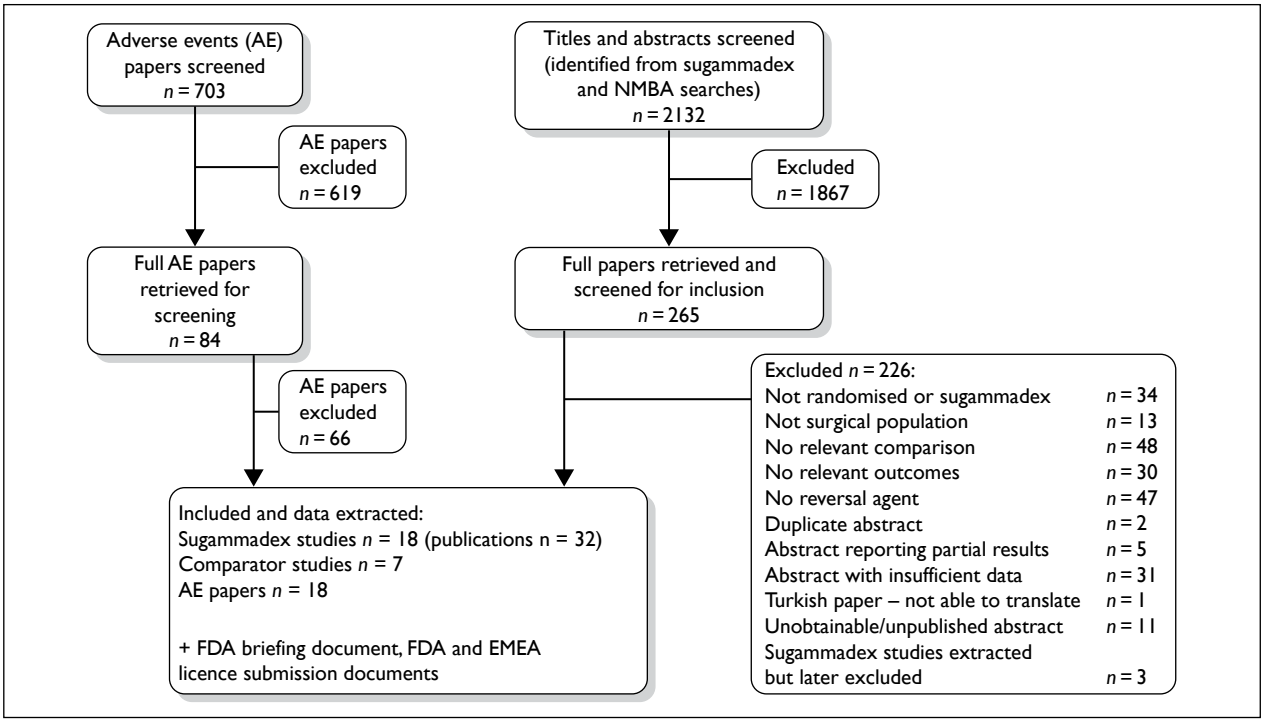

FIGURE 1 *Flow chart of studies through the review process.*

details or data were available on any of these trials, and they were excluded.

The quality assessment of the included trials was subject to some limitations. A number of the trials included in the review had: not yet been published (with only limited data available from licensing submissions); had been published as abstracts; or only single arms or sites of trials had been published as abstracts or full papers. As a result, many of the quality assessment criteria have been graded as 'unclear' because there were insufficient details on which to base a judgement. This does not necessarily mean that these studies are of poor quality – rather, simply, that without the relevant information we cannot be sure of the quality or reliability of the results. All of the sugammadex studies appear to have utilised blinded safety assessors. The primary outcomes (time to recovery of TOF 0.9) have not been measured blind to allocation. However, this was deemed unnecessary because the primary outcomes were measured by objective monitoring. There was generally good agreement between reviewers in validity assessment.

Reversal of moderate block
Eleven studies were included in the assessment of sugammadex for reversal of moderate block: two active-control trials comparing sugammadex with N&G[29,30] and nine placebo-controlled dose-finding and special population studies. Of these trials five have been published in full and six are available only as conference/poster abstracts, with supplementary information taken from the FDA and EMEA documents[10,23] and details reported on the ClinicalTrials.gov website. One trial (19.4.208A)[31] has not been published even in abstract form, but details were available in the Organon/Schering-Plough FDA submission.[23] Further details and quality assessment results for these trials are reported in the section Sugammadex for reversal of moderate NMB.

Reversal of profound block
A total of five studies (three active and two placebo-controlled trials) were included in the assessment of sugammadex for the reversal of profound NMB. Two of these studies have been published in full as journal articles,[32–34] two are available only as short abstracts or publications reporting incomplete results[35–38] and the final study has not yet been published.[39] In all cases, supplementary information was taken from the FDA and EMEA documents,[10,23] and details reported on the ClinicalTrials.gov website. Further details and results of the quality assessment process are reported in the section Sugammadex for reversal of profound NMB.

Immediate reversal of NMB
Three trials (one active and two placebo-controlled trials) were included in the assessment of sugammadex for the immediate reversal of NMB. Full publications were available for two of the trials,[34,40] but one[41] was initially published only as an abstract, with additional data extracted from the EMEA and FDA documents.[10,23] Further details and quality assessment results are reported in the section Sugammadex for immediate/rapid reversal of NMB.

Trials of comparator agents
A total of seven trials were eligible for inclusion in the planned MTC of NMBAs and reversal agents.[42–48] All included trials reported on time to TOF 0.7, 0.8 or 0.9 recovery measured from T2 or equivalent to facilitate comparison with the sugammadex trials. These trials used a variety of NMBAs (rocuronium, vecuronium, atracurium, cisatracurium), with placebo or neostigmine as reversal agents. Spontaneous recovery was of interest in this review, but only one study reported recovery times measured from time points comparable with those in an active treatment arm.[46] Further details and quality assessment results are reported in the section Non-sugammadex studies for reversal of moderate NMB.

Studies of adverse effects of NMBAs and reversal agents
Eighteen references (including one study also included in the MTC) were included in the review of adverse effects. Quality of these studies was not assessed because of the variety of study designs included. Further details are reported in the section Adverse effects.

Efficacy of sugammadex

Sugammadex for reversal of moderate NMB
The proposed indication for sugammadex for routine reversal of moderate NMB induced by rocuronium or vecuronium is 2 mg/kg, administered once spontaneous recovery has reached the reappearance of T2.

Study characteristics
Six studies were included in the assessment of sugammadex for reversal of moderate block.[16,29–31,49,50] The quality assessment results

and characteristics of the included studies are summarised in *Tables 3* and *4*. An additional five trials provided supplementary information on the use of sugammadex in special populations and are discussed in the section Other relevant evidence.[51–55] All 11 studies monitored NMB using acceleromyography (TOF-Watch®). Many of the included trials were dose-finding studies, with the included patients distributed across many treatment dose arms, such that sample sizes per treatment arm were very small. Total sample sizes for relevant treatment arms (i.e. sugammadex 2 mg/kg or placebo or comparator) ranged from 9 to 189 patients, with sample sizes per treatment group ranging from 1 to 48 patients.

Due to clinical and methodological differences among the active studies and special patient populations, meta-analyses across all studies were not appropriate, and data are therefore presented as a narrative synthesis. Furthermore, the results of the primary studies were reported variously using means and SDs, medians and ranges and geometric means and CI, indicating that much, if not all, of the data were likely to be skewed, making synthesis difficult.

Placebo-controlled trials

Four placebo-controlled studies were included in the review ($n = 89$): Sorgenfrei *et al.*,[16] Suy *et al.*,[49] an unpublished Japanese study 19.4.208A[31] and Puhringer *et al*.[50] Quality assessment of these studies (*Table 3*) indicated that allocation concealment was not described, and, while most studies described themselves as randomised, none gave sufficient details to establish if true randomisation had been used (both abstracts and full papers). Power calculations were not always mentioned or described in any detail, but this is not surprising as many of the placebo-controlled trials were dose-finding studies and were not designed to assess efficacy. The treatment groups were usually judged to be comparable and exclusions/dropouts accounted for except where insufficient details had been reported. Major protocol violations were observed in two patients (one in each treatment arm) in Sorgenfrei *et al.*,[16] and monitoring data could not be obtained for one patient in the rocuronium + placebo group in Suy *et al.*,[49] thus these patients were excluded from the per-protocol analysis. Data on patient exclusions and violations were not available for the unpublished Japanese study[31] or Puhringer *et al*.[50] In the first active-control study,[30] two patients in the rocuronium group and seven patients in the vecuronium group did not receive treatment and were therefore not included in the intention-to-treat (ITT) analysis. Five patients in the rocuronium group and seven patients in the vecuronium group experienced major protocol violations and were therefore not included in the per-protocol population. In the second study,[29] 11 patients did not receive treatment and were therefore not included in the ITT analysis, and eight patients experienced major protocol violations and were therefore not included in the per-protocol group.

Study characteristics are reported in *Table 4*. Patients in all four studies received propofol as the induction anaesthesia, two also received this as the maintenance anaesthesia, while patients in the unpublished Japanese study[23] and the Puhringer[50] study received sevoflurane as the maintenance anaesthesia. All four trials were dose-finding studies, not designed as comparator efficacy trials. Patients received fentanyl, remifentanil, alfentanil or morphine as the analgesic agent. Two studies[16,49] included patients undergoing surgery lasting at least 60 minutes and requiring muscle relaxation to facilitate tracheal intubation only, and one study included patients undergoing surgery in the supine position and lasting approximately 1.5–3 hours.

Suy *et al.*[49] and Sorgenfrei *et al.*[16] included patients belonging to ASA classes I and II, although there was a higher proportion of patients in ASA class I in Sorgenfrei,[16] and the unpublished Japanese study[23] included patients in ASA classes I–III. Comorbidity was not reported. Mean ages and mean weights differed slightly between Suy *et al.*[49] and Sorgenfrei *et al.*[16] (55 and 40 years, respectively, and 75 kg compared with 80 kg, respectively). Data were limited for the unpublished Japanese study[31] and Puhringer *et al.*[50] and it was not possible to compare baseline characteristics for these studies (see Appendix 3).

Table 5 shows the time from administration of sugammadex or placebo, administered at reappearance of T2 following rocuronium or vecuronium, to recovery of the TOF ratio to 0.7, 0.8 or 0.9. There were clear differences in recovery times to TOF 0.9, with patients receiving sugammadex 2 mg/kg recovering faster than those receiving the comparators: median recovery times were 1.3–2.9 minutes with sugammadex, compared with 21.0–86.2 minutes with placebo. Furthermore, the recovery time was more predictable with rocuronium + sugammadex: recovery to TOF 0.9 was 0.7–4.8 minutes compared with 15.0–153.0 minutes with rocuronium and placebo. Similar findings were seen with vecuronium: vecuronium + sugammadex recovery

TABLE 3 *Quality assessment results for studies of sugammadex in moderate NMB*

Author (main publication) and protocol number	Allocation concealment	True randomisation	Outcome assessor blinded	Power calculation reported	Comparable treatment groups	Withdrawals or exclusions accounted for
Sorgenfrei[16]						
Sugammadex protocol number 19.4.201	Unclear	Unclear	Yes *For safety outcomes*	No	Yes	Yes
Suy[49]						
Sugammadex protocol number 19.4.207	Unclear	No	Yes *Safety assessor blinded*	No	Yes	Yes
[a]***Unpublished trial***[31]						
Sugammadex protocol number 19.4.208A	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
[b]***Puhringer***[50]						
Sugammadex protocol number 19.4.208B	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
[b]***Blobner***[30]						
Sugammadex protocol number 19.4.301	Yes	Yes	Unclear	Yes	Yes	Yes
Flockton[29]						
Sugammadex protocol number 19.4.310	Yes	Yes	Yes *Safety assessor blinded*	Yes	Yes	Yes

a Trial not yet published.
b Trial available only as an abstract.

to TOF 0.9 was 1.3–7.1 minutes compared with 27.1–141.1 minutes with vecuronium and placebo.

Outcomes for mortality, patient experience/QoL, and costs and resources were not reported.

Active-control trials

Results of the quality assessment process are reported in *Table 3*. The two active-control studies[29,30] largely conformed to the expected quality criteria bearing in mind the lack of blinded primary outcome assessment, and it was unclear if the safety assessments were performed blind to treatment allocation in the study of Blobner *et al*.

The details of the two active-control trials[29,30] are summarised in *Table 4*. One study[30] compared rocuronium + sugammadex with rocuronium + neostigmine–glycopyrrolate, and also compared vecuronium + sugammadex with vecuronium + neostigmine–glycopyrrolate. The other active-control trial compared rocuronium + sugammadex with cisatracurium + neostigmine–glycopyrrolate.[29] The two active trials largely conformed to the expected quality criteria (*Table 3*) except that it was unclear if the safety assessments were performed blind to treatment allocation in the study of Blobner *et al*.[30]

Baseline characteristics were similar in both studies in terms of ASA Physical Status, with all patients classed as ASA I, II or III. Comorbidity was not reported. Both studies included patients undergoing surgery in the supine position and

TABLE 4 *Study characteristics in placebo-controlled and active-control studies of sugammadex for reversal of moderate NMB*

Author	Number of patients[a]	Age of population	Gender	ASA Physical Status	Weight	Treatment arms (*n* treated)	Outcome measures
Placebo-controlled studies							
Sorgenfrei[16]	9	Mean 40 years (SD 13)	29 (100%) male	ASA I: 22/27 (81%) ASA II: 5/27 (19%)	Mean 80 kg (SD 12)	1. Roc (0.6 mg/kg) + sugammadex (2 mg/kg) (*n* = 4) 2. Roc (0.6 mg/kg) + placebo (*n* = 5)	Time to TOF 0.7, 0.8 and 0.9
Suy[49]	23	Mean 55 years (calculated)	43/80 (54%) male	ASA I: 37/80 (47%) ASA II: 42/80 (53%)	Mean 75 kg (calculated)	1. Roc (0.6 mg/kg) + sugammadex 2 mg/kg (*n* = 8) 2. Vec (0.1 mg/kg) + sugammadex (2 mg/kg) (*n* = 8) 3. Roc (0.6 mg/kg) + placebo (*n* = 3) 4. Vec (0.1 mg/kg) + placebo (*n* = 4)	Time to TOF 0.7, 0.8 and 0.9
Puhringer[50]	31	Not reported	Not reported	Not reported	Not reported	1. Roc (0.9 mg/kg) + sugammadex 2 mg/kg (*n* = 9) 2. Vec (0.1 mg/kg) + sugammadex (2 mg/kg) (*n* = 7) 3. Roc (0.9 mg/kg) + placebo (*n* = 7) 4. Vec (0.1 mg/kg) + placebo (*n* = 8)	Time to TOF 0.9
Unpublished Japanese study 19.4.208A[23]	26	Not reported *Ages ranged between 20 and 65 years*	Not reported *Included both males and females*	Not reported in detail *All patients in ASA classes I–III*	Not reported	1. Roc (0.9 mg/kg) + sugammadex (2 mg/kg) (*n* = 6) 2. Roc (0.9 mg/kg) + placebo (*n* = 6) 3. Vec (0.1 mg/kg) + sugammadex (2 mg/kg) (*n* = 6) 4. Vec (0.1 mg/kg) + placebo (*n* = 7)	Time to TOF 0.9
Active-control studies							
Blobner[30]	189	Not reported	Not reported	Not reported in detail *All patients in ASA classes I–III*	Not reported	1. Roc (0.6 mg/kg) + sugammadex (2 mg/kg) (*n* = 48) 2. Roc (0.6 mg/kg) + neostigmine (0.05 mg/kg/glycopyrrolate 0.01 mg/kg) (*n* = 48) 3. Vec (0.1 mg/kg) + sugammadex (2 mg/kg) (*n* = 48) 4. Vec (0.1 mg/kg) + neostigmine (0.05 mg/kg/glycopyrrolate 0.01 mg/kg) (*n* = 45)	Time to TOF 0.9
Flockton[29]	73	Mean 45 years (calculated)	37/73 (41%) male	ASA I: 34/73 (47%) ASA II: 36/73 (49%) ASA III: 3/73 (4%)	Mean 75 kg (calculated)	1. Roc (0.6 mg/kg) + sugammadex (2 mg/kg) (*n* = 34) 2. Cis (0.15 mg/kg) + neostigmine [0.05 mg/kg (maximum of 5 mg)/glycopyrrolate 0.01 mg/kg] (*n* = 39)	Time to TOF 0.7 and 0.9

Cis, cisatracurium; Roc, rocuronium; Vec, vecuronium.
a Number in relevant treatment arms.

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TABLE 5 *Summary of time (minutes) from start of administration of sugammadex or placebo to recovery of TOF ratio to 0.7, 0.8 and 0.9 in placebo-controlled trials of sugammadex for reversal of moderate NMB*

Sorgenfrei[16]					
		Rocuronium + sugammadex (2 mg/kg) (*n* = 3)	**Rocuronium + placebo (*n* = 4)**		
Time to TOF 0.9	Mean (SD)[a]	1.3 (0.4)	23.1 (8.8)		
	Median (range)	1.3 (0.9 to 1.7)	21.0 (15.0 to 35.4)		
Time to TOF 0.8	Median (range)	1.1 (0.9 to 1.5)	15.8 (13.0 to 16.7)		
Time to TOF 0.7	Median (range)	0.9 (0.8 to 1.5)	14.8 (11.5 to 26.4)		
Suy[49]					
		Rocuronium + sugammadex (2 mg/kg) (*n* = 8)	**Rocuronium + placebo (*n* = 3)**	**Vecuronium + sugammadex (2 mg/kg) (*n* = 8)**	**Vecuronium + placebo (*n* = 4)**
Time to TOF 0.9	Mean (SD)	1.7 (0.6)	31.8 (21.0)	2.3 (0.8)	48.8 (27.9)
	Median (range)	1.7 (0.9 to 2.8)	31.8 (17.0 to 46.7)	2.3 (1.3 to 3.5)	39.8 (27.1 to 88.4)
Time to TOF 0.8	Mean (SD)	1.4 (0.4)	26.8 (17.5)	1.7 (0.4)	44.8 (28.2)
Time to TOF 0.7	Mean (SD)	1.4 (0.4)	21.8 (12.9)	1.5 (0.3)	33.7 (16.7)
Puhringer[50]					
		Rocuronium + sugammadex (2 mg/kg) (*n* = 9)	**Rocuronium + placebo (*n* = 7)**	**Vecuronium + sugammadex (2 mg/kg) (*n* = 7)**	**Vecuronium + placebo (*n* = 8)**
Time to TOF 0.9	Mean (SD)	1.4 (0.5)	96.3 (33.1)	3.4 (1.9)	79.0 (26.0)
	Median (range)	1.5 (0.7 to 2.4)	86.2 (55.7 to 153.0)	2.5 (2.1 to 7.1)	70.6 (59.8 to 141.1)
19.4.208A[31] ***(unpublished)***					
		Rocuronium + sugammadex (2 mg/kg) (*n* = 7)	**Rocuronium + placebo (*n* = 6)**	**Vecuronium + sugammadex (2 mg/kg) (*n* = 6)**	**Vecuronium + placebo (*n* = 7)**
Time to TOF 0.9	Mean (SD)	2.20 (1.2)	82.10 (27.60)	2.80 (0.8)	83.20 (20.6)
	Median (range)	1.6 (1.4 to 4.8)	86.0 (47.3 to 108.5)	2.9 (1.7 to 3.9)	82.7 (55.4 to 118.3)

a Taken from FDA document.[23]

all patients received propofol as the induction anaesthesia. Patients in the comparison with neostigmine[30] received sevoflurane as the maintenance anaesthesia, while patients in the comparison with cisatracurium and neostigmine[29] continued with propofol and also received an analgesic (remifentanil, fentanyl or sufentanil). The use of nitrous oxide was not reported in either study (see Appendix 3 for further details).

Table 6 shows the time from administration of sugammadex or neostigmine, administered at reappearance of T2 following rocuronium, vecuronium or cisatracurium to recovery of the TOF ratio to 0.9, based on ITT analysis. Statistical analysis conducted by the primary study authors[29,30] (two-way analysis of variance) indicated significantly faster recovery times after rocuronium + sugammadex (median 1.4 minutes) compared with rocuronium + neostigmine (median 17.6 minutes), and faster recovery times in patients receiving vecuronium + sugammadex (median 2.1 minutes) compared with patients receiving vecuronium + neostigmine (median 18.9 minutes).[30] A significant difference in recovery times was also reported between rocuronium + sugammadex (median 1.9 minutes) versus cisatracurium + neostigmine (median 7.3 minutes).[29] Furthermore, the recovery time was more predictable with rocuronium + sugammadex: recovery to TOF 0.9 was 0.9–5.4 minutes in one trial and 0.7–6.4 minutes in the other, compared with 3.7–106.9 minutes with rocuronium and neostigmine, and 4.2–28.2 minutes with cisatracurium and neostigmine.

Similar trends were also observed for recovery times to TOF 0.8 and 0.7 (*Table 6*), with median recovery times in the rocuronium + sugammadex group faster for both outcomes (1.5 and 1.2 minutes, respectively) compared with the cisatracurium + neostigmine group (5.9 and 4.7 minutes, respectively) both $p < 0.00001$ (primary authors' analysis).[29]

Clinical signs of recovery were reported in Flockton *et al.*,[29] with 22 out of 34 patients (65%) in the sugammadex group and 27 out of 39 patients (69%) in the neostigmine group awake and orientated before transfer to the recovery room. The majority of patients in both treatment groups were reported to be cooperative, able to perform a 5-second head-lift, and did not experience muscle weakness before transfer to or before discharge from the recovery room.

Summary of sugammadex for reversal of moderate block

Data from trials of sugammadex for the reversal of moderate block were reported variously as arithmetic mean, geometric mean and median + range. Based on small numbers of patients, the median time from administration of sugammadex 2 mg/kg at return of T2 to recovery of TOF 0.9 appears to be approximately 2 minutes (medians varied from 1.3 to 2.9 minutes). Placebo-controlled dose-finding studies indicate that recovery of the TOF ratio is significantly faster with sugammadex than placebo, although the magnitude of the difference varied between studies. Two active-control studies indicate significantly faster recovery times using sugammadex versus neostigmine after NMB induced with rocuronium, vecuronium or cisatracurium.[29,30] Furthermore, the recovery time was more predictable with sugammadex than with placebo or other reversal agent, as shown by much smaller ranges reported in all trials.

Non-sugammadex studies for reversal of moderate NMB

Seven non-sugammadex studies were found to be directly comparable with the main sugammadex trials, i.e. they were RCTs that measured time to recovery from T2 or an equivalent time point (T1 20% or 25%) to TOF 0.9, 0.8 or 0.7.[42–48] Details of these trials are summarised in *Table 7* and further details are provided in Appendix 3.

Two of these non-sugammadex RCTs included patients with comorbid disease. One[45] that included 7% of patients with preoperative pulmonary disease was included in full. From the second trial,[48] which had 51% of patients with renal disease, only the non-renal-disease patients were included.

Mean ages of adults ranged from 29.5 to 52 years, and mean weights of adults ranged between 58.7 kg and 75 kg. Five studies[42,44–46,48] mentioned ASA Physical Status, with patients belonging to ASA classes I–III. Comorbidity was not reported. Sample sizes ranged from 60 to 461 patients. With the exception of patients included in one study,[43] who were all female and had a lower mean age and mean weight than in other studies that reported these details, baseline characteristics were comparable to patients in the sugammadex studies.

Patients were undergoing various surgical procedures and were administered thiopental or propofol for induction of anaesthesia. Nitrous oxide was administered in six studies. Different

TABLE 6 *Summary of time (minutes) from start of administration of sugammadex or neostigmine to recovery of TOF ratio to 0.7, 0.8 or 0.9 in active-control studies of sugammadex for reversal of moderate NMB*

	Rocuronium + sugammadex (2 mg/kg) (*n* = 48)	**Rocuronium + neostigmine (0.05 mg/kg) (*n* = 48)**	**Vecuronium + sugammadex (2 mg/kg) (*n* = 48)**	**Vecuronium + neostigmine (0.05 mg/kg) (*n* = 45)**
Blobner,[30] FDA[56]				
Time to TOF 0.9				
Geometric mean (95% CI)	1.5 (1.3 to 1.7)	18.5 (14.3 to 23.9)	2.8 (2.3 to 3.4)	16.8 (12.9 to 21.9)
Median (range)	1.4 (0.9 to 5.4)	17.6 (3.7 to 106.9)	2.1 (1.2 to 64.2)	18.9 (2.9 to 76.2)
	Rocuronium + sugammadex (2 mg/kg) (*n* = 34)	**Cisatracurium + neostigmine (0.05 mg/kg) (*n* = 39)**		
Flockton[29]				
Time to TOF 0.9				
Geometric mean (95% CI)	1.9 (1.6 to 2.2)	9.0 (7.5 to 10.8)		
	FDA document: 1.9 (1.6 to 2.4)	FDA document: 9.0 (7.4 to 10.4)		
Median (range)	1.9 (0.7 to 6.4)	7.3 (4.2 to 28.2)		
Time to TOF 0.8				
Geometric mean (95% CI)	1.6[a]	6.5[a]		
Median (range)	1.5 (0.7 to 3.4)	5.9 (3.2 to 15.6)		
Time to TOF 0.7				
Geometric mean (95% CI)	1.4[a]	5.1[a]		
Median (range)	1.2 (0.7 to 2.9)	4.7 (2.4 to 10.9)		

a CIs could not be calculated.

TABLE 7 *Study characteristics in non-sugammadex studies for routine reversal of moderate NMB*

Author	Number of patients[a]	Mean age of population	Gender	ASA Physical Status	Mean weight	Treatment arms (*n* treated)	Measured time to TOF
Adamus (2006)[42]	120	51.1 years (calculated)	59/120 (49%) male	ASA I: 41/120 (34%) ASA II: 67/120 (56%) ASA III: 12/120 (10%)	75.05 kg (calculated)	1: Roc (0.6 mg/kg) + neostigmine (0.04 mg/kg) or atropine (0.015 mg/kg) (*n* = 15) 2: Roc (0.6 mg/kg) + spontaneous recovery (*n* = 15) 3: Roc (0.9 mg/kg) + neostigmine (0.04 mg/kg) or atropine (0.015 mg/kg) (*n* = 15) 4: Roc (0.9 mg/kg) + spontaneous recovery (*n* = 15) 5: Cis (0.1 mg/kg) + neostigmine (0.04 mg/kg) or atropine (0.015 mg/kg) (*n* = 15) 6: Cis (0.1 mg/kg) + spontaneous recovery (*n* = 15) 7: Cis (0.15 mg/kg) + neostigmine (0.04 mg/kg) or atropine (0.015 mg/kg) (*n* = 15) 8: Cis (0.15 mg/kg) + spontaneous recovery (*n* = 15)	0.9
Bailey (1988)[43]	60	29.5 years (calculated)	100% female	Not reported	58.7 kg (calculated)	1: Vec (0.6 mg/kg) + neostigmine (0.04 mg/kg) or atropine (0.02 mg/kg) (*n* = 29) 2: Atra (0.3 mg/kg) + neostigmine (0.04 mg/kg) or atropine (0.02 mg/kg) (*n* = 28)	0.7
Barrio (2007)[44]	40	44 years (calculated)	22/60 (37%) male	ASA I: 39/60 (65%) ASA II: 21/60 (35%)	71 kg (calculated)	1: Roc (0.6mg/kg) + neostigmine (0.03 mg/kg)/atropine (0.01 mg/kg) (*n* = 10) 2: Roc (0.6mg/kg) + placebo (*n* = 9) 3: Cis (0.1mg/kg) + neostigmine (0.03 mg/kg)/atropine (0.01 mg/kg) (*n* = 10) 4: Cis (0.1mg/kg) + placebo (*n* = 9)	0.8
Berg (1997)[45]	461	52 years (calculated)	Not reported	Not reported *ASA I–III: [131 (19%) patients ASA II or III]*	66 kg (calculated)	1: Vec (0.08–0.1 mg/kg) (if succinylcholine used, first dose was 0.05–0.06 mg/kg) + neostigmine (2.5 mg/kg)/glycopyrrolate (0.6 mg/kg) or atropine (1 mg/kg) (*n* = 230) 2: Atra (0.4–0.5 mg/kg) (if succinylcholine used, first dose was 0.3 mg/kg) + neostigmine (2.5 mg/kg)/glycopyrrolate (0.6 mg/kg) or atropine (1 mg/kg) (*n* = 231)	0.8

Author	Number of patients[a]	Mean age of population	Gender	ASA Physical Status	Mean weight	Treatment arms (*n* treated)	Measured time to TOF
Bevan (1999)[46]	176 (88 children and 88 adult women)	Adults 40 years (calculated); children 4.6 years (calculated)	Adults 88 (100%) female; children 39 (44%) female	Not reported *All patients in ASA class I or II*	Adults 61 kg (calculated); children 19 kg (calculated)	1: Roc (0.45 mg/kg) + neostigmine (0.07 mg/kg)/ glycopyrrolate (0.1 mg/kg) 2: Roc (0.45 mg/kg) + spontaneous recovery 3: Vec (0.075 mg/kg) + neostigmine (0.07 mg/kg)/ glycopyrrolate (0.1 mg/kg) 4: Vec (0.075 mg/kg) + placebo	0.9, 0.7
Carroll (1998)[47]	60	31 years (calculated)	Not reported	Not reported	69 kg (calculated)	1: Cis (0.1 mg/kg) + neostigmine (0.05 mg/kg)/ glycopyrrolate (0.01 mg/kg) (*n* = 10) 2: Cis (0.1 mg/kg) + spontaneous recovery (*n* = 10) 3: Cis (0.15 mg/kg) + neostigmine (0.05 mg/kg)/ glycopyrrolate (0.01 mg/kg) (*n* = 10) 4: Cis (0.15 mg/kg) + placebo (*n* = 10) 5: Atra (0.5 mg/kg) + neostigmine (0.05 mg/kg)/ glycopyrrolate (0.01 mg/kg) (*n* = 10) 6: Atra (0.5 mg/kg) + placebo (*n* = 10)	0.8
Della Rocca (2003)[48]	124	Mean 47 years (calculated)	Not reported 67/126 (53%) male	Not reported *All patients in ASA class I or II*	58 kg (calculated)	1: Atra (0.5 mg/kg) + neostigmine (0.05 mg/kg)/atropine (0.02 mg/kg) (*n* = 31; 15 uraemic, 16 healthy) 2: Cis (0.15 mg/kg) + neostigmine (0.05 mg/kg)/atropine (0.02 mg/kg) (*n* = 31; 16 uraemic, 15 healthy) 3: Vec (0.1 mg/kg) + neostigmine (0.05 mg/kg)/atropine (0.02 mg/kg) (*n* = 30; 16 uraemic, 14 healthy) 4: Roc (0.6 mg/kg) + neostigmine (0.05 mg/kg)/atropine (0.02 mg/kg) (*n* = 32; 17 uraemic, 15 healthy)	0.8

Atra, atracurium; Cis, cisatracurium; Roc, rocuronium; Vec, vecuronium.
a Number in relevant treatment arm.

types of monitoring equipment were used to assess levels of NMB (see Appendix 3).

Validity assessment of non-sugammadex studies

As shown in *Table 8*, only one study met all of the quality assessment criteria;[44] however, the sample size was still relatively small. Methods of randomisation were not always reported, and the use of allocation concealment was difficult to establish for most studies. Outcome assessors were not always reported as being blinded but three trials appear to have used full blinding. Overall, the treatment groups were usually judged as being comparable, and all withdrawals and exclusions were accounted for. These studies all used small samples with multiple treatment arms and only three reported power calculations informing the sample size decisions. Despite being published within the last 10 years, overall the reporting was poor, making it difficult to judge the quality of the research.

Results of non-sugammadex studies

The results of the various comparisons made in these seven trials are summarised in *Table 9*. Neostigmine significantly decreased time to recovery of the TOF ratio 0.8 or 0.9 compared with placebo or spontaneous recovery after administration of both rocuronium and cisatracurium ($p < 0.05$ based on primary authors' analysis).[42,44] Bailey and Nicholas[43] reported significantly faster recovery times to TOF 0.7 following vecuronium + neostigmine (mean 2.57 minutes) compared with atracurium + neostigmine (mean 4.26 minutes) ($p < 0.001$ based on primary authors' analysis). By comparison, Della Rocca *et al.*[48] showed faster times to recovery of the TOF ratio to 0.8 following administration of atracurium or cisatracurium + neostigmine compared with rocuronium or vecuronium + neostigmine, and Berg *et al.*[45] reported similar recovery times to TOF 0.8 for all patients following administration of vecuronium + neostigmine and atracurium + neostigmine [median 25 (6–52) and 23 (7–52) minutes, respectively].

Other trials indicate that recovery rates are similar with rocuronium + neostigmine and vecuronium + neostigmine,[46] and between cisatracurium + neostigmine and atracurium + neostigmine.[47]

Overall, these trials demonstrate that neostigmine is effective at shortening time to recovery from T2, or its equivalent (T1 20% or 25%), to TOF ratio 0.7, 0.8 or 0.9 after administration of rocuronium or cisatracurium.

Comparison of all NMBAs and reversal agents

Mixed-treatment comparison

The purpose of the MTC was to bring together the clinical evidence regarding the routine reversal of shallow/moderate block. In order to conduct a MTC, treatments need to be linked into a chain or network of evidence. In this instance those treatments that could be linked (i.e. those with time of recovery measured as time from T2 or equivalent to TOF 0.9) included rocuronium + sugammadex (2 mg/kg), rocuronium + placebo, vecuronium + sugammadex (2 mg/kg), vecuronium + placebo, rocuronium + neostigmine, vecuronium + neostigmine, cisatracurium + neostigmine and cisatracurium + placebo. Summary statistics showing mean or median time to TOF 0.9 were identified. In addition, a number of trials reported TOF 0.7 or 0.8, which it was hoped would allow us

TABLE 8 *Quality assessment results for non-sugammadex studies in reversal of moderate NMB*

Author	Allocation concealment	True randomisation	Outcome assessor blinded	Power calculation reported	Comparable treatment groups	Withdrawals or exclusions accounted for
Adamus[42]	Unclear	Yes	Unclear	Yes	Yes	Yes
Bailey[43]	Yes	Unclear	Yes	No	Yes	Yes
Barrio[44]	Yes	Yes	Yes	Yes	Yes	Yes
Berg[45]	Unclear	Yes	Yes	Yes	Yes	Yes
Bevan[46]	Unclear	Yes	Unclear	No	Yes	Yes
Carroll[47]	Unclear	Unclear	Unclear	No	Yes	Yes
Della Rocca[48]	Unclear	Unclear	Unclear	No	No	Yes

TABLE 9 *Time from administration of neostigmine or placebo/spontaneous recovery to recovery of the TOF ratio 0.7, 0.8 or 0.9 in non-sugammadex studies*

Study and comparisons	Outcome				
Adamus[42]		Roc (0.6 mg/kg) + neostigmine (*n* = 15)	Roc (0.6 mg/kg) + spontaneous recovery (*n* = 15)	Roc (0.9 mg/kg) + neostigmine (*n* = 15)	Roc (0.9 mg/kg) + spontaneous recovery (*n* = 15)
	Time to TOF 0.9 mean (SD)	9.8 (2.0)	43.10 (13.10)	10.0 (2.70)	56.7 (12.90)
Adamus[42]		Cis (0.1 mg/kg) + neostigmine (*n* = 15)	Cis (0.1 mg/kg) + spontaneous recovery (*n* = 15)	Cis (0.15 mg/kg) + neostigmine (*n* = 15)	Cis (0.15 mg/kg) + spontaneous recovery (*n* = 15)
	Time to TOF 0.9 mean (SD)	11.5 (2.80)	49.20 (8.0)	11.7 (2.70)	52.50 (7.0)
Barrio[44]		Roc + neostigmine (*n* = 10)	Roc + placebo (*n* = 9)	Cis + neostigmine (*n* = 10)	Cis + placebo (*n* = 9)
	Time to TOF 0.9 mean (SD)	5.8 (2.4)	24.4 (12)	7 (1.8)	20.3 (4)
Bevan[46]		Roc + neostigmine (*n* = not reported)	Vec + neostigmine (*n* = not reported)		
	Time to TOF 0.9 mean (SD)	4.5 (2.4)	6.0 (4.0)		
	Time to TOF 0.7 mean (SD)	2.6 (0.9)	2.6 (2.0)		
Bailey[43]		Vec + neostigmine (*n* = 29)	Atra + neostigmine (*n* = 28)		
	Time to TOF 0.7 mean (SD)	2.57 (1.1)	4.26 (1.4)		
Berg[45]		Vec + neostigmine (*n* = 230)	Atra + neostigmine (*n* = 231)		
	Time to TOF 0.8 median (range)	25 (6.0 to 51.0)	23 (7.0 to 52.0)		
Carroll[47]		Cis (0.1 mg/kg) + neostigmine (*n* = 10)	Cis (0.15 mg/kg + neostigmine (*n* = 10)	Atra (0.5 mg/kg) + neostigmine (*n* = 10)	
	Time to TOF 0.8 median (range)	5.4 (3.2 to 9.0)	5.2 (3.8 to 13.3)	5.9 (3.4 to 8.6)	
Della Rocca[48]		Cis (0.15 mg/kg) + neostigmine (*n* = 15)	Vec (0.1 mg/kg) + neostigmine (*n* = 14)	Cis (0.15 mg/kg) + neostigmine (*n* = 15)	Atra (0.5 mg/kg) + neostigmine (*n* = 15)
	Time to TOF 0.8 mean (SD)	16 (2.1)	20 (3.3)	16 (2.1)	14.2 (4)
Della Rocca[48]		Cis (0.15 mg/kg) + neostigmine (*n* = 15)	Roc (0.6 mg/kg) + neostigmine (*n* = 15)	Vec (0.1 mg/kg) + neostigmine (*n* = 14)	Atra (0.5 mg/kg) + neostigmine (*n* = 15)
	Time to TOF 0.8 mean (SD)	16 (2.1)	32.3 (4)	20 (3.3)	14.2 (4)
Della Rocca[48]		Vec (0.1 mg/kg) + neostigmine (*n* = 14)	Roc (0.6 mg/kg) + neostigmine (*n* = 15)	Atra (0.5 mg/kg) + neostigmine (*n* = 15)	Roc (0.6 mg/kg) + neostigmine (*n* = 15)
	Time to TOF 0.8 mean (SD)	20 (3.3)	32.3 (4)	14.2 (4)	32.3 (4)

Atra, atracurium; Cis, cisatracurium; Roc, rocuronium; Vec, vecuronium.

with the use of econometric techniques to estimate a TOF 0.9. This would also have allowed an additional comparator, atracurium + neostigmine, to be incorporated into the network. However, in order to estimate TOF 0.9 using the TOF 0.7 and 0.8 data, it would have been necessary to assume that the relationship between the TOF ratios was the same across all comparators. After some discussion it was felt that this was unreasonable and all studies reporting TOF 0.7 and 0.8 were excluded from the network.

However, despite the exclusion of these studies, there were still a number of problems identified with the remaining data. Firstly, it was unclear whether the mean data reported for TOF 0.9 were appropriate. Given the small sample sizes and unequal variances it is possible that the data were in fact skewed data, rather than normally distributed. Also, where medians were reported it was necessary to have or to calculate the 95% CIs of those summary estimates, in order to undertake the analysis. Unfortunately, this was not possible from the published data available to us and we were unable to obtain data from the manufacturer of sugammadex, Schering-Plough, despite repeated requests. In order to estimate the 95% CIs we would have needed to make some assumption about the likely distribution of the data, and while such an assumption was possible, it was not possible without further data to validate any such distributional assumption. If a false distributional assumption was made, the results generated could be spurious and any inferences made on the basis of these calculations would need to be made in a highly conservative fashion. Therefore, it was concluded that the MTC analysis could not be undertaken at this time. Further research into the possibility and implications of using different statistical methods to achieve the MTC could be investigated, but this would be outside of the resources and scope of this project.

Narrative synthesis

The available trial data indicate that in patients without comorbid disease, recovery to a TOF ratio of 0.9 is substantially faster when NMB is reversed with sugammadex following rocuronium or vecuronium (mean recovery times ranged between 1.4 and 2.2 minutes, and between 2.3 and 3.4 minutes, respectively) compared with reversal with neostigmine after rocuronium (between 4.5 and 10 minutes) or vecuronium (mean 6.0 minutes) and spontaneous recovery after rocuronium (43.1 and 56.7 minutes). Similar trends were observed in studies of cisatracurium, with recovery times to TOF 0.9 of 11.5 and 11.7 minutes following reversal with neostigmine, and 49.2 and 52.5 minutes for spontaneous recovery.

Overall, the non-sugammadex trials demonstrate that neostigmine is effective at shortening time to recovery (from T2 or an equivalent time point to TOF 0.7, 0.8 or 0.9) with all NMBAs studied, including rocuronium, vecuronium, cisatracurium and atracurium. The evaluation of the evidence for sugammadex demonstrated that the combination of rocuronium + sugammadex and vecuronium + sugammadex resulted in a substantially shorter time to recovery than did rocuronium + neostigmine and vecuronium + neostigmine. In addition, rocuronium + sugammadex resulted in a statistically significantly shorter time to recovery compared with cisatracurium + neostigmine.[29] Therefore, the data would suggest that use of rocuronium or vecuronium + sugammadex would result in shorter recovery times than the use of these NMBAs with neostigmine, and use of sugammadex with rocuronium or vecuronium may be shorter than cisatracurium/atracurium neostigmine combinations. However, these tentative conclusions are limited by the lack of a more formal and explicit analysis.

Sugammadex for reversal of profound NMB

The proposed indication for the reversal of profound NMB is the administration of 4-mg/kg sugammadex when recovery has reached a PTC of 1–2 (PTC 1–2) following rocuronium or vecuronium. The depth of block at 15 minutes is generally seen as equivalent to a PTC of 1–2.[57]

A total of five studies were included for this indication: three active-control trials, one of which is based on three publications,[35–39] and two placebo-controlled trials.[32,34] Three studies assessed this indication based on reversal at PTC 1–2,[33,36,37,39] and two studies[32,34] evaluated reversal after 15 minutes.

The quality assessment results are shown in *Table 10*. No studies were judged as having met all of the quality criteria, even where a full publication was accessible. For the three partially published or unpublished studies the limited information available is reflected in the many 'unclear' judgements. In those studies with full publications, allocation concealment and use of true randomisation was reported in one out of two trials. One efficacy trial reported using a power calculation (the remaining trials were dose-finding studies), and all accounted for their withdrawals

TABLE 10 *Quality assessment results for studies of sugammadex in profound NMB*

Author (main publication) and protocol number	Allocation concealment	True randomisation	Outcome assessor blinded	Power calculation reported	Comparable treatment groups	Withdrawals or exclusions accounted for
Sparr[32] Sugammadex protocol number 19.4.202	Unclear	Unclear	Yes *Safety assessors blinded*	No	Yes	Yes
Puhringer[34] Sugammadex protocol number 19.4.206	Yes	Yes	Yes *Safety assessor blinded*	No	Yes	Yes
[a]**Schering-Plough**[39] 19.4.209A	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
[b]**Duvaldstein**[35] Sugammadex protocol number 19.4.209B	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Jones,[36,38] **Lemmens**[37] Sugammadex protocol number 19.4.302	Unclear	Unclear	Yes *Safety assessor blinded*	Yes	Yes	Yes

a Trial not yet published.
b Trial available only as an abstract.

and appeared to have used comparable treatment groups.

Study characteristics are summarised in *Table 11*. Where reported, patients were mainly in ASA classes I and II and undergoing elective surgery lasting up to 120 minutes or more. No trial reported comorbidity. Propofol was used for induction of anaesthesia and propofol or sevoflurane for maintenance, with fentanyl or intravenous opioid analgesia.

Table 12 summarises results of the included studies for recovery of the TOF ratio. Where studies were primarily designed as dose finding, and various doses of sugammadex had been used, only those doses relevant to clinical practice and recommended for use were considered.

Placebo-controlled trials (reversed at 15 minutes)

Both placebo-controlled trials on profound block[32,34] evaluated reversal after 15 minutes of 0.6-mg/kg rocuronium block with sugammadex (4 mg/kg). Both trials assessed the dose–response relationship and efficacy of five doses of sugammadex or placebo for the reversal of profound rocuronium block (0.6-mg/kg intubating dose[32] and 1.0-mg/kg or 1.2-mg/kg intubating dose[34]). The results for times to recovery of TOF 0.7, 0.8 and 0.9 are presented in *Table 12*. Results of one trial[32] were reported based on the per-protocol population, as the ITT population included one patient assigned to sugammadex who received placebo and this was deemed to inappropriately influence the dose–response curve. The results of the second trial were reported for the ITT population. For the primary outcome of time to TOF 0.9, recovery with 4-mg/kg sugammadex was clearly faster than the placebo group for all three doses of rocuronium investigated (medians of 1.5–5.6 minutes versus 30.6–94.2 minutes).

Both of these small placebo-controlled dose-finding studies appear to be of high internal validity, although neither was designed as an efficacy trial, and provide some support to the hypothesis that sugammadex can reverse profound NMB.

TABLE 11 *Patient characteristics in studies of sugammadex for reversal of profound NMB*

Author/protocol number	Number of patients[a]	Age of population	Gender	ASA Physical Status	Weight	Treatment arms (*n* treated)	Outcome measures
Placebo controlled trials (reversed at 15 minutes)							
Sparr[32] Study 19.4.202	9	Mean 38.8 years (calculated) (range 19–63)	99 (100%) male	ASA I: 77/98 (79%) ASA II: 21/98 (21%)	Mean 81.8 kg (calculated)	1. Roc 0.6 mg/kg + sugammadex (*n* = 6) 2. Roc 0.6 mg/kg + placebo (*n* = 3)	Time to TOF 0.7, 0.8 and 0.9 Measured from reversal at 15 minutes
Puhringer[34] Study 19.4.206	14	Mean 50 (SD 16) years	93/173 males (54%)	ASA I: 66/173 (38%) ASA II: 88/173 (51%) ASA III: 19/173 (11%)	Mean 77 kg (SD 15)	1. Rocuronium (1.0 mg/kg) + sugammadex (*n* = 4) 2. Rocuronium (1.0 mg/kg) + placebo (*n* = 3) 3. Rocuronium (1.2 mg/kg) + sugammadex (*n* = 4) 4. Rocuronium (1.2 mg/kg) + placebo (*n* = 3)	Time to TOF 0.7 and 0.9 Measured from reversal at 15 minutes
Active-control trials (reversed at PTC 1–2)							
Schering-Plough[39] Study 19.4.209A	21	Unknown (all Japanese)	Not reported	Not reported	Not reported	1. Rocuronium (0.9 mg/kg) + sugammadex (*n* = 11) 2. Vecuronium (0.1 mg/kg) + sugammadex (*n* = 10)	Time to TOF 0.9 Measured from reversal at PTC 1–2
Duvaldstein[35] Study 19.4.209B	18	Range 21–64 years	Not reported	*All patients in ASA classes I–III*	Not reported	1. Rocuronium (0.9 mg/kg) + sugammadex (*n* = 10) 2. Vecuronium (0.1 mg/kg) + sugammadex (*n* = 8)	Time to TOF 0.9 Measured from reversal at PTC 1–2
Jones,[36,38] **Lemmens**[37] Study 19.4.302	187 (187 randomised, 157 treated)	Adults aged ≥ 18 years	Not reported	Not reported *All patients in ASA classes I–III*	Not reported	1. Rocuronium (0.6 mg/kg) + sugammadex (*n* = 37) 2. Rocuronium (0.6 mg/kg) + neostigmine–glycopyrrolate (*n* = 37) 3. Vecuronium (0.1 mg/kg) + sugammadex (*n* = 47) 4. Vecuronium (0.1 mg/kg) + neostigmine–glycopyrrolate (*n* = 36)	Time to TOF 0.9 Measured from reversal at PTC 1–2

a Total number in treatment arms that received a 4-mg/kg dose of sugammadex, placebo or relevant comparator.

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TABLE 12 *Results from studies of sugammadex for reversal of profound NMB*

Author/protocol number	Number of patients[a]	Time to TOF 0.7		Time to TOF 0.8		Time to TOF 0.9	
		Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)
Placebo-controlled trials (reversed at 15 minutes)							
Sparr[32]	1. Rocuronium 0.6 mg/kg + sugammadex ($n = 5$)	1.2 (0.3)		1.3 (0.5)		2.10 (1.2)	1.5 (1.1–4.2)
Study 19.4.202	2. Rocuronium 0.6 mg/kg + placebo ($n = 3$)	31.2 (6.6)		33.4 (8.1)		35.6 (9.10)	30.6 (30.1–46.0)
Puhringer[34]	1. Rocuronium (1.0 mg/kg) + sugammadex ($n = 4$)	3.3 (1.6)	3.1 (1.6–5.3)			5.5 (3.1)	5.4 (1.8–9.3)
Study 19.4.206	2. Rocuronium (1.0 mg/kg) + placebo ($n = 3$)	81.7 (34.2)	79.3 (48.8–117.1)			127.4 (92.8)	91.0 (58.3–232.8)
	3. Rocuronium (1.2 mg/kg) + sugammadex ($n = 5$)	3.1 (0.9)	3.6 (1.9–3.9)			6.0 (2.5)	5.6 (2.6–9.2)
	4. Rocuronium (1.2 mg/kg) + placebo ($n = 3$)	111.4 (53.0)	81.6 (79.8–172.6)			139.6 (79.9)	94.2 (92.8–231.9)
Active-control trials (reversed at PTC 1–2)							
Study 19.4.209A[39]	1. Rocuronium (0.9 mg/kg) + sugammadex ($n = 11$)					1.6 (0.9)	1.2 (0.8–4.0)
	2. Vecuronium (0.1 mg/kg) + sugammadex ($n = 10$)					3.0 (2.4)	1.9 (0.9–8.4)
Duvaldstein[35]	1. Rocuronium (0.9 mg/kg) + sugammadex ($n = 10$)					1.6 (0.7)	1.5 (0.8–2.9)
Study 19.4.209B	2. Vecuronium (0.1 mg/kg) + sugammadex ($n = 8$)					3.3 (3.5)	2.3 (1.0–11.7)
Jones,[36,38] **Lemmens**[37]	1. Rocuronium (0.6 mg/kg) + sugammadex ($n = 37$)					2.9 (2.5–3.4)[b]	2.7 (1.2–16.1)
Study 19.4.302	2. Rocuronium (0.6 mg/kg) + neostigmine–glycopyrrolate ($n = 37$)					50.4 (43.5–58.4)[b]	49.0 (13.3–145.7)
	3. Vecuronium (0.1 mg/kg) + sugammadex ($n = 47$)					4.5 (3.3–6.0)[b]	3.3 (1.4–68.4)
	4. Vecuronium (0.1 mg/kg) + neostigmine–glycopyrrolate ($n = 36$)					66.2 (55.6–78.9)[b]	49.9 (46.0–312.7)

a Number in relevant treatment arms.
b Geometric mean (95% CI); $p < 0.0001$ for comparisons of NMBA + sugammadex versus NMBA + neostigmine.

Active-control trials (reversed at PTC 1–2)

Two of these studies[35,39] were randomised dose-finding rather than efficacy studies, of which only the arms using 4 mg/kg of sugammadex for reversal are of interest and discussed in this section. Two arms within these studies used 4 mg/kg of sugammadex for reversal at PTC 1–2; one arm used 0.9 mg/kg of rocuronium, and the other used vecuronium 0.1 mg/kg. The results (*Table 12*) are based only on per-protocol summaries, which excluded data from any major protocol violations. Median time to recovery of TOF 0.9 was 1.2 minutes and 1.5 minutes in the rocuronium arms, while in the vecuronium arms median recovery time was 1.9 minutes and 2.3 minutes, suggesting that recovery from NMB may be faster when induced by rocuronium than with vecuronium.

The key comparative study for this indication[36–38] was a multicentre trial that compared sugammadex and neostigmine in the reversal of profound vecuronium- or rocuronium-induced blockade. *Table 12* shows the study results for time to recovery of TOF 0.9 after reversal of profound block at PTC 1–2 with sugammadex or neostigmine. Statistical analysis by the study authors, using two-way analysis of variance on log-transformed recovery times, indicated that there was a significant difference between sugammadex and neostigmine in both the rocuronium and vecuronium groups ($p < 0.001$). Within the rocuronium group, median recovery time after reversal with sugammadex was 2.7 minutes compared with 49.0 minutes with neostigmine. In the vecuronium group, reversal time with sugammadex was 3.3 minutes compared with 49.9 minutes with neostigmine; however, there was a greater interindividual variation in recovery times for vecuronium + sugammadex than for rocuronium + sugammadex.

In summary, this trial provides randomised evidence that sugammadex can effectively reverse profound NMB (vecuronium or rocuronium induced) when the patient has recovered to PTC 1–2, a situation where there is currently no other alternative reversal agent available.

Summary of sugammadex for reversal of profound blockade

The ability to reverse profound NMB using sugammadex 4 mg/kg, administered at PTC 1–2 or an equivalent time point, is potentially an important benefit of sugammadex, as existing reversal agents are not able to reverse this level of blockade. Placebo-controlled dose-finding studies (based on reversal 15 minutes after administration of the NMBA) indicate a substantially faster recovery with sugammadex than placebo, although the magnitude of the effect varies. A single trial[36–38] found significantly faster recovery times to TOF 0.9 for sugammadex compared with neostigmine–glycopyrrolate for both rocuronium- and vecuronium-induced blockade (medians of 2.7 versus 49.0 minutes for rocuronium and 3.3 versus 49.9 minutes for vecuronium).

Sugammadex for immediate rapid reversal of NMB

The proposed indication for sugammadex for immediate/rapid reversal of NMB involves administration of 16-mg/kg sugammadex 3 minutes after administration of high doses (1.0 or 1.2 mg/kg) rocuronium. Three trials were identified related to this indication: two placebo-controlled trials[34,40] and one active-control trial.[58] The full publication of the active-control trial became available during revision of this report (April 2009). Before that, data were extracted from the published abstract[41] and regulatory documents.[10,12] Publication of the full trial did not provide any relevant data that had not already been extracted. For ease of reference, the full paper is treated as the main reference for the trial in this report.

The quality assessment results for the three trials are shown in *Table 13*. The placebo-controlled studies were clearly reported and met all of the quality criteria except power calculation reporting. While the active-control study did report power calculation, and comparability of treatment groups and withdrawals were accounted for, it was not clear if true randomisation was used or if allocation had been concealed. Secondary end points included time to recovery of T1 to 90% and clinical signs of recovery. Time to recovery of the TOF ratio to 0.7, 0.8 and 0.9 was recorded in the rocuronium + sugammadex group from administration of sugammadex.[10] The main potential source of bias in the study, a higher rate of exposure in the sugammadex group to drugs that could enhance the effect of NMBAs, could have biased the study results against sugammadex if it meant that sugammadex-treated patients had a more profound block than those treated with succinylcholine.

Study characteristics

Characteristics of the three studies are summarised in *Table 14*. Patients were almost all in ASA classes I and II, although one trial[34] had a higher proportion of ASA II patients than the others. About one-half of the patients were male. Patients

TABLE 13 *Quality assessment results for studies of sugammadex in rapid reversal of NMB*

Author (main publication) and protocol number	Allocation concealment	True randomisation	Outcome assessor blinded	Power calculation reported	Comparable treatment groups	Withdrawals or exclusions accounted for
de Boer[40] Sugammadex protocol number 19.4.205	Yes	Yes	Yes *Safety assessor blinded*	No	Yes	Yes
Puhringer[34] Sugammadex protocol number 19.4.206	Yes	Yes	Yes *Safety assessor blinded*	No	Yes	Yes
Lee[58] Sugammadex protocol number 19.4.303	Unclear	Unclear	Yes *Safety assessors blinded*	Yes	Yes	Yes

in the placebo-controlled trials were undergoing surgery lasting 90 minutes or more, while those in the active-control trial required only a short duration of muscle relaxation. No trial reported comorbidity. All the trials used propofol for induction and maintenance of anaesthesia.

The two placebo-controlled trials were dose-finding studies.[34,40] The main active-controlled trial compared sugammadex for reversal of rocuronium-induced block with spontaneous recovery from NMB induced by succinylcholine. This study was not fully published at the time of writing and data were extracted from the abstract by Lee *et al.*[41] and various other publications (see Appendix 3).

Placebo-controlled studies

Two randomised safety assessor-blinded placebo-controlled trials assessed recovery from rocuronium-induced NMB in patients treated with sugammadex (16 mg/kg) or placebo. In one trial, sugammadex or placebo was administered 5 minutes after an intubating dose (1.2 mg/kg) of rocuronium.[40] In the second trial, sugammadex or placebo was administered 3 minutes after an intubating dose (1.0 or 1.2 mg/kg) of rocuronium.[34] Both trials were designed to explore dose–response relationships and had small numbers of patients in the 16-mg/kg and placebo arms (*Table 14*). Randomised patients who received treatment and had at least one postbaseline efficacy assessment without any major protocol violations were included in the efficacy analyses. The results of the two trials (*Table 15*) were similar to one another and support the hypothesis that sugammadex provides a rapid reversal of NMB induced by high doses of rocuronium when administered shortly after the NMBA. The differences in time to recovery of the TOF ratio between patients treated with placebo and 16-mg/kg sugammadex were large. The results are summarised in *Table 15*.

Active-control study: rocuronium + sugammadex versus succinylcholine

One multicentre RCT involved adult patients aged 18–65 years, and belonging to ASA class I or II, who were undergoing elective surgery requiring a short duration of NMB. Patients were randomised to receive an intubating dose of rocuronium (1.2 mg/kg), followed by sugammadex (16 mg/kg), 3 minutes after the start of rocuronium administration or an intubating dose of succinylcholine (1 mg/kg), followed by spontaneous recovery. NMB was monitored by acceleromyography using the TOF-Watch®. Unlike all other sugammadex trials, the primary efficacy end point was time to recovery of T1 (first twitch of the TOF) to 10% of the control value. This end point was chosen as a surrogate for the appearance of signs of clinical recovery, such as diaphragm movement and return of ventilation

TABLE 14 *Characteristics of studies of sugammadex for rapid reversal of rocuronium-induced NMB*

Author/ protocol number	Number of patients	Age of population	Gender	ASA Physical Status	Weight	Treatment arms (*n* treated)	Outcome measures
Placebo-controlled studies							
de Boer[40] Study 19.4.205	45	Mean 42 (SD 15) years (43 patients)	22/43 (51%) male	ASA I: 32/43 (74%) ASA II: 11/43 (26%)	Overall weight Mean 76 kg (SD 18)	1. Roc 1.2 mg/kg + sugammadex 16 mg/kg (*n* = 7) 2. Roc 1.2 mg/kg + placebo (*n* = 4)	Time to TOF ratio 0.9 from administration of sugammadex or placebo (5 minutes after rocuronium)
Puhringer[34] Study 19.4.206	176	Mean 50 (SD 16) years	93/173 males (54%)	ASA I: 66/173 (38%) ASA II: 88/173 (51%) ASA III: 19/173 (11%)	Overall weight Mean 77 kg (SD 15)	1. Roc 1 mg/kg + sugammadex 16 mg/kg (*n* = 10) 2. Roc 1 mg/kg + placebo (*n* = 5) 3. Roc 1.2 mg/kg + sugammadex 16 mg/kg (*n* = 11) 4. Roc 1.2 mg/kg + placebo (*n* = 5)	Time to TOF ratio 0.7 and 0.9 from administration of sugammadex or placebo (3 minutes after rocuronium)
Active-control study							
Lee[58] Study 19.4.303	115 randomised	Mean 42 years (range 18–65 years)	42% male (46/110 calculated)	ASA I: 70/110 (64%) calculated ASA II: 40/110 (36%) calculated	Not reported Mean BMI 25 kg/m^2 (SD 3 kg/m^2)	1. Roc 1.2 mg/kg + sugammadex 16 mg/kg (*n* = 55) 2. Succinylcholine 1 mg/kg (*n* = 55)	Time to T1 0.1 and 0.9 from administration of NMBA Time from administration of sugammadex (3 minutes after rocuronium) to TOF ratio 0.7, 0.8, 0.9 (sugammadex group only) Clinical signs of recovery

Roc, rocuronium.

TABLE 15 *Summary of time to recovery in placebo-controlled trials of sugammadex for rapid reversal of rocuronium-induced NMB*

Study and time of reversal	Time to TOF (in minutes)	Rocuronium 1 mg/kg		Rocuronium 1.2 mg/kg	
		Sugammadex (*n* = 10)	Placebo (*n* = 5)	Sugammadex (*n* = 11)	Placebo (*n* = 5)
Puhringer[34]					
3 minutes after administration of rocuronium	**TOF 0.7**				
	Mean (SD)	1.3 (0.5)	91.6 (27.4)	1.2 (0.2)	122.9 (36.2)
	Median (range)	1.1 (0.7–2.6)	86.8 (54.2–119.9)	1.3 (0.8–1.5)	107.5 (81.3–173.1)
	TOF 0.9				
	Mean (SD)	1.8 (1.1)	108.4 (31.2)	1.3 (0.4)	123.0 (28.5)
	Median (range)	1.6 (0.9–4.8)	111.1 (63.7–144.8)	1.3 (0.8–2.3)	124.3 (87.3–156.1)
de Boer[40]					
5 minutes after administration of rocuronium	**TOF 0.9**			**Sugammadex (*n* = 7)**	**Placebo (*n* = 4)**
	Mean (SD)			1.9 (2.2)	122.1 (18.1)
	Median (range)			1.3 (0.7–6.9)	126.1 (96.8–139.4)

on the capnogram, which were expected to occur 4.5 minutes or more after administration of succinylcholine.[23]

A total of 115 patients were randomised in this study, 57 to rocuronium + sugammadex and 58 to succinylcholine; 56 and 54 patients, respectively, received treatment and the ITT population for which results were reported contained 55 patients in each group. There were no major differences between groups in baseline characteristics (see Appendix 3). However, 18 patients in the sugammadex group received medication expected to enhance the effects of NMBAs (primarily inhalational anaesthetics) compared with 11 in the succinylcholine group.[12] This was classed as a major protocol violation and could have biased the study results against sugammadex.

Table 16 shows the study results for time from administration of rocuronium or succinylcholine to T1 of 10% and 90%. The study authors' analysis by two-way analysis of variance indicated that the difference between groups was significant ($p < 0.001$) for both outcomes. The time from the start of administration of sugammadex to recovery of the TOF ratio to 0.9 was measured in the rocuronium + sugammadex group (*Table 16*).[58] This ancillary analysis also showed that most patients (87%) had recovered to a TOF ratio of 0.9 by 3 minutes after administration of sugammadex.[58] Times to TOF ratios of 0.7 and 0.8 (assumed to be means) were 1.3 and 1.5 minutes, respectively. Clinical signs of recovery did not show any differences between groups.[58]

In summary, this study provides randomised evidence that recovery of T1 to 10% and 90% of control values is significantly faster following blockade induced by rocuronium and reversed by sugammadex 16 mg/kg compared with blockade induced by succinylcholine followed by spontaneous recovery. However, there was a degree of overlap in the range of recovery times between the two groups, and it would be interesting to have more data on the distribution of recovery times.

None of the studies involving rapid reversal of blockade reported on outcomes related to QoL, costs or resource use, although a Quality of Recovery questionnaire was used in the active-control study.[12] Safety outcomes were assessed and the results included in the summary documents discussed in Other relevant evidence.

Summary of sugammadex for immediate/rapid reversal

The ability to rapidly reverse rocuronium-induced NMB using 16-mg/kg sugammadex could be a valuable tool for the clinician in a situation of rapid sequence induction of anaesthesia or if a 'cannot intubate–cannot ventilate' emergency arises. The three studies included in this section indicate that the end point of TOF ratio 0.9 can be reached rapidly in most patients.

TABLE 16 *Summary of time to recovery in active-control trial of sugammadex for rapid reversal of rocuronium-induced NMB[58]*

	Rocuronium + sugammadex × (16 mg/kg) (*n* = 55)[a]	**Succinylcholine (1 mg/kg) (*n* = 55)**
Time to T1 of 10%		
Mean (SD)	4.4 (0.7)	7.1 (1.6)
Median (range)	4.2 (3.5–7.7)	7.1 (3.7–10.5)
Time to T1 of 90%		
Mean (SD)	6.2 (1.83)	10.9 (2.42)
Median (range)	5.7 (4.2–13.6)	10.7 (5.0–16.2)
Time to TOF ratio 0.9		
Mean (SD)	2.2 (2.2)	
Median (range)	1.73 (0.48–14.3)	

a Sugammadex was administered 3 minutes after rocuronium.

Other relevant evidence

Efficacy of sugammadex in special populations

Four RCTs of sugammadex in special populations (renal disease,[51] children,[52] patients with pulmonary complications,[53] cardiac patients[54] and one non-RCT in elderly patients[55]) were included in the review. These special population studies, including the non-RCT of elderly patients, were included in the review because the use of acetylcholinesterase inhibitors in special patient populations may result in adverse effects, and therefore the use of sugammadex in these populations is clinically relevant.[23] Only limited quality assessment was possible for these studies (*Table 17*) because in most cases the relevant details were not reported.

Details of the studies in special populations are summarised in *Table 18*. The three RCTs[52,59,60] reporting anaesthesia type used propofol for both induction and maintenance. Two studies reported using an analgesic: Staals[59] administered opiates and Plaud[52] administered opioids or caudal analgesics to infants. All five studies administered rocuronium (0.6 mg/kg) followed by sugammadex (2 mg/kg); two studies also included a placebo arm (see Appendix 3).

Renal patients

This study[51] compared the response to sugammadex in patients with and without renal impairment. Thirty patients were included in the study; 15 with renal impairment (CR_{CL} < 30 ml/minute) and 15 healthy control patients (CR_{CL} > 80 ml/minute). The majority of patients with renal failure belonged to ASA class III (93%), compared with control patients who belonged to ASA class I or II.[10] The results for one control patient were unreliable and were therefore excluded from the analysis.

Baseline characteristics were comparable for both groups in terms of age, weight, height, gender and ethnicity. There was a substantial difference in mean CR_{CL} for patients with renal impairment (12 ml/minute) compared with healthy control

TABLE 17 *Quality assessment results for sugammadex special population trials*

Author (main publication) and protocol number	Allocation concealment	True randomisation	Outcome assessor blinded	Power calculation reported	Comparable treatment groups	Withdrawals or exclusions accounted for
Staals[51] Sugammadex protocol number 19.4.304	Unclear	Unclear	Unclear	Yes	No *Renal failure*	Yes
[a]**McDonagh[55]** Sugammadex protocol number 19.4.305	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
[a]**Plaud[52]** Sugammadex protocol number 19.4.306	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
[a]**Amao[53]** Sugammadex protocol number 19.4.308	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
[a]**Dahl[54]** Sugammadex protocol number 19.4.309	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

a Trial available only as an abstract.

TABLE 18 *Study characteristics in special population studies of sugammadex for reversal of moderate NMB*

Author	Number of patients[a]	Age of population	Gender	ASA Physical Status	Weight	Comorbid disease	Treatment arms (*n* treated)	Outcome measures
Staals[51]	29	Mean 57.5 years (calculated)	14/30 (47%) male	ASA I: 5/30 (17%) ASA II: 11/30 (37%) ASA III: 14/30 (46%)	Mean 80 kg (calculated)	Renal disease 15 patients	1. Roc (0.6 mg/kg) + sugammadex (2 mg/kg) (*n* = 15 renal patients) 2. Roc (0.6 mg/kg) + sugammadex (2 mg/kg) (*n* = 14 healthy patients)	Time to TOF 0.7, 0.8 and 0.9
McDonagh[55]	150; 48 adults (aged 18–64), 62 elderly (aged 65–74), 40 old elderly (aged 75 years or older)	Range 18 to >75 years	Not reported	Not reported *ASA classes I–III (no further details)*	Not reported	Not reported	1. Roc (0.6mg/kg) + sugammadex (2 mg/kg) (*n* = 150)	Time to TOF 0.9
Plaud[52]	29 (3 infants, 8 children, 11 adolescents, 7 adults)	Not reported	Not reported	Not reported *All patients in ASA classes I–II*	Not reported	Not reported	1. Roc (0.6 mg/kg) + sugammadex (2 mg/kg) (*n* = 16) 2. Roc (0.6 mg/kg) + placebo (*n* = 13)	Time to TOF 0.9
Amao[53]	39 patients with pulmonary disease	Not reported *All patients aged 18 years or more*	Not reported	Not reported *All patients in ASA classes II–III*	Not reported	All patients had a diagnosis or known history of pulmonary disease	1. Roc (0.6 mg/kg) + sugammadex (2 mg/kg) (*n* = 39)	Time to TOF 0.9
Dahl[54]	78	Range 36–90 years	Not reported	Not reported *All patients in ASA classes II–IV*	Not reported	All patients had cardiac disease	1. Roc (0.6 mg/kg) + sugammadex (2 mg/kg) (*n* = 38) 2. Roc (0.6 mg/kg) + placebo (*n* = 40)	Time to TOF 0.9

Roc, rocuronium.
a Number in relevant treatment arms.

patients (103 ml/minute). Ten renal patients with end-stage renal failure were receiving dialysis.

Recovery times were slightly slower in renally impaired patients compared with control patients, but this was not significantly different ($p = 0.06$), and NMB was effectively reversed in both patient groups. Similar results were reported for time to recovery of TOF 0.7 and 0.8, with no significant differences between the two patient groups (*Table 19*).

Elderly patients
Time to recovery of TOF 0.9 following administration of rocuronium and sugammadex, was reported as 2.3 minutes (geometric mean) in adult patients (≤ 65 years) compared with elderly (65–74 years) and old-elderly patients (≥ 75 years) (geometric means of 2.6 and 3.6 minutes, respectively).[55] This difference was statistically significant ($p = 0.022$, based on primary authors' analysis), but may not be clinically relevant.

Children
Patients were scheduled for general surgery requiring at least 60 minutes of anaesthesia.[52] *Table 20* shows the time from administration of sugammadex or placebo administered at reappearance of T2 following rocuronium, to recovery of the TOF ratio to 0.9.

The difference in mean recovery times indicate that recovery to TOF 0.9 with sugammadex is substantially faster than recovery times after placebo across all ages investigated. Recovery times in adults may be slower than in adolescents, children and infants.

Pulmonary patients
This randomised placebo-controlled study[53] compared recovery times in adult patients with a diagnosis or known history of pulmonary disease, such as asthma.[23] The geometric mean time to recovery of the TOF ratio to 0.9 was 2.1 minutes, similar to recovery times reported in the two active-controlled studies: 1.5 minutes[30] and 1.9 minutes.[29]

Cardiac patients
This multicentre, randomised, placebo-controlled study[54] assessed the safety of sugammadex for the reversal of NMB induced by rocuronium in adult patients with cardiac disease (e.g. ischaemic heart disease, chronic heart failure or arrhythmia).[23] Patients belonged to ASA classes II, III or IV, but no further details were reported. Patients were undergoing elective, non-cardiac surgery in the supine position.

Time to recovery of the T4/T1 ratio to 0.9 was substantially faster in patients receiving sugammadex compared to patients in the placebo group (geometric mean 1.7 versus 34.4 minutes).

Summary of sugammadex special population studies
In special population studies, recovery times differed between the age groups, with infants showing the quickest recovery times. However, due to the low number of patients included, and the lack of statistical analysis, these findings should be interpreted with caution. Recovery times for reversal of rocuronium NMB using sugammadex were comparable for patients at increased risk of pulmonary disease and patients without pulmonary complications, and for patients with and without cardiac or renal disease.

TABLE 19 *Summary of time (minutes) from start of administration of sugammadex at reappearance of T2 to recovery of TOF ratio to 0.7, 0.8 and 0.9 in patients with poor and good renal function (per-protocol analysis)*

	Poor renal function: CR_{CL} < 30 ml/minute ($n = 15$)	Good renal function: CR_{CL} > 80 ml/minute ($n = 14$)	p-value
Time to TOF 0.7			
Arithmetic mean (SD)	1.45 (0.47)	1.17 (0.38)	NS
Time to TOF 0.8			
Arithmetic mean (SD)	1.6 (0.57)	1.32 (0.45)	NS
Time to TOF 0.9			
Arithmetic mean (SD)	2.00 (0.72)	1.65 (0.63)	NS

CR_{CL}, creatinine clearance.

TABLE 20 *Summary of time (min) from start of administration of sugammadex to recovery of TOF ratio to 0.9 in children*

Time to TOF 0.9	Rocuronium 0.6 mg/kg + 2-mg/kg sugammadex	Rocuronium 0.6 mg/kg + placebo
Infants	*n* = 1	*n* = 2
Arithmetic mean (SD)[a]	0.6 (–)	21.0 (11.3)
Median (range)	0.6	21.0 (13.0–29.0)
Children	*n* = 4	*n* = 4
Arithmetic mean (SD)[a]	1.2 (0.4)	19.6 (11.0)
Median (range)	1.2 (0.9–1.6)	19.0 (8.4–31.8)
Adolescents	*n* = 6	*n* = 5
Arithmetic mean (SD)[a]	1.9 (1.7)	22.8 (13.1)
Median (range)	1.1 (0.7–5.2)	23.4 (6.8–41.7)
Adults	*n* = 5	*n* = 2
Arithmetic mean (SD)[a]	1.3 (0.3)	29.5 (8.4)
Median (range)	1.4 (1.0–2.0)	28.5 (19.6–44.0)

a Based on primary analysis of EMEA report.[10]

Ongoing trials

Relevant ongoing trials include a comparison of sugammadex administered at PTC 1–2 with neostigmine administered at reappearance of T2 in patients undergoing laparoscopic cholecystotomy or appendectomy,[26] and a comparison of 4-mg/kg sugammadex administered at PTC 1–2 in renal and control patients.[27]

Adverse effects

Summary of adverse effects of sugammadex

Summary data on adverse events in patients treated with sugammadex were extracted from the manufacturer's submission to the US FDA[23] and the EMEA assessment report for sugammadex.[10] These are the most comprehensive sources of data on the adverse effects of sugammadex because they include both published and unpublished studies and report more fully on adverse events/effects than do the published trials. Most of the patients included were aged 18–64 years, were white or Asian and in ASA class II.

In the Organon/Schering-Plough submission to the FDA, data were pooled from all 26 trials in which patients received an NMBA followed by sugammadex or placebo (n = 1926 patients treated with sugammadex).[23] Data were also pooled to compare sugammadex with placebo (10 trials: sugammadex n = 640 patients, placebo n = 140 patients), and with neostigmine (two trials: sugammadex n = 179 patients, neostigmine n = 167 patients) . Similar data were reported in the EMEA assessment, although numbers of patients involved were slightly different (24 trials and 1713 patients). *Table 21* summarises the data extracted from the two documents. Full details can be found in Appendix 3.

Overall, 76.3% of patients exposed to any dose of sugammadex plus an NMBA experienced at least one adverse event; the incidence of adverse events did not increase markedly with increasing dose.[23] High rates of adverse events would be expected for patients who had recently undergone a surgical procedure. The only treatment-related adverse events that occurred in at least 2% of sugammadex patients and at a twofold higher incidence with sugammadex than with placebo were anaesthetic complication and cough. Adverse events thought to be possibly related to trial medication occurred more frequently with sugammadex than with placebo (13.3% versus 7.9%), but less frequently than with neostigmine (18.4% versus 25.1%). The FDA submission reports that the only treatment-related adverse event that occurred at a twofold higher incidence with sugammadex than neostigmine was vomiting.[23]

Deaths and serious adverse events

There were no deaths related to the administration of sugammadex. The incidence of serious adverse events following administration of sugammadex

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TABLE 21 *Summary of adverse event/effects data for sugammadex*

Data source	Type of data source	Drug(s) evaluated	Rates of adverse effects reported by drug
EMEA[10]	Regulatory agency assessment report	Sugammadex standard doses of 2, 4 and 16 mg/kg	EMEA document data based on 29 clinical trials of Sugammadex (n = 1833). Of these, there were 24 trials (n = 1713), where a NMBA had been administered as well as sugammadex or placebo. Further subsets: sugammadex vs neostigmine (2 trials: sugammadex n = 179, neostigmine n = 167) and sugammadex vs placebo (10 trials: sugammadex n = 640, placebo n = 140) Overall, 80% of patients exposed to any dose of sugammadex experienced at least one AE: 2 mg/kg 79%; 4 mg/kg 89%; 16 mg/kg 81% sugammadex vs neostigmine. Total with at least one AE: sugammadex 88% (157/179); neostigmine 89% (149/167) Sugammadex vs placebo: Total with at least one AE – sugammadex 68% (435/640), placebo 72% (101/140) *Serious adverse events (SAEs)* Experiencing at least one SAE across all clinical trials (regardless of NMBA used): sugammadex 6%, placebo 4% *Specific adverse events* Anaesthetic complications reported in 3% of patients but most were related to immediate reversal of NMB Allergic reactions: No specific rate reported, 7 cases of possible hypersensitivity reactions to sugammadex across all clinical trials. Cardiac rhythm disturbances: prolongation of QTc interval seen in all phase I–III studies, especially with sevoflurane, but no specific rate reported Prolonged blockade: 2% in pooled phase I–III studies (0% with placebo); < 1% overall (0% placebo)
Organon, Schering-Plough (2008)[23]	Manufacturer's report for regulatory authority	Sugammadex	Submission to FDA by Organon. Data based on pooled phase I–III trials (n = 1926). Subsets: sugammadex vs neostigmine [2 trials (19.4.301 and 19.4.302): sugammadex n = 179, neostigmine n = 167] and sugammadex vs placebo (10 trials: sugammadex n = 640, placebo n = 140) Overall, 76.3% of patients exposed to any dose of NMBA + sugammadex experienced at least one AE: 2 mg/kg 78.9%; 4 mg/kg 88.7%; 16 mg/kg 80.8%. 5.1% experienced at least one SAE. Of these 8 (0.4%) were considered possibly related to treatment by the investigator Sugammadex vs neostigmine: AEs considered treatment related by investigator: sugammadex 18.4%, neostigmine 25.1%. SAEs (regardless of NMBA used): sugammadex 3.4%, neostigmine 3.6% Sugammadex vs placebo: AEs considered treatment related by investigator: sugammadex 13.3%, placebo 7.9%. SAEs (regardless of NMBA used): sugammadex 5.8%, placebo 4.3% *Specific adverse events* Anaesthetic complications 3% (57/1926): 16 mg/kg 9.1%, 2 mg/kg 2.0%, 4 mg/kg 1.5% Allergic or hypersensitivity reactions: < 1% in pooled phase I–III trials; 7 cases of possible hypersensitivity reactions, 6 of which were in response to 32-mg/kg dose Dysgeusia 12.6% (most cases occurred at 32 mg/kg dose); nausea 23.2% (447/1926), vomiting 10.5% (202/1926) Adverse events related to ventilation: dyspnoea 1.5%; oxygen saturation decreased 1%; bronchospasm, wheezing and obstructive airways disorder 0.5% (10/1926) Prolonged blockade or recurrence of blockade during monitoring 1.2% (24/1926). Of these cases, 20 were following subtherapeutic dose (< 2 mg/kg) of sugammadex Cardiac rhythm disturbances: prolongation of QTc interval examined in two specific trials. Administration of sugammadex at 4 or 32 mg/kg (± NMBA) did not lead to QTc prolongations of regulatory concern, i.e. both trials found negative results according to the criteria of the ICH E14 guideline

ICH, International Conference on Harmonisation; QTc, corrected QT interval; SAE, serious adverse event.

plus an NMBA was 5.1% (in placebo controlled trials rates were 5.8% with sugammadex and 4.3% with placebo). Eight patients (0.4% of the total sugammadex group) experienced a serious adverse event that was considered to be related to treatment. In the two controlled trials included in the FDA submission (19.4.301 and 19.4.302),[30,36–38] the incidence of serious adverse events was similar for sugammadex (3.4%) and neostigmine (3.6%).

Adverse events considered particularly relevant to the use of anaesthesia and reversal agents were evaluated in both reports, although rates were more clearly reported in the FDA submission.[23] These events included recurrence of blockade or residual blockade, anaesthetic complications, adverse events related to ventilation and allergic reactions.

Recurrence of blockade or residual blockade

In the total sugammadex population, 1.2% of patients (24/1926) had evidence of recurrence of blockade or residual blockade based on acceleromyographic monitoring and 0.3% (6/1926) showed clinical signs of recurrence or residual blockade.[23] Of the 24 cases identified, 20 were in patients who received subtherapeutic doses (< 2 mg/kg) of sugammadex, suggesting that residual blockade was most frequent when doses lower than the licensed doses of sugammadex were given. In the pooled phase I–III trials with a placebo group, the rate was 1.7% (11 patients) in patients treated with sugammadex and zero in the placebo group. Doses of sugammadex in these trials ranged from < 2 mg/kg to 16 mg/kg, but the number of patients who received specific doses was not reported.[23] However, given that only four patients in the total sugammadex population with recurrence of blockade or residual blockade received licensed doses of sugammadex, it seems reasonable to assume that at least 7 out of these 11 patients received subtherapeutic doses. One patient, who received 0.5-mg/kg sugammadex, had clinical evidence of recurrence of blockade or residual blockade at recovery.[23]

Adverse events representative of recurrence of blockade or residual blockade were reported in 0.4% (7/1926) of patients treated with sugammadex, 2.4% (4/167) neostigmine-treated patients and zero placebo-treated patients. The lack of residual blockade in the placebo-treated patients may reflect the fact that monitoring was continued until 60 minutes after recovery of the TOF ratio to 0.9, so patients treated with placebo could have recovered slowly but without meeting the criteria for residual blockade (final TOF ratio < 0.9).

In the controlled trials of sugammadex versus neostigmine for reversal of moderate or profound NMB, no patient in either group had residual blockade or recurrence of blockade.[29,30,36,37,56] Two of these trials used clinical signs to define this outcome, and one[29] used TOF monitoring in addition to clinical evidence; it is possible that some cases would have been detected if TOF monitoring (which is more sensitive) had been used throughout. In the trial comparing rocuronium + sugammadex 16 mg/kg for immediate reversal of NMB with spontaneous recovery from succinylcholine-induced block, one patient in the sugammadex group had evidence of recurrence of blockade based on TOF monitoring, although this was attributed to movement and an unstable trace.[41] No patients showed clinical evidence of recurrence of blockade or residual blockade.

Anaesthetic complications

Anaesthetic complications (including movement or coughing, grimacing or sucking on the endotracheal tube) occurred in 3% (57/1926) of patients in the total sugammadex population. Anaesthetic complication and cough were twofold higher with sugammadex than with placebo. Airway complications of anaesthesia were reported in < 1% (12/1926) of patients in the total sugammadex population.[23]

Adverse events related to ventilation

Most adverse events related to ventilation occurred at a low rate (0.4% or less) in the total sugammadex population. Dyspnoea and decreased oxygen saturation were reported in > 1% of patients but at a similar rate to the placebo group. Bronchospasm was reported as a serious adverse event related to treatment with sugammadex in two patients, both of whom had a history of asthma.

Allergic or hypersensitivity reactions

Possible allergic or hypersensitivity reactions to sugammadex were identified in seven patients (< 1%) across the clinical trials. One case of probable hypersensitivity to sugammadex in a healthy volunteer was confirmed by skin-prick and intradermal tests. In trials performed in non-anaesthetised healthy volunteers to assess the effects of sugammadex on the corrected QT interval (QTc), six participants showed signs of possible hypersensitivity to sugammadex following

the administration of 32-mg/kg sugammadex.[23] In August 2008, the US FDA issued a 'not approvable' letter for sugammadex. The manufacturer stated that the letter related to issues 'primarily related to hypersensitivity/allergic reactions'.[61] The EMEA, which granted marketing authorisation for sugammadex in the European Union in July 2008, recommended continued pharmacovigilance to ensure detection of rare adverse events such as hypersensitivity reactions.[10]

Prolonged QTc interval

An abnormally prolonged QTc interval may lead to torsade de pointes, an arrhythmia that is normally self-terminating but has the potential to be life-threatening. The EMEA assessment stated that significant prolongations of the QTc interval have been reported in all the phase I–III studies with sugammadex, although the rate of this event was not reported in the EMEA document.[10] No cases of torsade de pointes have been reported. The EMEA document also reported that QTc prolongation appears to be a particular issue when sugammadex is used in combination with sevoflurane for anaesthesia. The manufacturers have carried out two trials (protocol numbers 19.4.105 and 19.4.109) to evaluate the effects of sugammadex on QTc interval in non-anaesthetised, healthy volunteers. Brief details of these trials are reported in the FDA submission, where it is stated that administration of sugammadex at doses of 4 mg/kg and 32 mg/kg (with or without an NMBA) did not lead to QTc interval prolongations of regulatory concern (i.e. the one-sided upper CI of the largest time-matched mean difference in QTc change compared with placebo did not exceed 10 milliseconds); i.e. both trials found negative results according to the criteria of the International Conference on Harmonisation (ICH) E14 guideline.[23]

Summary

The safety of sugammadex has to date been evaluated in a limited number of patients in phase I–III trials (n = 1926 patients treated with sugammadex) and special studies. The patients in these studies were mostly relatively young and in good general health, and may not be fully representative of those who would receive sugammadex in routine clinical practice. Overall, rates of adverse events are similar between sugammadex administered after rocuronium or vecuronium and comparators (neostigmine or placebo). The most significant adverse events following treatment with sugammadex appear to be anaesthetic complications (up to 3%), and possibly allergic reactions. Recurrence of blockade and residual blockade were reported in clinical trials but most cases were in patients receiving subtherapeutic doses and hence not of clinical significance. Further monitoring is required to determine the incidence and significance of rare but potentially life-threatening adverse events such as allergic/hypersensitivity reactions and to determine any clinical significance of the QTc interval prolongation seen in clinical trials.

Summary of adverse effects: other agents

We reviewed the adverse effects of non-depolarising NMBAs, succinylcholine and neostigmine–glycopyrrolate. The analysis of non-depolarising NMBAs was undertaken to inform the network of evidence comparing different options for routine reversal of 'moderate' NMB. Succinylcholine and neostigmine–glycopyrrolate were considered as direct comparators for rocuronium + sugammadex and sugammadex, respectively.

We included 18 studies in this section of the review (*Table 22*). The most important adverse effects addressed in these studies were prolonged blockade (encompassing residual blockade and recurrence of blockade), allergic and anaphylactic reactions, cardiac arrest, myalgia (a specific adverse effect associated with succinylcholine), malignant hyperthermia (also associated with succinylcholine) and nausea/vomiting (particularly associated with reversal of blockade by neostigmine–glycopyrrolate).

Adverse effects of non-depolarising NMBAs

A UK national survey reported on fatal and non-fatal adverse events associated with NMBAs in the UK between 1967 and 2000. There were 44 fatalities (13 identified as allergic events) attributed to succinylcholine, 19 (2) to atracurium, four (1) to vecuronium and zero to mivacurium.[62] No results were reported for rocuronium. These data are limited by lack of a denominator but they suggest that the risk of a fatal adverse event may be higher with succinylcholine than with other NMBAs.

Residual blockade/recurrence of blockade

Eight studies reported on residual blockade or recurrence of blockade.[45,62,63,65,69,71,72,78] The UK national survey by Light *et al*.[62] provided absolute numbers of events rather than specific rates. Three studies (two single-centre surveys[63,65] and

TABLE 22 *Summary of included studies for adverse effects of NMBAs and reversal agents other than sugammadex*

Author	Type of data source	Adverse effect(s) reported
Studies of non-depolarising NMBAs		
Baillard[63]	Single-centre survey	Prolonged blockade
Berg[45]	RCT	Prolonged blockade
		Other
Bhanaker[64]	National survey	Anaphylactic reactions
[a]Cammu[65]	Single-centre survey	Prolonged blockade
Laake[66]	National survey	Anaphylactic reactions
[a]Laxenaire[67]	National survey	Anaphylactic reactions
[a]Light[62]	National survey	Allergic reactions
		Cardiac arrest
		Cardiac rhythm disturbances
		Malignant hyperthermia
		Prolonged blockade
		Other
Malinovsky[68]	Single-centre survey	Anaphylactic reactions
Maybauer[69]	RCT	Prolonged blockade
[a]Mertes[70]	National survey	Anaphylactic reactions
Murphy[71]	RCT	Nausea/vomiting
		Prolonged blockade
Murphy[72]	Single-centre survey	Prolonged blockade
		Other
Studies of succinylcholine		
Neal[73]	Single-centre survey	Anaphylactic reactions
Dexter[74]	Non-systematic review	Cardiac arrest
		Malignant hyperthermia
Rosenberg[75]	Non-systematic review	Malignant hyperthermia
Schreiber[76]	Systematic review	Myalgia
Studies of neostigmine–glycopyrrolate		
Cheng[77]	Systematic review	Nausea/vomiting
Tramer[78]	Systematic review	Nausea/vomiting
		Prolonged blockade

a Also includes data on succinylcholine.

one RCT[69]) reported rates of residual blockade in the absence of reversal or with reversal agents not routinely used. The studies differed in their use of reversal agents, definition of residual blockade and the point at which blockade was evaluated (*Table 23*). In the study by Cammu *et al.*,[65] reversal agent use was not reported by drug but blockade was reversed in 25% of outpatients and 26% of inpatients. These three studies suggest that in the absence of reversal 25–50% of patients could have some degree of residual NMB (TOF ratio < 0.9) on arrival in the recovery room after treatment with a non-depolarising NMBA as part of their anaesthetic protocol. There were no obvious differences between the NMBAs that can be used with sugammadex (rocuronium and vecuronium) and those that cannot (atracurium, cisatracurium and mivacurium). Only Cammu *et al.*[65] reported on residual blockade following succinylcholine but the numbers involved were very small (overall 2/8, 25%).

TABLE 23 *Summary of studies of residual blockade with no reversal agent*

Drug(s) evaluated	Definition of residual blockade/ recurrence of blockade	Rates reported	Source
Rocuronium	TOF ratio < 0.9 on arrival in the postanaesthetic care unit	Outpatients 39% (28/71) Inpatients 48% (67/141)	Cammu[65]
	TOF ratio < 0.9 at time of scheduled extubation (skin closure)	Total 44% (62/142)	Maybauer[69]
Vecuronium	TOF ratio < 0.7 on arrival in the recovery room	Total 42% (239/568)	Baillard[63]
Atracurium	TOF ratio < 0.9 on arrival in the postanaesthetic care unit	Outpatients 51% (38/75) Inpatients 43% (49/114)	Cammu[65]
Cisatracurium	TOF ratio < 0.9 on arrival in the postanaesthetic care unit	Outpatients 33% (2/6) Inpatients 62% (5/8)	Cammu[65]
	TOF ratio < 0.9 at time of scheduled extubation (skin closure)	Total 57% (99/175)	Maybauer[69]
Mivacurium	TOF ratio < 0.9 on arrival in the postanaesthetic care unit	Outpatients 23% (37/160) Inpatients 35% (17/48)	Cammu[65]

Residual blockade despite the use of a reversal agent is more relevant to the assessment of sugammadex and data on incidence of this outcome were obtained from two RCTs[45,71] and a systematic review[78] (*Table 24*). The two RCTs reported rates of 5–6% of patients with residual blockade (TOF ratio < 0.7) following reversal of vecuronium, rocuronium or atracurium-induced block. The systematic review[78] found no residual blockade following reversal of mivacurium or vecuronium-induced block in two trials ($n = 90$). These studies suggest that the risk of residual blockade following reversal with neostigmine–glycopyrrolate is at least in the range 0–6%, although if the more stringent criterion of a TOF ratio < 0.9 is used the rate is likely to be higher.

A second study by Murphy *et al.*[72] examined the association between residual blockade and critical respiratory events in a large sample of patients ($n = 7459$). Of 61 patients with a respiratory event, 42 were matched with control patients without an event. Thirty-one of the cases (73.8%) and none of the control patients had a TOF ratio of < 0.7 on arrival in the postanaesthesia care unit. This study is significant because it suggests that improvements in the effectiveness of reversal as measured by TOF monitoring may be associated with a decrease in important adverse events occurring in the immediate postoperative period. In contrast, Berg *et al.*[45] found no significant difference in rates of postoperative pulmonary complications (evaluated 2–6 days after surgery) between patients with and without residual blockade for patients treated with vecuronium or atracurium.

Anaphylactic and allergic reactions

Six studies provided data on rates of anaphylactic reactions to NMBAs (*Table 25*): four national surveys[64,66,67,70] and two single-centre surveys.[68,73] Only one of these studies, a single-centre survey, provided a rate based on a known number of patients and even this was approximate: Malinowsky *et al.*[68] reported 6 cases of anaphylaxis among approximately 70,000 exposures, a rate of 1/11,667. Three cases were attributed to succinylcholine and one each to rocuronium, atracurium and cisatracurium. However, this study did not provide data on the number of exposed patients for individual agents.

Two national surveys have examined anaphylactic reactions to NMBAs in France.[67,70] In these studies, the number of patients exposed to each agent was estimated from data on market share and agents were compared based on the ratio of percentage total reactions–percentage market share. The value of these data in estimating risk of anaphylactic reactions is thus limited, although both surveys showed that rocuronium and succinylcholine had high ratios of anaphylactic reactions to market share (2.92 and 4.9 for rocuronium, and 3.05 and 3.37 for succinylcholine). The other NMBAs evaluated had ratios of 1 or less.

A survey reporting data from Scandinavian countries found 29 cases of anaphylaxis among an estimated (from sales data) 150,000 patients exposed to rocuronium, a rate of 1/5000 (95% CI: 1/3600 to 1/7700). However, rates from other

TABLE 24 *Summary of studies of residual blockade with use of a reversal agent*

Drug(s) evaluated	Definition of residual blockade/ recurrence of blockade	Rates reported	Source
Rocuronium	TOF ratio <0.7 on arrival in the postanaesthesia care unit	5.9% (2/34)	Murphy[71]
Vecuronium	TOF ratio <0.7 on arrival in the recovery room	5.5% (13/230)	Berg[45]
Atracurium	TOF ratio <0.7 on arrival in the recovery room	4.8% (11/231)	Berg[45]
NMBAs not specified	Clinically relevant muscle weakness	From two trials of mivacurium and vecuronium respectively rates of residual blockade associated with no reversal agent were 3/90 compared with 0/90 following use of reversal agent (RR 4.00, 95% CI 0.46 to 35.1)	Tramer[78]

RR, relative risk.

Scandinavian countries were substantially lower: 95% CIs of 1/28,000 to 0 in Sweden, 1/45,000 to 0 in Denmark, and 1/32,000 to 1/350,000 in Finland.[66] For vecuronium, the rate of anaphylactic reactions in Norway was estimated to be 1/22,000 (95% CI: 1/7400 to 1/105,000). The authors of this study suggested that differences between countries were probably caused by differences in reporting. This is in line with the conclusion of Malinowsky *et al*.[68] that careful follow-up of adverse reactions increases the incidence of anaphylactic reactions reported.

A survey in the USA found 33 reports of adverse events that could indicate anaphylaxis to rocuronium and 20 to vecuronium; rates per number of vials sold were around 1/1,000,000.[64] The value of this study was limited by the fact that actual patient numbers were not used and that suspected anaphylactic reactions were not followed up.

A single-centre survey in the UK found three confirmed anaphylactic reactions to rocuronium among an estimated 8800 exposed patients over 2 years, a rate of approximately 1/3000.[73] This is in line with the data from Norway, although the UK data are limited by being from a single hospital and based on estimated rather than actual patient numbers.

A study of the UK yellow card reporting system based on data for 1967–2000 reported more allergic reactions to atracurium (151) and succinycholine (165) than to vecuronium or mivacurium (45 each).[62] However, these data are limited by not knowing the number of exposed patients.

The limited data available thus suggest that around 1/10,000 exposed patients may show an anaphylactic reaction to NMBA treatment, although the level of uncertainty is high.[66,73]

Adverse effects of succinylcholine

Three references focusing on adverse effects of succinylcholine were found: two non-systematic reviews[74,75] and a systematic review.[76]

Residual blockade/recurrence of blockade

Patients with butyrylcholinesterase deficiency are at risk of prolonged NMB after treatment with succinylcholine. A non-systematic review[74] estimated that the frequency of this enzyme deficiency in the population is 1/2886 (95% CI 1/4327 to 1/1967).

Cardiac arrest

A non-systematic review[74] provided estimates of rates of cardiac arrest associated with succinylcholine. In three large observational studies there were 21 cases of cardiac arrest among 457,609 patients, giving an overall rate of 1/21,970. However, the upper and lower limits of the 95% CI were taken to be 0 and 1/11,930 because all of the observed cardiac arrests occurred in one study ($n = 250,541$).

Malignant hyperthermia

Malignant hyperthermia is a rare but potentially dangerous event in genetically susceptible people

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TABLE 25 *Summary of studies providing data on anaphylactic reactions*

Drug	Rates of anaphylactic/allergic reactions reported	Country	Source	Denominator based on actual patient data?	Immunological testing used?
Rocuronium	33 reports of AEs with 'anaphylaxis' term Rate per number of vials sold = 1/1,008,000	USA	Bhanaker[64]	No	No
	29 cases of anaphylaxis (95% CI 19–42) per 150,000 patients exposed to rocuronium Rate estimated to be 1/5000, 95% CI 1/3600–1/7700	Norway	Laake[66]	No	No
	3 cases of anaphylaxis (95% CI 0–9) per 250,000 patients exposed to rocuronium Rate estimated to be 95% CI 1/28,000–0	Sweden			
	0 cases of anaphylaxis (95% CI 0–4) per 180,000 patients exposed to rocuronium Rate estimated to be 95% CI 1/45,000–0	Denmark			
	4 cases of anaphylaxis (95% CI 1–11) per 350,000 patients exposed to rocuronium Rate estimated to be 95% CI 1/32,000–1/350,000	Finland			
	Ratio % reactions to % market share = 2.92	France	Laxenaire[67]	No	Yes
	Ratio % reactions to % market share[a] = 4.9	France	Mertes[70]	No	Yes
	3 cases reported. Estimated 8800 patients received rocuronium over 2 years; estimated rate 1/3000	UK	Neal[73]	No	Yes
Vecuronium	20 reports of AEs with 'anaphylaxis' term. Rate per number of vials sold = 1/1,107,250	USA	Bhanaker[64]	No	No
	3 cases of anaphylaxis per 65,000 patients exposed to vecuronium. Rate estimated to be 1/22,000, 95% CI 1/7400–1/105,000	Norway	Laake[66]	No	No
	Ratio % reactions to % market share[a] = 1.0	France	Laxenaire[67]	No	Yes
	Ratio % reactions to % market share[a] = 0.75	France	Mertes[70]	No	Yes
Atracurium	Ratio % reactions to % market share[a] = 0.41	France	Laxenaire[67]	No	Yes
	Ratio % reactions to % market share[a] = 0.35	France	Mertes[70]	No	Yes
Cisatracurium	Ratio % reactions to % market share[a] = 0.21	France	Laxenaire[67]	No	Yes
	Ratio % reactions to % market share[a] = 0.15	France	Mertes[70]	No	Yes
Mivacurium	Ratio % reactions to % market share[a] = 0.39	France	Laxenaire[67]	No	Yes
	Ratio % reactions to % market share[a] = 0.47	France	Mertes[70]	No	Yes
Succinylcholine	Ratio % reactions to % market share[a] = 3.05	France	Laxenaire[67]	No	Yes
	Ratio % reactions to % market share[a] = 3.37	France	Mertes[70]	No	Yes
NMBAs not specified	6 cases of anaphylaxis (IgE-mediated hypersensitivity reactions) with NMBAs as main causative agent from approximately 70,000 anaesthesias	France	Malinovsky[68]	Yes	Yes

IgE, immunoglobulin E.
a Calculated during data extraction.

treated with succinylcholine. A non-systematic review[74] reported the risk of hyperthermia associated with succinylcholine as 1/96,046 (95% CI: 1/302,755 to 1/41,442). This is in line with the overall risk of hyperthermia in anaesthesia quoted by Rosenberg *et al*.[75] of between 1/5000 and 1/100,000. The same review[75] reports the estimated incidence of genetic susceptibility to malignant hyperthermia to be between 1/3000 and 1/8500.

Myalgia

Succinylcholine-associated myalgia is a relatively minor adverse effect that affects patient QoL and can last for several days. In a systematic review of interventions to prevent myalgia, the incidence of myalgia at 24 hours after surgery in patients who received succinylcholine with no treatment to reduce myalgia was 51% (range 10–83%) across 35 trials.[76]

Adverse effects of neostigmine–glycopyrrolate

Nausea and vomiting were identified as the major adverse effects associated with the neostigmine–glycopyrrolate combination. However, two systematic reviews found that the use of neostigmine and glycopyrrolate (or atropine) to reverse NMB did not significantly increase nausea or vomiting compared with no reversal.[77,78] In the more recent review, the relative risk for vomiting within 24 hours was 0.95 (95% CI: 0.72 to 1.25) across five trials; corresponding values for nausea were 1.26 (95% CI: 0.98 to 1.62). Metaregression found no association between dose of neostigmine and risk of vomiting.[77] Tachyarrhythmia is another recognised adverse effect of the neostigmine–glycopyrrolate combination[79] but no data on its incidence in surgical patients were located.

Discussion of clinical evaluation

Main findings

The evidence base for efficacy of sugammadex includes randomised trials comparing rocuronium or vecuronium + sugammadex with one another, or placebo, or with appropriate active comparators for reversal of moderate or profound block or for immediate reversal. There are a limited number of trials, many of which were dose-finding studies with very few patients exposed to the relevant doses of sugammadex. Total numbers of patients receiving 2 mg, 4 mg and 16 mg of sugammadex in the pooled phase I–III trials were 606, 582 and 99, respectively. However, all of the trials demonstrated a markedly more rapid and predictable reversal of blockade (measured by recovery of the TOF ratio to 0.9) with sugammadex compared with placebo or neostigmine. Reversal of rocuronium-induced block by sugammadex administered 3 minutes after the NMBA was also shown to be quicker than spontaneous recovery from succinylcholine-induced block.

Evidence concerning the safety of sugammadex comes from trials involving 1926 patients treated with sugammadex at doses ranging from < 2 to 32 mg/kg; most patients received one of the standard doses of 2, 4 or 16 mg/kg. Overall rates of adverse events were similar between sugammadex administered after rocuronium or vecuronium and comparators (neostigmine or placebo). The most significant adverse events following treatment with sugammadex appear to be anaesthetic complications (up to 3%) and possibly allergic reactions. Recurrence of blockade and residual blockade were reported in clinical trials but most cases were in patients receiving subtherapeutic doses and hence not of clinical significance. Further monitoring in clinical practice is required to determine the incidence and significance of rare but potentially life-threatening adverse events, such as allergic/hypersensitivity reactions.

Reversal of moderate block

In the four relevant randomised dose-finding trials, reversal of moderate block was faster and more predictable with sugammadex 2 mg/kg than placebo; median times to recovery of the TOF ratio to 0.9 ranged from 1.3 to 1.7 minutes with rocuronium + sugammadex 2 mg/kg, and 2.3 to 2.9 minutes with vecuronium + sugammadex 2 mg/kg, compared with 21–86 minutes with placebo. The recovery times we found for sugammadex are comparable with those reported in published pooled analyses (presumably of many of the same trials): the weighted average of 1.7 minutes reported by Abrishami *et al*.[80] for reversal of rocuronium-induced moderate block, and the medians of 1.9 minutes for rocuronium + sugammadex and 2.3 minutes for vecuronium + sugammadex in the pooled analyses of Blobner *et al*.[81] and Khuenl-Brady *et al*.[82] Abrishani *et al*.'s weighted average time to recovery for the placebo group (28.9 minutes) was relatively low, but it is difficult to compare their findings with

ours as it is unclear which trials were included or how the weighted average was calculated.

In the more clinically relevant comparison with neostigmine, sugammadex again produced quicker and more reliable recovery of the TOF ratio to 0.9, with median (range) times of 1.4 (0.9–5.4) versus 17.6 (3.7–106.9) minutes when rocuronium was used in each group and 2.1 (1.2–64.2) versus 18.9 (2.9–76.2) minutes with vecuronium. The figures for vecuronium + sugammadex suggest a greater interindividual variability in response to sugammadex following vecuronium compared with rocuronium. In addition, the comparison of rocuronium + sugammadex with cisatracurium + neostigmine reported respective medians (ranges) of 1.9 (0.7–6.4) versus 7.3 (4.2–28.2). Again, our findings were similar to the medians reported by Blobner *et al.*[81] and Khuenl-Brady *et al.*[82] (1.9 minutes for rocuronium + sugammadex, 2.3 minutes for vecuronium + sugammadex, 17.6 minutes for rocuronium + neostigmine, and 18.9 minutes for vecuronium + neostigmine). Although a formal MTC could not be conducted, the available data do suggest that reversal of moderate block when the NMBA–reversal agent combination is rocuronium/sugammadex may be faster than when other NMBA–reversal agent combinations are used.

These results suggest a clear pharmacological benefit of sugammadex over the current standard treatment for reversal of moderate NMB, i.e. N&G. However, whilst the faster and more predictable reversal obtained with sugammadex could save time and allow more efficient scheduling of procedures, no data were available on resource use or patient-reported outcomes to demonstrate these efficiency gains in practice. The time savings achieved with sugammadex compared with neostigmine, might also be reduced by careful monitoring and early administration of neostigmine but it is uncertain how far current clinical practice reflects this ideal. The ability of the anaesthetist to predict the end of the procedure and reduce the level of blockade accordingly may vary depending on such factors as the experience of the anaesthetist and his/her experience of working with a particular surgeon. A further limitation of the trials comparing rocuronium + sugammadex with rocuronium + neostigmine–glycopyrrolate is that the data were collected without the inhalational anaesthetics (which potentiate block) being switched off, as would be the case in clinical practice. The effect of this could be to overestimate the time required for recovery from moderate block with neostigmine.

Reversal of profound block

Reversal of profound blockade is a very important indication because there is unmet clinical need. Within current anaesthetic practice there are no reversal agents capable of rapid recovery times from profound NMB. The most commonly used reversal agent, neostigmine, is only effective when the patient has recovered to at least a T2 level, i.e. moderate block (see Chapter 1, Description of health problem), such that when reversal of a deeper level of block is required, the anaesthetist must wait for partial spontaneous recovery to occur before administering neostigmine.

A single RCT demonstrated that not only is N&G relatively ineffective for the reversal of profound block, but that sugammadex (4 mg/kg) is capable of reversing both rocuronium- and vecuronium-induced block at PTC 1–2 (profound level). Median (range) times to recovery of the TOF ratio to 0.9 were 2.7 (1.2–16.1) minutes for rocuronium + sugammadex, 49.0 (13.3–145.7) minutes for rocuronium + neostigmine, 3.3 (1.4–68.4) for vecuronium + sugammadex and 49.9 (46.0–312.7) for vecuronium + neostigmine. As in reversal of moderate block, the range of recovery times with sugammadex was wider following vecuronium than rocuronium. Additional dose-finding studies demonstrated a more rapid and predictable reversal of profound blockade with sugammadex compared with placebo. This potentially has implications for both the management of patients and duration of the NMB in terms of safety, and time spent waiting for recovery after the end of surgery. This could facilitate better management of the NMB and reduce time to recovery at the end of the operation. It should be noted that none of the studies in this indication met all of the quality criteria, suggesting possible limitations in study conduct and/or reporting, and that all the placebo-controlled studies were relatively small.

Rapid reversal

The ability to rapidly reverse high-dose rocuronium-induced NMB using a high dose (16 mg/kg) of sugammadex is potentially another

important benefit of sugammadex. When rapid induction of NMB is required, the main current option is to use succinylcholine, which is effective with the added benefit of rapid recovery, should that be necessary, but has a wide range of potentially dangerous adverse effects (see Other relevant evidence). High-dose rocuronium could be used for rapid induction of blockade, but carries the danger that the patient could not be recovered rapidly if the need arose; sugammadex enables this danger to be overcome. Thus, high-dose rocuronium with 16-mg/kg sugammadex could potentially replace succinylcholine, providing at least as rapid induction and reversal of blockade when necessary, with fewer adverse effects.

In the event of a 'cannot intubate–cannot ventilate' emergency, in either the rapid induction or routine intubation setting, there is currently no reversal agent available and invasive treatment is required to prevent the risk of hypoxia leading to permanent brain damage or death. Current reversal agents used with non-depolarising NMBAs, such as neostigmine, require a period of spontaneous recovery before they can be effective and are thus not suitable for the rapid reversal of profound NMB, while succinylcholine's mechanism of action means that it cannot be reversed.

The main evidence for sugammadex for rapid reversal of NMB comes from a single RCT[58] that demonstrated that recovery of T1 to 10% of control values is significantly faster ($p < 0.001$ by analysis of variance) following blockade induced by rocuronium and reversal by sugammadex 16 mg/kg than blockade induced by succinylcholine followed by spontaneous recovery. The primary end point used in this study was recovery of T1 to 10% of control value, a relevant end point for comparison with succinylcholine but one that was not used in any of the other studies. The clinical relevance of this end point is uncertain because, although some signs of breathing may be present, T1 of 10% does not represent a sufficient degree of recovery to allow safe extubation. However, the more clinically relevant end point of recovery of the TOF ratio to 0.9 was also measured in this study in the sugammadex group, giving a median of 1.7 minutes (range 0.48–14.3). The wide range of times required to reach this end point in the active-control study may be of concern if there is a significant group of patients for whom sugammadex, even at 16 mg/kg, is not fully effective. Similar median times of less than 2 minutes from administration of 16-mg/kg sugammadex to recovery of the TOF ratio to 0.9 were obtained in the placebo-controlled dose-finding studies.

A potential issue with the use of 16-mg/kg sugammadex in an emergency is that the relevant clinical trials were only simulations of this situation, and the appropriate dose of sugammadex was drawn up and ready for immediate administration. In routine practice, drawing up this dose in advance in anticipation of a very rare event would be highly wasteful and expensive. On the other hand, the time required to prepare the dose, including opening three ampoules and drawing the contents into a syringe, would increase the time the patient was exposed to hypoxia. The exact time this might take under the stress of an emergency situation is difficult to estimate. The benefit of sugammadex in terms of facilitating the handling of 'cannot intubate–cannot ventilate' emergencies and avoiding catastrophic events, such as hypoxic brain damage and death, is difficult to assess fully until the drug has been widely used in clinical practice.

Limitations

The main limitation of the evidence, and hence of the clinical assessment based on it, is availability of data. Furthermore, many of the trials of sugammadex have not been published in full at the time of writing; only one of the four main active-control trials and one arm of another have been published as peer-reviewed papers. To supplement the data available from published journal articles and conference abstracts, we extracted data from abstracts and documents prepared as part of regulatory assessments to obtain as much relevant information as possible. However, information on methods and patient characteristics was often lacking, making it difficult to assess the quality of many of the studies, and this, to some extent, limits the conclusions that can be drawn from the evidence.

Our assessment was very much concerned with comparing sugammadex with the other available reversal agents. In the context of clinical practice this meant comparing the rocuronium–sugammadex and vecuronium–sugammadex combinations with other NMBA–reversal agent combinations. Unfortunately, the limitations of the published data and our failure to obtain unpublished data from Schering-Plough resulted in our being unable to conduct the appropriate indirect comparison analysis, i.e. MTC, and thus any conclusions regarding the relative effectiveness

of all NMBA–reversal agent combinations are based solely on a narrative synthesis of the available data.

A further limitation of the evidence for sugammadex is that the only outcomes reported in any depth are time to recovery determined by acceleromyography and adverse events. There are no data available on patient-reported outcomes, such as quality of recovery or on resource use and cost outcomes. Finally, there is uncertainty about the extent to which time savings observed in clinical trials under carefully controlled conditions are likely to be reflected in routine clinical practice.

Chapter 4

Assessment of cost-effectiveness evidence

Systematic review of existing cost-effectiveness evidence

The searches for sugammadex studies as described in Chapter 3 (see Methods for reviewing clinical effectiveness, Search strategy) did not include a methodological search filter, so attempted to retrieve both clinical effectiveness and cost-effectiveness evidence. Supplementary searches for economic evaluations of sugammadex were undertaken in NHS Economic Evaluation Database (NHS EED) and Health Economic Evaluations Database (HEED).

A broader search to identify economic studies about NMBAs was also undertaken. The economic evaluation databases NHS EED and HEED were searched. In addition the following databases were searched using an economic/cost methodological search filter: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, CINAHL, Science Citation Index (SCI), ISI Proceedings: Science & Technology, and Cochrane Central Register of Controlled Trials (CENTRAL). Searches to help populate the economic model were undertaken: anaesthesia-controlled time, TOF/NMBAs and utility values, overlapping induction and rapid intubation mortality rates.

The search strategies, dates and results of all searches are listed in Appendix 1.

The search uncovered a number of papers related to the costing or cost-effectiveness of NMBAs[74,83–88] but none related to the cost-effectiveness of the *reversal* of NMB, nor were any of the costings carried out in a UK setting. No full economic evaluations (comparing two or more options and considering both costs and consequences, including cost-effectiveness, cost–utility and cost–benefit analyses) were identified for either NMBAs or reversal strategies.

As such, no published studies are available to detail in this section.

Economic assessment

Owing to the lack of published evidence concerning the cost-effectiveness of sugammadex, a de novo economic assessment was carried out into strategies for the induction and subsequent reversal of NMB. The assessment separately considered two settings: the routine induction of NMB and rapid sequence induction of NMB.

The economic assessment was severely hindered by the lack of suitable evidence needed to inform many of the parameters. As a result, the assessment is much more restricted in its scope than would otherwise be the case. These limitations are discussed in more detail below.

The assessment took the perspective of the NHS & Personal Social Services (NHS & PSS), with costs expressed in UK pounds sterling at a 2008–9 price base, and health outcomes expressed in QALYs. As all of the costs considered in the assessment are incurred on the day that the NMBA is administered, no costs are discounted. QALYs forgone through death resulting from adverse events are considered over a lifetime horizon and so are discounted using a 3.5% annual discount rate following the National Institute for Health and Clinical Excellence (NICE) reference case.

Routine reversal of NMB

Methods

Strategies

The strategies considered for routine NMB and subsequent reversal were limited by the available data; as such, a number of the comparators listed in *Table 2* (atracurium, cisatracurium and mivacurium) were not considered.

The strategies considered were as follows:

- rocuronium (0.6 mg/kg)-induced NMB followed by reversal using neostigmine (2.5 mg) with glycopyrrolate (0.5 mg) (hereafter referred to as 'rocuronium with N&G')
- rocuronium (0.6 mg/kg)-induced NMB followed by reversal using sugammadex (2 mg/kg or

4 mg/kg) (hereafter referred to as 'rocuronium with sugammadex')
- vecuronium (0.1 mg/kg)-induced NMB followed by reversal using neostigmine (2.5 mg) with glycopyrrolate (0.5mg) (hereafter referred to as 'vecuronium with N&G')
- vecuronium (0.1 mg/kg)-induced NMB followed by reversal using sugammadex (2 mg/kg or 4 mg/kg) (hereafter referred to as 'vecuronium with sugammadex').

The routine reversal of moderate blockade was considered separately from that of profound (deep) blockade. It was assumed that a dosage of 2 mg/kg of sugammadex would be used in the former scenario and a dosage of 4 mg/kg would be used in the latter scenario, as per the manufacturer's recommendations.[89]

Owing to the lack of suitable evidence it was decided that a full incremental analysis of all possible strategies was not suitable. Rather, pairwise threshold analyses were undertaken comparing:

- rocuronium with sugammadex versus rocuronium with N&G
- vecuronium with sugammadex versus vecuronium with N&G.

These strategies and those considered in the rapid sequence induction (RSI) setting (see Reversal of NMB used in the RSI setting) are summarised in the decision tree given in *Figure 2*.

Key economic considerations and assumptions

To simplify the economic modelling, it was assumed that the choice of NMBA or reversal agent had no impact on surgery itself (time spent in surgery, adverse events resulting from surgery, etc.) or on the staff mix in the operating room. It was assumed that the anaesthetist was equally proficient at administering each strategy.

The possible drivers for differences between the costs and health outcomes of each strategy were identified as the following:

- the cost of acquiring rocuronium, vecuronium, N&G and sugammadex
- time spent in recovery
- rates of serious adverse events (including death) associated with the anaesthetic strategies
- rates of recurrence of blockade or residual blockade associated with the anaesthetic strategies.

The aim of the modelling was to integrate as many of these possible drivers as was feasible, given the evidence constraints faced. The general framework was to use threshold and sensitivity analysis to assess what combination of price and clinical parameters for sugammadex would be consistent with the new intervention being cost-effective if used as an alternative to an existing anaesthetic strategy.

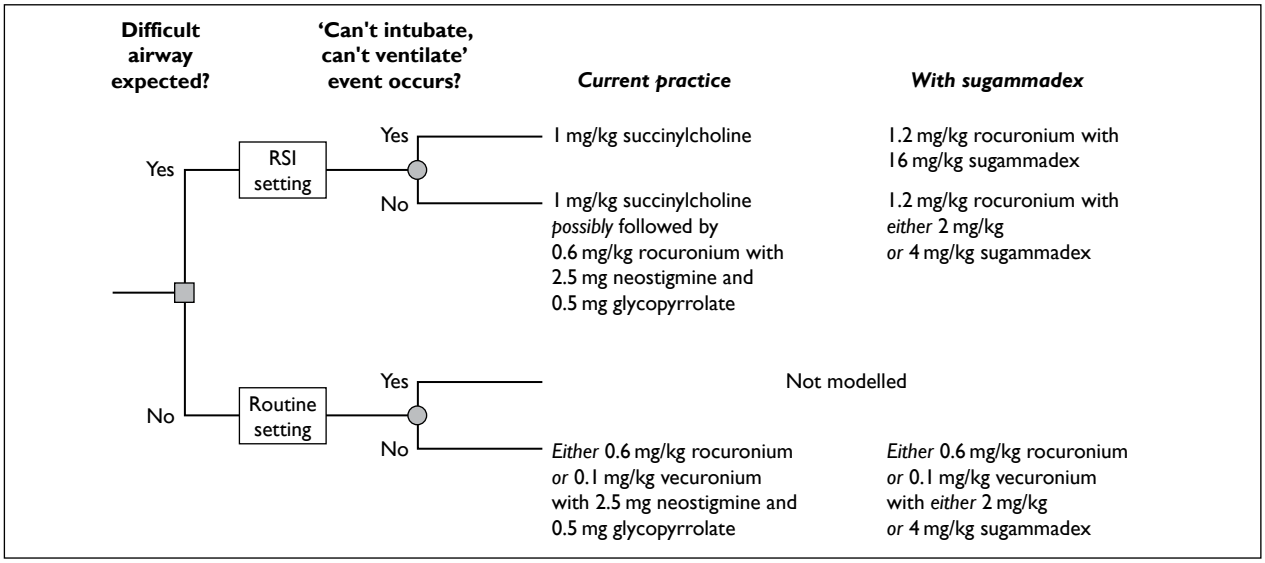

FIGURE 2 *Summary of strategies considered in the routine and RSI settings.*

Prices

The prices for rocuronium (Esmeron; Organon), vecuronium (Norcuron; Organon) and N&G (Robinul-Neostigmine; Anpharm) were taken from the *British National Formulary 56*.

Cost per average dose was calculated on the assumptions that:

- the average patient had a weight of 75 kg
- the cheapest combination of vials specified by the BNF was used
- any unused drug in a vial was wasted.

The assessment group was made aware of the list prices by the manufacturer: 10 × 2-ml vials £596.40; 10 × 5-ml vials £1491.00; 100 mg of sugammadex per millilitre. For an average 75-kg patient, reversal of moderate blockade with 2 mg/kg of sugammadex therefore requires one 2-ml vial (£59.64), whereas reversal of profound blockade with 4 mg/kg of sugammadex requires two 2-ml vials (£119.28).

The costs per dose used in the model are given in *Table 26*.

Time spent in recovery

A key difference between sugammadex and existing anaesthetic strategies is the time it takes a patient to recover from the NMB. It was assumed that time to TOF 0.9 was a meaningful measure of time to recovery in routine practice, and that any reduction in recovery time achieved through adopting sugammadex could potentially represent a resource saving to the NHS if the member(s) of staff monitoring patients' recovery could put the time saved to productive use.

As reported in Chapter 3 (see Results of review of clinical effectiveness), two active-controlled trials[29,30] compared sugammadex versus N&G for the reversal of moderate block, while one active-controlled trial[36] compared sugammadex versus N&G for the reversal of profound block. The results from Flockton *et al.*[29] were unsuitable as the study compared rocuronium with sugammadex against cisatracurium with N&G, which is not considered as a comparator in the economic analysis.

Blobner *et al.*[30] and Jones *et al.*[36] reported the median and geometric mean times for recovery to TOF 0.9 for rocuronium with sugammadex compared to rocuronium with N&G, and for vecuronium with sugammadex compared with vecuronium with N&G. These are reported in *Tables 6* and *12*. In order to estimate the arithmetic mean times to recovery in each instance (necessary to estimate the time saved), it was assumed that the distribution of recovery times was approximately exponential, such that the arithmetic mean time to recovery was the inverse of the baseline hazard, derived by dividing –ln(0.5) by the median time to recovery.[36,90]

In each of the pairwise comparisons, the sugammadex strategy was associated with the shorter arithmetic mean time to recovery. As such, the model considered the reduction in recovery time associated with sugammadex. These are reported in *Table 27*.

Given the uncertainty and the anticipated heterogeneity around these estimates, the time spent in recovery was modelled as a variable taking values from 0 to 90 minutes inclusive.

It was assumed that any reduction in recovery time by adopting sugammadex would result in productivity benefits for the NHS. Since the value of these productivity benefits are subject to considerable uncertainty, the per-minute value of reductions in recovery time was modelled as a variable.

TABLE 26 *Cost of drugs (per dose)*

Drug	Average dose	Vial size (cost, £)	Cost per dose (£)
Rocuronium (0.6 mg/kg)	45 mg	50 mg (3.01)	3.01
Vecuronium (0.1 mg/kg)	7.5 mg	10 mg (3.95)	3.95
Neostigmine–glycopyrrolate	2.5 mg/0.5 mg	2.5 mg/0.5 mg (1.01)	1.01
Sugammadex (2 mg/kg)	150 mg	200 mg (59.64)	59.64
Sugammadex (4 mg/kg)	300 mg	2 × 200 mg (119.28)	119.28

TABLE 27 *Reduction in recovery time associated with sugammadex*

	Arithmetic mean time to recovery (minutes) (derived from Blobner *et al.*[30] and Jones *et al.*[36])	
Strategy	**Moderate blockade**	**Profound blockade**
Rocuronium with N&G	25.39	70.69
Rocuronium with sugammadex	2.02	3.90
Reduction associated with sugammadex	23.37	66.80
Vecuronium with N&G	27.27	71.99
Vecuronium with sugammadex	3.03	4.76
Reduction associated with sugammadex	24.24	67.23

To aid discussion, two possible valuations of these productivity benefits were considered and are presented with the results: in the first, the value of each minute of recovery time saved was estimated as being the pro rata cost of employing the operating room staff (on the basis that all time savings would be achieved in the operating room); in the second, the value of each minute saved was estimated as the pro rata cost of employing a single nurse in the recovery room (on the basis that all time savings would be achieved in the recovery room).

Following expert clinical opinion it was assumed that the operating room staff comprised a consultant surgeon, a specialist registrar surgeon, a consultant anaesthetist, a nurse team manager (band 7) and two staff nurses (one band 5 and one band 6), while the recovery room nurse was assumed to be of band 5 ($p = 0.75$), band 6 ($p = 0.125$) or band 7 ($p = 0.125$). A potential criticism of these estimates is that they represent the opinion of a single clinical expert only. The cost associated with this time was calculated on a per-minute basis by taking the annual cost of employing each member of staff (including salary, national insurance and pension costs) from the Personal Social Services Research Unit[91] (*Table 28*).

The major uncertainty is the extent to which any time saved in recovery could be put to alternative productive use, for example in caring for another patient or some other activity. The proportion of recovery time saved which could be put to productive use is ultimately unknown – no evidence was identified in the literature. There is also the possibility that extra operations could be scheduled as a result of any reduced recovery time but again there is a lack of suitable evidence on the associated impact on costs and health effects.

Serious adverse events

The clinical trials of sugammadex were not sufficiently powered to estimate the rates of significant adverse events (including death) with any level of precision, nor were there any observational data to inform these rates. As such, in the absence of clear evidence to the contrary, it was assumed that there were no differences in rates of adverse events between the strategies. This is a limitation of the modelling and should be considered when interpreting the results. In particular, the modelling assumed that in the routine setting there was no possibility of a difficult airway and/or 'cannot intubate, cannot ventilate' event occurring; while rare in this setting, the consequences of such an event may be extremely serious – this assumption will be returned to in the Discussion.

Recurrence of blockade or residual blockade

It was assumed that any incidence of recurrence of blockade, or residual blockade, in patients who had been considered to have recovered would represent a resource cost to the NHS. This is because additional time would have to be spent by the member(s) of staff monitoring the patients' recovery. The incidence and cost of this event have been considered explicitly in the modelling. Following expert clinical opinion, it was assumed in the base case that patients suffering from recurrence of blockade or residual blockade were monitored by a single nurse of band 5 ($p = 0.75$), band 6 ($p = 0.125$) or band 7 ($p = 0.125$), and that the additional time associated with caring for a patient with recurrence of blockade or residual blockade was 1 hour. It was assumed that this time would be taken from other productive uses so its use had a value equal to the cost of employing the nurse over that period of time (calculated on a

TABLE 28 *Estimated staff costs associated with the recovery period*

Staff member	Annual salary (£)	Annual national insurance and pension (£)	Working time	Cost per minute (£)
Consultant surgeon	117,450	29,686	41.4 weeks, 43.4 hours	1.36
Specialist registrar surgeon	48,038	11,084	42.4 weeks, 40.0 hours	0.58
Consultant anaesthetist	117,450	29,686	41.4 weeks, 43.4 hours	1.36
Nurse (band 5)	22,900	4793	41.3 weeks, 37.5 hours	0.3
Nurse (band 6)	29,200	6249	41.3 weeks, 37.5 hours	0.38
Nurse (band 7)	34,000	7357	41.3 weeks, 37.5 hours	0.45
Total	**369,038**	**88,855**		**4.44**

per-minute basis – *Table 29*). The additional hour of recovery time, therefore, represented a resource cost of £19.61.

Due to a lack of suitable evidence, it was assumed that there was no decrement in patients' health-related quality of life (HRQoL) associated with recurrence of blockade or residual blockade. By implication, the health outcomes associated with each strategy were therefore assumed to be identical.

As discussed in Chapter 3 (see Summary of adverse effects of sugammadex), the manufacturer of sugammadex's submission to the regulatory authority[23] found that, in the phase III placebo-controlled trials for sugammadex, 1.7% of patients (11/640) had evidence of recurrence of blockade or residual blockade based on acceleromyographic monitoring. However, as the majority of these patients received subtherapeutic doses of sugammadex it was decided that this estimate was not appropriate for consideration in the model and so no residual blockade or recurrence of blockade was assumed for sugammadex.

The rates for other comparators were taken from RCTs reported in *Tables 23* and *24*. As these trials had no common comparator it was not possible to carry out an indirect comparison of the evidence. Rather, the rates used in the model were taken directly from the relevant treatment arm of each trial. Considerable care should, therefore, be taken when interpreting the results.

The rates of recurrence of blockade or residual blockade used in the model are reproduced in *Table 30* along with the associated resource cost.

Analysis

Since the strategies were assumed to have identical health outcomes but generally different costs, the analysis effectively simplifies to a cost minimisation. Given the fact that particular variables are unknown, a threshold analysis was undertaken. The critical variables in this analysis were the reduction in recovery time by using sugammadex and the value of each minute of recovery time saved.

The threshold analysis sought to derive the minimum value of each minute of recovery time

TABLE 29 *Estimated nurse costs associated with recurrence of blockade or residual blockade*

Nurse	Weight	Annual salary (£)	Annual national insurance and superannuation (£)	Cost per minute (£)
Band 5	0.75	22,900	4793	0.3
Band 6	0.125	29,200	6249	0.38
Band 7	0.125	34,000	7357	0.45
Weighted average		**25,075**	**5296**	**0.33**

TABLE 30 *Expected resource costs due to recurrence of blockade or residual blockade*

Strategy	Rate of recurrence of blockade or residual blockade (source)	Expected resource cost (£)
Rocuronium followed by N&G	5.9% (2/34)[71]	1.15
Vecuronium followed by N&G	5.5% (13/230)[45]	1.11

saved for sugammadex to be cost-effective (i.e. cost saving with equal health outcomes) at the current list price for any given (absolute) reduction in the recovery time associated with sugammadex.

Results of economic assessment

Under the base-case assumptions made for the routine setting, if sugammadex provides no reduction in recovery time then it is not cost-effective at the current list price (*Table 31* and *Figure 3*). As the reduction in recovery time increases, the minimum value of each minute of saved recovery time required for sugammadex to be cost-effective falls. The results are broadly similar for rocuronium- and vecuronium-induced blockade, with any differences driven by the small differences between the prices of rocuronium and vecuronium and the rates of recurrence of blockade or residual blockade. However, the results differ substantially between moderate and profound blockade.

In patients with moderate (profound) blockade, the data from Blobner *et al.*[30] and Jones *et al.*[36] suggest that sugammadex reduces the arithmetic mean time to recovery to TOF 0.9 by 23.37 (66.80) minutes for rocuronium-induced blockade and 24.24 (67.23) minutes for vecuronium-induced blockade (assuming recovery times are exponentially distributed); this is represented in *Figure 3* by the dotted and dashed vertical lines.

Under the base-case assumptions and these estimates of the recovery time saved with sugammadex, sugammadex is cost-effective in patients with moderate (profound) blockade where the value of each minute of recovery time saved with sugammadex is approximately £2.40 (£1.75) or greater (this is represented in *Figure 3*). The assessment group estimated that time saved in the operating room has a value of £4.44 per minute, whereas time saved in the recovery room has a value of £0.33 per minute (*Tables 28* and *29*); 2 mg/kg (4 mg/kg) sugammadex therefore appears to be cost-effective for the routine reversal of rocuronium-induced moderate (profound) blockade at the current list price, if all reductions in recovery time that are associated with sugammadex are achieved in the operating room, but does not appear cost-effective if all of the reductions in recovery time are achieved in the recovery room. Where savings in recovery time are achieved in both the operating room and the recovery room, or where there is additional value in reducing recovery times (e.g. in preventing operations from being delayed or forgone), the cost-effectiveness of sugammadex is likely to be highly dependent on the setting in which it is administered.

Reversal of NMB used in the RSI setting

Methods

As discussed in Chapter 3 (see Sugammadex for reversal of profound neuromuscular blockade), the ability to rapidly reverse NMB induced with high-dose rocuronium, using a high dose (16 mg/kg) of sugammadex is potentially an important benefit of sugammadex. When rapid induction of NMB followed by rapid reversal is required, the main current option is to use succinylcholine, which is effective but has a wide range of potentially dangerous adverse effects, including death (see Chapter 3, Other relevant evidence). The combination of high-dose rocuronium and high-dose sugammadex could potentially replace succinylcholine, providing at least as rapid induction and reversal of blockade with fewer adverse effects.

An alternative scenario is where rapid *induction* of neuromuscular blockade is required but rapid *reversal* is not ultimately necessary. In this scenario, succinylcholine is the main current option due to its rapid onset, but this strategy could potentially be replaced by that of administering a high dose of rocuronium and a smaller and less costly dose of sugammadex (2 mg/kg or 4 mg/kg), which would reverse the NMB less rapidly.

Strategies

To simplify the modelling, it was assumed that rapid *reversal* of NMB would only be required in the case of a 'cannot intubate–cannot ventilate' event, in which case it was assumed that surgery would not be performed. Where a 'cannot intubate–cannot ventilate' event does *not* occur, it was assumed that

TABLE 31 *Threshold analysis comparing reversal of blockade with sugammadex versus reversal with N&G*[a]

Reduction in recovery time (minutes)	Minimum value (£) of each minute of reduced recovery time for sugammadex to be considered cost-effective			
	Moderate blockade		Profound blockade	
	Rocuronium	Vecuronium	Rocuronium	Vecuronium
0	N/A	N/A	N/A	N/A
1	57.47	57.55	117.11	117.19
2	28.74	28.78	58.56	58.60
3	19.16	19.18	39.04	39.06
4	14.37	14.39	29.28	29.30
5	11.49	11.51	23.42	23.44
10	5.75	5.76	11.71	11.72
15	3.83	3.84	7.81	7.81
20	2.87	2.88	5.86	5.86
25	2.30	2.30	4.68	4.69
30	1.92	1.92	3.90	3.91
35	1.64	1.64	3.35	3.35
40	1.44	1.44	2.93	2.93
50	1.15	1.15	2.34	2.34
60	0.96	0.96	1.95	1.95
70	0.82	0.82	1.67	1.67
80	0.72	0.72	1.46	1.46
90	0.64	0.64	1.3	1.3

N/A, not available.
a The table shows the minimum value of each minute of recovery time saved for sugammadex to be considered cost-effective under the base-case assumptions given a particular reduction in recovery time associated with sugammadex.

surgery would proceed as usual, with the drugs and doses administered being dependent on the length of the procedure and/or whether the procedure requires profound blockade throughout.

As the differences in results between rocuronium- and vecuronium-induced blockade are so slight (see Results of economic assessment), and also because the 16-mg/kg dose of sugammadex is specifically indicated for reversal of rocuronium-induced blockade, only rocuronium-induced blockade was considered in the RSI setting.

The strategies considered for NMB and subsequent reversal are summarised below and also in *Figure 2*. The choice of strategy is dependant on the *ex poste* realisation of whether a 'cannot intubate–cannot ventilate' event occurs.

Where a 'cannot intubate–cannot ventilate' event occurs:

- succinylcholine (1 mg/kg)-induced NMB followed by spontaneous recovery (hereafter referred to as 'succinylcholine')
- rocuronium (1.2 mg/kg)-induced NMB followed by immediate reversal using 16-mg/kg sugammadex (hereafter referred to as 'rocuronium with 16-mg/kg sugammadex').

Where a 'cannot intubate–cannot ventilate' event does not occur and the subsequent procedure is very short:

- succinylcholine (1 mg/kg)-induced NMB (for rapid induction and to maintain block throughout the procedure) followed by

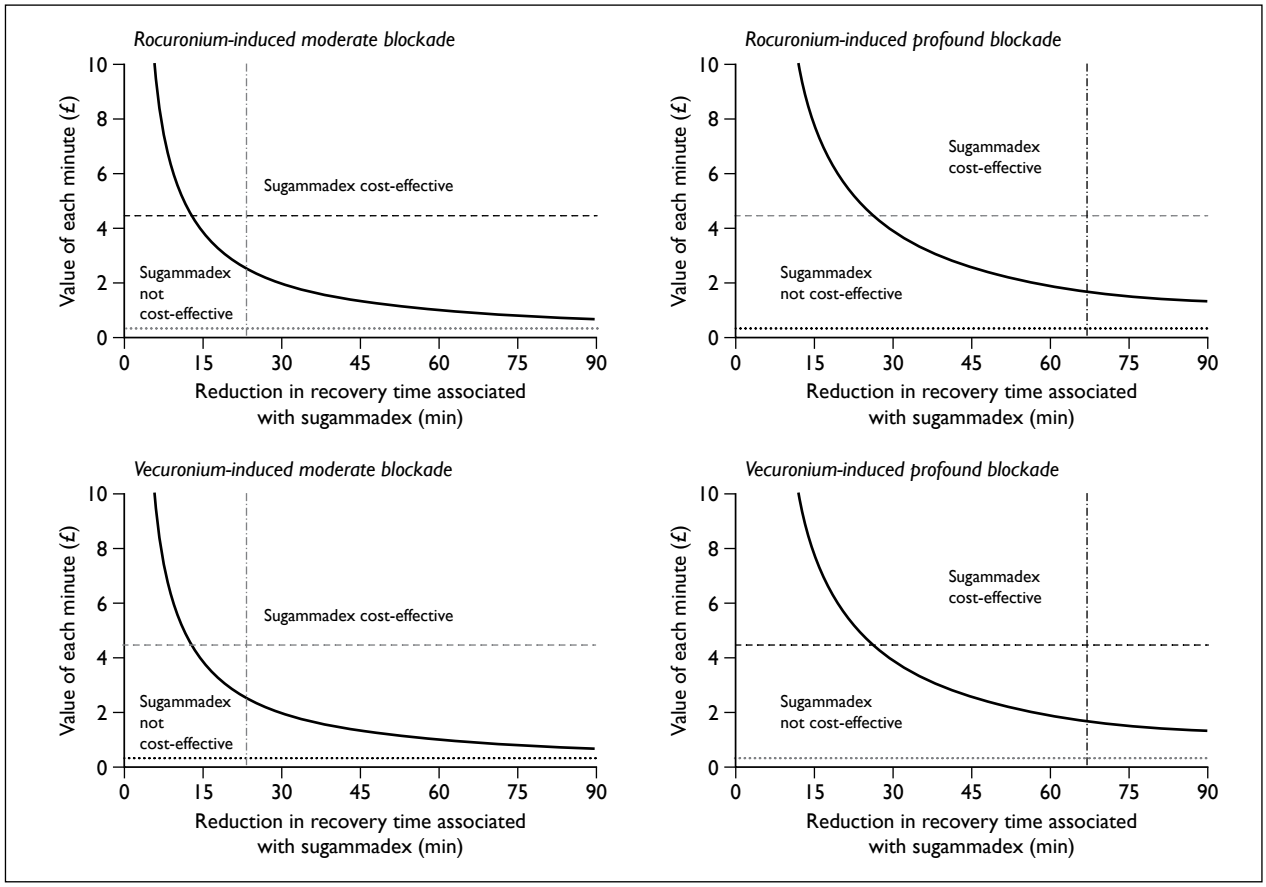

FIGURE 3 *Threshold analysis comparing reversal of blockade with sugammadex versus reversal with neostigmine with glycopyrrolate. The region above (below) the bold line represents the combinations of reduction in recovery time associated with sugammadex and value of each minute of recovery time saved at which sugammadex is (is not) cost-effective under the base-case assumptions for each scenario. Separate graphs are plotted for rocuronium- and vecuronium-induced blockade and for moderate and profound blockade. The horizontal dashed (dotted) line represents an estimate of the value of each minute saved were all the time savings to occur in the operating room (recovery room), while the dotted and dashed vertical line represents an estimate of the reduction in recovery time associated with sugammadex (see Routine reversal of neuromuscular block, Methods).*

spontaneous recovery (hereafter referred to as 'succinylcholine')
- rocuronium (1.2 mg/kg)-induced NMB (for rapid induction and to maintain block throughout the procedure) followed by reversal using 4-mg/kg sugammadex (hereafter referred to as 'rocuronium with 4-mg/kg sugammadex').

Where a 'cannot intubate–cannot ventilate' event does not occur and the subsequent procedure is short (< 60 minutes) or requires profound blockade throughout:

- succinylcholine (1 mg/kg)-induced NMB (for rapid induction) followed by rocuronium (0.6 mg/kg)-induced NMB (to maintain block throughout the procedure) followed by reversal using neostigmine (2.5 mg) with glycopyrrolate (0.5 mg) (hereafter referred to as 'succinylcholine followed by rocuronium with N&G')
- rocuronium (1.2 mg/kg)-induced NMB (for rapid induction and to maintain block throughout the procedure) followed by reversal using 4-mg/kg sugammadex (hereafter referred to as 'rocuronium with 4-mg/kg sugammadex').

Where a 'cannot intubate–cannot ventilate' event does not occur and the subsequent procedure is long (> 60 minutes) and does not require profound blockade throughout:

- succinylcholine (1 mg/kg)-induced NMB (for rapid induction) followed by rocuronium (0.6 mg/kg)-induced NMB (to maintain block throughout the procedure) followed by reversal using neostigmine (2.5 mg) with glycopyrrolate (0.5 mg) (hereafter referred to as

'succinylcholine followed by rocuronium with N&G')
- rocuronium (1.2 mg/kg)-induced NMB (for rapid induction and to maintain block throughout the procedure) followed by reversal using 2-mg/kg sugammadex (hereafter referred to as 'rocuronium with 2-mg/kg sugammadex').

Key economic considerations and assumptions

As with the routine reversal of NMB, it was assumed that the choice of NMBA or reversal agent had no impact on surgery itself or on the staff mix in the operating room. It was assumed that the anaesthetist was equally proficient at administering each strategy.

The possible drivers for differences between the costs and health outcomes of each strategy were identified as the following:

- the cost of acquiring rocuronium, N&G, sugammadex and succinylcholine
- time spent in recovery
- rates of serious adverse events (including death) associated with the anaesthetic strategies
- rates of recurrence of blockade or residual blockade associated with the anaesthetic strategies.

Prices

The prices for rocuronium (Esmeron; Organon) and succinylcholine (Anectine; GlaxoSmithKline) were taken from the *British National Formulary 56*.

As in the routine setting, cost per average dose was calculated on the assumptions that:

- the average patient has a weight of 75 kg
- the cheapest combination of vials specified by the *British National Formulary* was used
- any unused drug in a vial was wasted.

As discussed in the routine setting, the assessment group was made aware of the list prices for sugammadex by the manufacturer (see Routine reversal of neuromuscular block). For an average 75-kg patient, rapid reversal of blockade with 16 mg/kg of sugammadex requires two 5-ml vials and one 2-ml vial (£357.84).

The costs per dose used in the model are given in *Tables 26* and *32*.

'Cannot intubate–cannot ventilate' events

It was considered that 'cannot intubate–cannot ventilate' events are more likely to occur in the RSI setting than in the routine setting, but that the probability of a 'cannot intubate–cannot ventilate' event occurring in any given procedure is highly variable, depending on patients' characteristics, but clinical judgements about this risk can be made for individual patients. As such – unlike in the routine setting – 'cannot intubate–cannot ventilate' events were explicitly considered in the modelling of the RSI setting, with the probability of a 'cannot intubate–cannot ventilate' event modelled as a variable from 0 to 1 inclusive.

In the absence of any data to the contrary, it was assumed that there were no systematic differences between each strategy in terms of the direct or indirect health consequences of a 'cannot intubate–cannot ventilate' event, and that the only cost/resource differences between the strategies resulted from (1) differences in the acquisition cost of sugammadex and rocuronium compared with succinylcholine, and (2) the negation of any potential productivity benefits from sugammadex (due to reduced recovery time) that may have arisen had the procedure gone ahead. These assumptions are returned to in the discussion.

Other serious adverse events

The clinical review identified a number of adverse events associated with succinylcholine (see Chapter 3, Adverse effects of succinylcholine). However, there was an absence of evidence to inform the expected costs and HRQoL decrements associated

TABLE 32 *Cost of drugs (per average dose) (complementary to* Table 26*)*

Drug	Average dose	Vial size (cost, £)	Cost per dose (£)
Rocuronium (1.2 mg/kg)	90 mg	100 mg (6.01)	6.01
Succinylcholine (1 mg/kg)	75 mg	100 mg (0.71)	0.71
Sugammadex (16 mg/kg)	1200 mg	2 × 500 mg (298.20) and 1 × 200 mg (59.64)	357.84

with adverse events other than death. As such, these were not considered in the base-case analysis.

An attempt was made to estimate the expected costs incurred by the NHS due to succinylcholine-related morbidity in order to inform further discussion. From expert opinion, it was assumed that 1 in every 1000 patients administered with succinylcholine would require a single additional day in hospital as a result of an adverse event directly attributable to succinylcholine. An estimate of the cost to the NHS of this additional day in hospital was derived from the National Schedule of Reference Costs 2006/07 for NHS Trusts[92] by taking a weighted average of the national average unit cost for an excess bed-day across all surgery-related health-care resource group (HRG) codes (for both elective and non-elective procedures), with the weights corresponding to the number of excess bed days associated with each code; this cost was estimated to be £252.27 or £0.25 per patient administered with succinylcholine. Furthermore, the assessment group received expert clinical advice that approximately 1 in every 100 patients administered with succinylcholine would contact their local primary care centre in response to a succinylcholine-related adverse event. Whilst the cost to the NHS of this contact with primary care is difficult to estimate, it is perhaps reasonable to assume that the expected cost per patient administered with succinylcholine would not be significantly greater than that associated with the possibility of an excess bed-day.

Clinical trials have not established any effect on mortality associated with sugammadex (see Chapter 3), although it is possible that such trials were not sufficiently powered to do so. Whilst there is a paucity of evidence linking succinylcholine directly to rates of mortality, expert clinical opinion suggests that the most likely cause of mortality in patients who are administered succinylcholine was cardiac arrest. As reported in Chapter 3 (see Adverse effects of succinylcholine), the non-systematic review by Dexter *et al*.[74] provided estimates of rates of cardiac arrest associated with succinylcholine: in three large observational studies there were 21 cases of cardiac arrest among 457,609 patients, giving an overall rate of 1/21,970. As not all cardiac arrests are fatal, the average rate of mortality across all patients may be expected to be lower than this, although it is likely that the rate of mortality is highly heterogeneous and may be substantially higher in some groups of patients (e.g. the elderly and/or seriously ill). Schwartz *et al*.[93] (cited in Smith[94]) reported that, in 238 critically ill patients, emergency intubation was associated with a 3% rate of death within 30 minutes of intubation; it is unknown how many of those deaths could be attributed directly to succinylcholine.

Given the lack of suitable data on mortality with existing anaesthetic regimens, it was decided that the baseline probability of mortality associated with succinylcholine should be modelled as an unknown variable. It was assumed that the risk of mortality with sugammadex would be relatively lower than that for succinylcholine, and various scenarios were explored where this relative risk took a value of zero (mortality risk removed with sugammadex), 0.25 (75% risk reduction), 0.50 (50% risk reduction) or 0.75 (25% risk reduction). It was assumed that this baseline probability of mortality associated with succinylcholine was independent of the probability of a 'cannot intubate–cannot ventilate' event occurring.

It was assumed that deaths resulting from succinylcholine incurred no additional costs but resulted in forgone QALYs. These were calculated for patients aged 20 or 60 years by taking their expected survival duration from the most recent national mortality data for England and Wales (National Statistics 2008[95]), weighing each year of life forgone according to the HRQoL indexes published in Kind *et al*.[96] (*Table 33*). These forgone QALYs were discounted at 3.5% per annum to calculate the discounted, quality-adjusted life expectancy of patients of each age (representing the QALYs forgone in the event of death) (*Table 34*).

Recurrence of blockade or residual blockade

It was assumed that there was no residual blockade or recurrence of blockade with sugammadex or succinylcholine.

Analysis

As the strategies were assumed to have generally different expected costs and health outcomes, a cost-effectiveness analysis was carried out in the form of a threshold analysis. Critical variables included the probability of a 'cannot intubate, cannot ventilate' event occurring, the baseline probability of mortality of succinylcholine, the relative risk of mortality of adopting sugammadex, the age of the patient (and hence the QALYs forgone in the case of death) and (where a 'cannot intubate, cannot ventilate' event does not occur) the number of minutes of recovery time saved

TABLE 33 *HRQoL index by age (adapted from table A in Kind et al.[96])*

Age range	Average HRQoL weight
0–24	0.94
25–34	0.93
35–44	0.91
45–54	0.85
55–64	0.8
65–74	0.78
75+	0.73

TABLE 34 *Discounted, QALYs lost due to a fatality at age 20 and 60 years*

Example age (years)	Life expectancy (years)	Discounted, quality-adjusted life expectancy (QALYs)
20	59.96	22.91
60	22.52	12.33

by adopting sugammadex and the value of each minute saved.

It was assumed that each minute of recovery time saved through using sugammadex was valued either at £4.44 (on the basis that all time savings would be in the operating room) or £0.33 (on the basis that all time savings would be in the recovery room) (see Routine reversal of neuromuscular block) and that the amount of recovery time saved for each procedure was 23.37 minutes for reversal of moderate blockade, and 66.80 minutes for reversal of profound blockade (*Table 27*). The cost-effectiveness threshold, used to value QALYs forgone in monetary terms, was assumed to be £20,000 per QALY following the NICE methods guidance.[97]

The analysis sought to derive the minimum baseline probability of death directly due to succinylcholine for sugammadex to be considered cost-effective for any given probability of a 'cannot intubate–cannot ventilate' event.

Results

Under the base-case assumptions, for any given probability of a 'cannot intubate–cannot ventilate' event occurring, the determinants of the cost-effectiveness of sugammadex are the baseline probability of death from succinylcholine, the relative risk of mortality due to sugammadex compared with succinylcholine, the value of each minute of recovery time saved due to sugammadex (should the procedure go ahead), whether sugammadex is required to reverse moderate or profound blockade, and the age of the patient (and hence the discounted QALYs forgone in the case of mortality). The results for various combinations of these key variables are given in *Tables 35–46* and are plotted in *Figures 4* and *5*.

Sugammadex is more cost-effective for higher baseline probabilities for mortality with succinylcholine, as for any particular relative risk of mortality with sugammadex (less than one) the number of QALYs saved by adopting sugammadex will be greater. For moderate (profound) blockade, where the saved recovery time with sugammadex is achieved entirely in the operating room and the probability of a 'cannot intubate–cannot ventilate' event in the RSI setting is below approximately 0.20 (0.40), sugammadex is cost-effective under the base-case assumptions irrespective of the probability of mortality associated with succinylcholine, as the value of the saved recovery time is sufficient in itself for sugammadex to appear cost-effective.

Where the saved recovery time with sugammadex is achieved in the operating room (recovery room), a lower (higher) baseline risk of mortality with succinylcholine is required for sugammadex to be cost-effective for the reversal of short procedures or long procedures requiring profound blockade throughout than for the reversal of long procedures not requiring profound blockade throughout. This is because where the value of saved recovery time is £4.44 per minute (time savings are achieved entirely in the operating room) the additional time savings associated with the reversal of profound blockade over moderate blockade more than outweigh the additional cost of administering 4-mg/kg sugammadex over 2-mg/kg sugammadex, but where the value of saved recovery time is £0.33 per minute (time savings are achieved entirely in the recovery room) this is not the case. For very short procedures (where rocuronium followed by N&G is not required in current practice), a higher baseline risk of mortality with succinylcholine is required for sugammadex to be cost-effective than for other procedures, as any benefit of sugammadex reducing the recovery time associated with N&G is not realised.

TABLE 35 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £4.44, very short procedures, 20-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	**0.25**	**0.50**	**0.75**
0.0	0.000272	0.000363	0.000544	0.001088
0.1	0.000324	0.000432	0.000648	0.001296
0.2	0.000376	0.000501	0.000752	0.001504
0.3	0.000428	0.000571	0.000856	0.001712
0.4	0.000480	0.000640	0.000960	0.001921
0.5	0.000532	0.000710	0.001065	0.002129
0.6	0.000584	0.000779	0.001169	0.002337
0.7	0.000636	0.000849	0.001273	0.002546
0.8	0.000688	0.000918	0.001377	0.002754
0.9	0.000741	0.000987	0.001481	0.002962
1.0	0.000793	0.001057	0.001585	0.003170

CICV, 'cannot intubate–cannot ventilate'.

TABLE 36 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £4.44, very short procedures, 60-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	**0.25**	**0.50**	**0.75**
0.0	0.000505	0.000674	0.001011	0.002021
0.1	0.000602	0.000803	0.001204	0.002408
0.2	0.000699	0.000932	0.001398	0.002795
0.3	0.000796	0.001061	0.001591	0.003182
0.4	0.000892	0.001190	0.001785	0.003569
0.5	0.000989	0.001319	0.001978	0.003956
0.6	0.001086	0.001448	0.002172	0.004344
0.7	0.001183	0.001577	0.002365	0.004731
0.8	0.001279	0.001706	0.002559	0.005118
0.9	0.001376	0.001835	0.002752	0.005505
1.0	0.001473	0.001964	0.002946	0.005892

All other things being equal, a higher baseline probability of mortality with succinylcholine is required for sugammadex to be cost-effective for 60-year-old patients than for 20-year-old patients, as fewer QALYs are gained through the avoidance of mortality in older patients. Similarly, a higher baseline probability of mortality with succinylcholine is required for sugammadex to be cost-effective where the relative risk of mortality with sugammadex is higher.

Finally, *Figures 4* and *5* show that – in all scenarios – as the probability of a 'cannot intubate–cannot ventilate' event increases, a higher baseline probability of mortality with succinylcholine is required for sugammadex to be cost-effective. This can be explained in the following way: where a 'cannot intubate–cannot ventilate' event occurs, it is assumed that the procedure does not go ahead and so any potential benefits to sugammadex from reduced recovery time are not realised;

TABLE 37 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £4.44, short procedures, 20-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	0.25	0.50	0.75
0.0	N/A	N/A	N/A	N/A
0.1	N/A	N/A	N/A	N/A
0.2	N/A	N/A	N/A	N/A
0.3	N/A	N/A	N/A	N/A
0.4	0.000085	0.000114	0.000171	0.000342
0.5	0.000203	0.000271	0.000407	0.000813
0.6	0.000321	0.000428	0.000642	0.001285
0.7	0.000439	0.000585	0.000878	0.001756
0.8	0.000557	0.000743	0.001114	0.002228
0.9	0.000675	0.000900	0.001349	0.002699
1.0	0.000793	0.001057	0.001585	0.003170

N/A, not available.

TABLE 38 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £4.44, short procedures, 60-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	0.25	0.50	0.75
0.0	N/A	N/A	N/A	N/A
0.1	N/A	N/A	N/A	N/A
0.2	N/A	N/A	N/A	N/A
0.3	N/A	N/A	N/A	N/A
0.4	0.000159	0.000212	0.000318	0.000635
0.5	0.000378	0.000504	0.000756	0.001511
0.6	0.000597	0.000796	0.001194	0.002387
0.7	0.000816	0.001088	0.001632	0.003264
0.8	0.001035	0.001380	0.002070	0.004140
0.9	0.001254	0.001672	0.002508	0.005016
1.0	0.001473	0.001964	0.002946	0.005892

furthermore, it has been assumed that there is no systematic difference between succinylcholine and rocuronium with sugammadex in terms of any serious health consequences resulting from a 'cannot intubate–cannot ventilate' event, while the cost of administering rocuronium with 16-mg/kg sugammadex is considerably greater than that of administering succinylcholine. As such, sugammadex is more cost-effective in the RSI setting where a 'cannot intubate–cannot ventilate' does *not* occur than where it does, and, hence, where the probability of a 'cannot intubate–cannot ventilate' event is greater, a higher baseline probability of mortality with succinylcholine is required to compensate in terms of cost-effectiveness. Note that this intuition should not be applied to the routine setting, where sugammadex may appear very cost-effective in the case of a 'cannot intubate–cannot ventilate' event due to the potentially serious consequences of being unable to quickly reverse profound blockade with N&G (although this is not modelled).

TABLE 39 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved £4.44, long procedures, 20-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	**0.25**	**0.50**	**0.75**
0.0	N/A	N/A	N/A	N/A
0.1	N/A	N/A	N/A	N/A
0.2	0.000082	0.000109	0.000164	0.000328
0.3	0.000171	0.000228	0.000341	0.000683
0.4	0.000260	0.000346	0.000519	0.001038
0.5	0.000348	0.000465	0.000697	0.001394
0.6	0.000437	0.000583	0.000874	0.001749
0.7	0.000526	0.000701	0.001052	0.002104
0.8	0.000615	0.000820	0.001230	0.002460
0.9	0.000704	0.000938	0.001408	0.002815
1.0	0.000793	0.001057	0.001585	0.003170

TABLE 40 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £4.44, long procedures, 60-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	**0.25**	**0.50**	**0.75**
0.0	N/A	N/A	N/A	N/A
0.1	N/A	N/A	N/A	N/A
0.2	0.000152	0.000203	0.000304	0.000609
0.3	0.000317	0.000423	0.000635	0.001269
0.4	0.000482	0.000643	0.000965	0.001929
0.5	0.000647	0.000863	0.001295	0.002590
0.6	0.000813	0.001083	0.001625	0.003250
0.7	0.000978	0.001304	0.001955	0.003911
0.8	0.001143	0.001524	0.002285	0.004571
0.9	0.001308	0.001744	0.002616	0.005231
1.0	0.001473	0.001964	0.002946	0.005892

Discussion of economic assessment

The evidence base for modelling cost-effectiveness is very limited and no published economic evaluation in this area was identified. In particular, no evidence appears to exist linking measures of clinical efficacy such as time to TOF 0.9 to patients' HRQoL and mortality risks. As a result, direct cost-effectiveness modelling was not considered feasible. Rather, a series of threshold analyses was undertaken, which essentially establish how effective sugammadex needs to be, relative to existing practice, in order to justify its acquisition cost.

In the routine setting, the analyses were undertaken on the assumption that sugammadex shortens patients' recovery time and reduces the rate of recurrence of blockade or residual blockade, resulting in resource savings to the NHS. The size of these resource savings depends on the extent to which the time saved due to more rapid recovery would allow clinicians to undertake

TABLE 41 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £0.33, very short procedures, 20-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	0.25	0.50	0.75
0.0	0.000272	0.000363	0.000544	0.001088
0.1	0.000324	0.000432	0.000648	0.001296
0.2	0.000376	0.000501	0.000752	0.001504
0.3	0.000428	0.000571	0.000856	0.001712
0.4	0.000480	0.000640	0.000960	0.001921
0.5	0.000532	0.000710	0.001065	0.002129
0.6	0.000584	0.000779	0.001169	0.002337
0.7	0.000636	0.000849	0.001273	0.002546
0.8	0.000688	0.000918	0.001377	0.002754
0.9	0.000741	0.000987	0.001481	0.002962
1.0	0.000793	0.001057	0.001585	0.003170

TABLE 42 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £0.33, very short procedures, 60-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	0.25	0.50	0.75
0.0	0.000505	0.000674	0.001011	0.002021
0.1	0.000602	0.000803	0.001204	0.002408
0.2	0.000699	0.000932	0.001398	0.002795
0.3	0.000796	0.001061	0.001591	0.003182
0.4	0.000892	0.001190	0.001785	0.003569
0.5	0.000989	0.001319	0.001978	0.003956
0.6	0.001086	0.001448	0.002172	0.004344
0.7	0.001183	0.001577	0.002365	0.004731
0.8	0.001279	0.001706	0.002559	0.005118
0.9	0.001376	0.001835	0.002752	0.005505
1.0	0.001473	0.001964	0.002946	0.005892

other productive activities. Under the base-case assumptions, if sugammadex provides no reduction in recovery time then it is not cost-effective at the current list price. As the reduction in recovery time increases, the minimum value of each minute of saved recovery time required for sugammadex to be cost-effective falls.

The estimates of the reduction in recovery time derived from Blobner[30] and Jones[36] suggest that sugammadex is cost-effective in patients with moderate (profound) blockade where the value of each minute of recovery time saved with sugammadex is approximately £2.40 (£1.75) or greater. The assessment group estimated that time saved in the operating room has a value of £4.44 per minute while time saved in the recovery room has a value of £0.33 per minute; 2 mg/kg (4 mg/kg) sugammadex therefore appears cost-effective for the routine reversal of rocuronium-induced moderate (profound) blockade at the current list price if all reductions in recovery time associated with sugammadex are achieved in the operating room, but does not appear cost-

TABLE 43 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £0.33, short procedures, 20-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	0.25	0.50	0.75
0.0	0.000213	0.000284	0.000426	0.000852
0.1	0.000271	0.000361	0.000542	0.001084
0.2	0.000329	0.000439	0.000658	0.001316
0.3	0.000387	0.000516	0.000774	0.001547
0.4	0.000445	0.000593	0.000890	0.001779
0.5	0.000503	0.000670	0.001006	0.002011
0.6	0.000561	0.000748	0.001121	0.002243
0.7	0.000619	0.000825	0.001237	0.002475
0.8	0.000677	0.000902	0.001353	0.002707
0.9	0.000735	0.000980	0.001469	0.002939
1.0	0.000793	0.001057	0.001585	0.003170

TABLE 44 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £0.33, short procedures, 60-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	0.25	0.50	0.75
0.0	0.000396	0.000528	0.000792	0.001583
0.1	0.000503	0.000671	0.001007	0.002014
0.2	0.000611	0.000815	0.001222	0.002445
0.3	0.000719	0.000959	0.001438	0.002876
0.4	0.000827	0.001102	0.001653	0.003307
0.5	0.000934	0.001246	0.001869	0.003737
0.6	0.001042	0.001389	0.002084	0.004168
0.7	0.001150	0.001533	0.002300	0.004599
0.8	0.001258	0.001677	0.002515	0.005030
0.9	0.001365	0.001820	0.002730	0.005461
1.0	0.001473	0.001964	0.002946	0.005892

effective if all reductions in recovery time are achieved in the recovery room. Where savings in recovery time are achieved in both the operating room and the recovery room, or where there is additional value in reducing recovery times (e.g. in preventing operations from being delayed or forgone), the cost-effectiveness of sugammadex is highly dependent on the setting in which it is administered. The results are broadly similar for rocuronium- and vecuronium-induced blockade, with any differences driven by the small differences between the prices of rocuronium and vecuronium and the rates of recurrence of blockade or residual blockade.

One scenario not modelled in the routine setting (due to the lack of available data) is that where a 'cannot intubate–cannot ventilate' event occurs. In current practice, such an event has potentially serious consequences (for both patient health and resource use) due to the inability to quickly reverse profound blockade with neostigmine. Administering 16-mg/kg sugammadex may therefore appear very cost-effective in such

TABLE 45 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £0.33, long procedures, 20-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	**0.25**	**0.50**	**0.75**
0.0	0.000114	0.000152	0.000228	0.000455
0.1	0.000182	0.000242	0.000363	0.000727
0.2	0.000250	0.000333	0.000499	0.000998
0.3	0.000317	0.000423	0.000635	0.001270
0.4	0.000385	0.000514	0.000771	0.001541
0.5	0.000453	0.000604	0.000906	0.001813
0.6	0.000521	0.000695	0.001042	0.002084
0.7	0.000589	0.000785	0.001178	0.002356
0.8	0.000657	0.000876	0.001314	0.002627
0.9	0.000725	0.000966	0.001449	0.002899
1.0	0.000793	0.001057	0.001585	0.003170

TABLE 46 *Minimum baseline probability of death from succinylcholine for sugammadex to be cost-effective (value of each minute of recovery time saved = £0.33, long procedures, 60-year-old patients)*

Probability of CICV event	Relative risk of mortality due to sugammadex			
	0.00	**0.25**	**0.50**	**0.75**
0.0	0.000211	0.000282	0.000423	0.000846
0.1	0.000338	0.000450	0.000675	0.001350
0.2	0.000464	0.000618	0.000927	0.001855
0.3	0.000590	0.000787	0.001180	0.002360
0.4	0.000716	0.000955	0.001432	0.002864
0.5	0.000842	0.001123	0.001684	0.003369
0.6	0.000968	0.001291	0.001937	0.003873
0.7	0.001094	0.001459	0.002189	0.004378
0.8	0.001221	0.001628	0.002441	0.004883
0.9	0.001347	0.001796	0.002694	0.005387
1.0	0.001473	0.001964	0.002946	0.005892

circumstances. However, there is a possible issue over the time it would take to prepare such a high dose of sugammadex in a high-pressure situation, with the assessment group's clinical expert suggesting around 30 seconds, but one anonymous reviewer suggesting that up to 2 minutes would be required, possibly resulting in serious adverse events occurring. If such a strategy therefore requires that a 16-mg/kg dose of sugammadex be prepared beforehand, this may prove extremely costly, as any unused sugammadex at the end of each patient list would have to be disposed of, and it is not clear that such a strategy is likely to be cost-effective where 'cannot intubate–cannot ventilate' events are rare. Conversely, if it is possible for the sugammadex to be prepared quickly under such circumstances (prepreparation is not necessary) then it would appear likely that such a strategy is cost-effective.

In the context of reversal of NMB used in the RSI setting, where sugammadex is assumed to be associated with a reduced risk of mortality, the decision over whether or not sugammadex

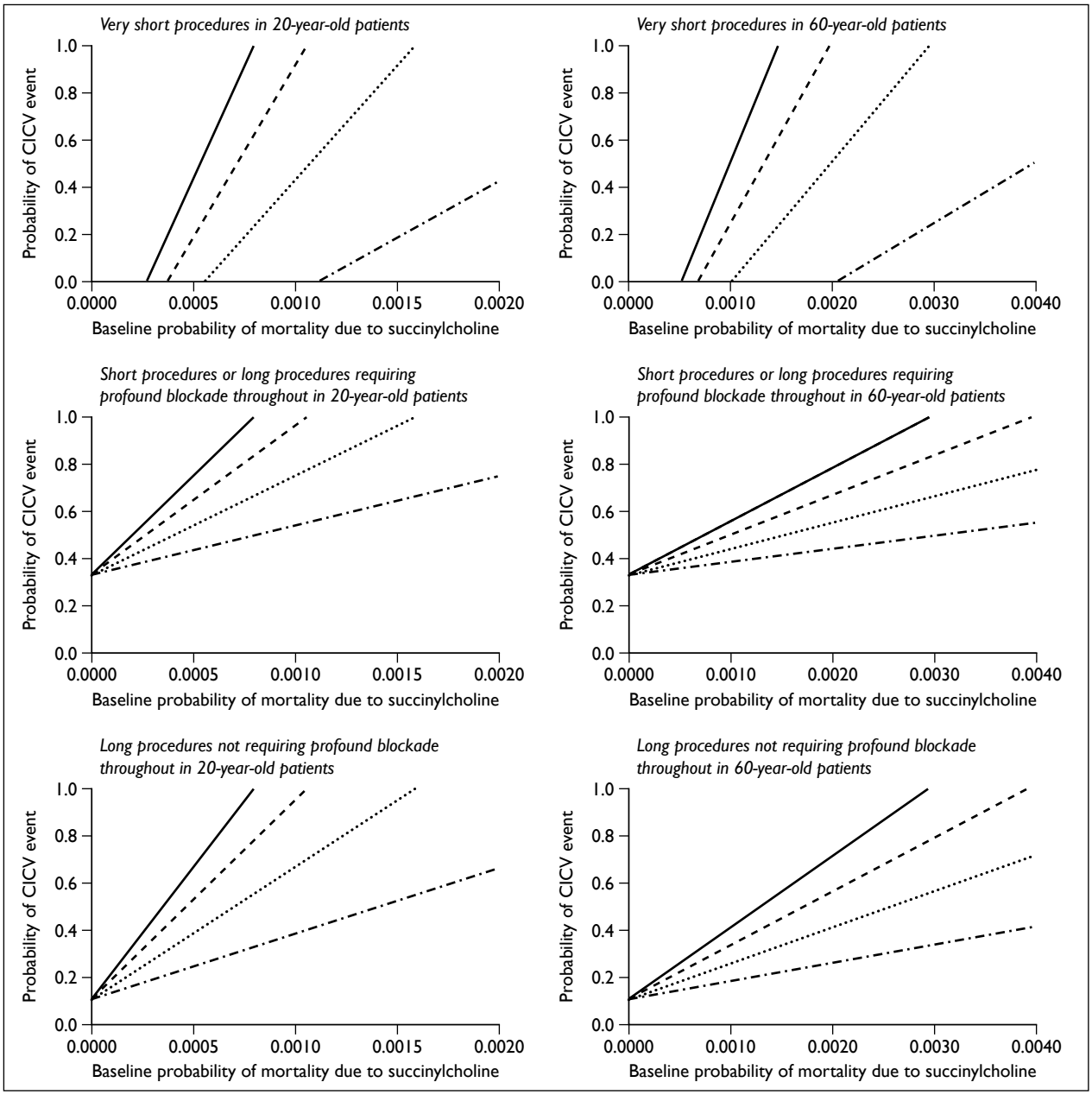

FIGURE 4 *Threshold analysis (rapid sequence induction setting) where value of each minute of recovery time saved is £4.44. The region above (below) each line represents the combinations of probability of 'cannot intubate–cannot ventilate' event and baseline probability of mortality due to succinylcholine at which sugammadex is not (is) cost-effective under the base-case assumptions. The solid, dashed, dotted and 'dotted and dashed' lines represent the boundary of the region of cost-effectiveness where the relative risk of mortality due to sugammadex is 0.00, 0.25, 0.50 and 0.75, respectively. Separate graphs are plotted for very short procedures, short procedures (or long procedures requiring profound blockade throughout), and long procedures not requiring profound blockade throughout, in each case for patients who are 20 years old and 60 years old.*

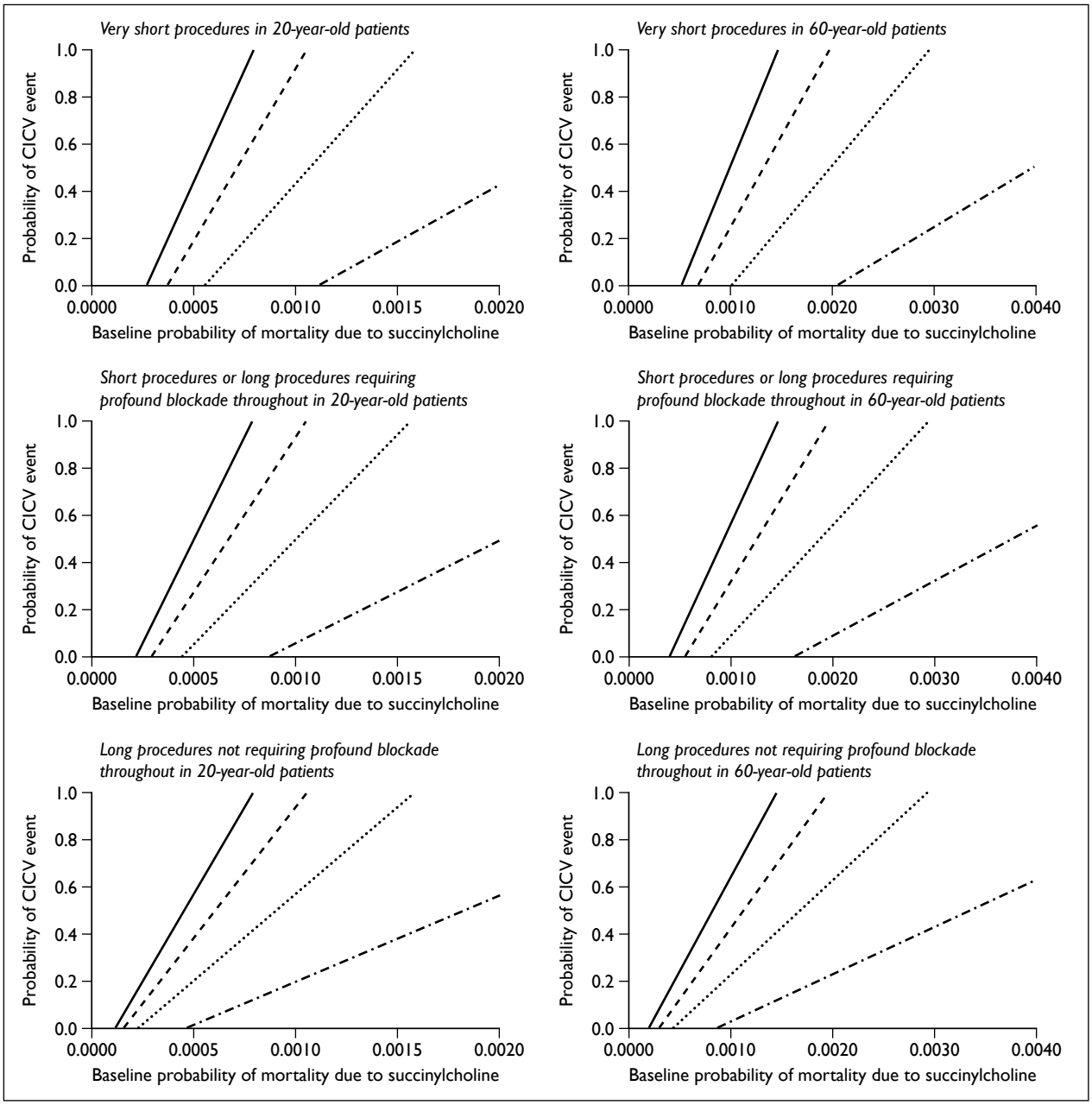

FIGURE 5 *Threshold analysis (rapid sequence induction setting) where value of each minute of recovery time saved is £0.33. The region above (below) each line represents the combinations of probability of 'cannot intubate–cannot ventilate' event and baseline probability of mortality due to succinylcholine at which sugammadex is not (is) cost-effective under the base-case assumptions. The solid, dashed, dotted and 'dotted and dashed' lines represent the boundary of the region of cost-effectiveness where the relative risk of mortality due to sugammadex is 0.00, 0.25, 0.50 and 0.75, respectively. Separate graphs are plotted for very short procedures, short procedures (or long procedures requiring profound blockade throughout), and long procedures not requiring profound blockade throughout, in each case for patients 20 years old and 60 years old.*

is cost-effective depends upon the baseline probability of death from succinylcholine, the relative risk of mortality due to sugammadex compared with succinylcholine, the probability of a 'cannot intubate–cannot ventilate' event, the value of each minute of recovery time saved due to sugammadex (should the procedure go ahead), whether sugammadex is required to reverse moderate or profound blockade and the age of the patient (and hence the discounted QALYs forgone in the case of mortality). It would appear that any reduction in morbidity from adopting sugammadex is unlikely to result in significant cost savings for the NHS.

Under the base-case assumptions, sugammadex is more cost-effective for higher baseline probabilities for mortality with succinylcholine. For moderate (profound) blockade, where the saved recovery time with sugammadex is achieved entirely in the operating room and the probability of a 'cannot intubate–cannot ventilate' event is below approximately 0.20 (0.40), sugammadex is cost-effective irrespective of the probability of mortality associated with succinylcholine, as the value of the saved recovery time is sufficient in itself for sugammadex to appear cost-effective. Where the saved recovery time with sugammadex is achieved in the operating room (recovery room), a lower (higher) baseline risk of mortality with succinylcholine is required for sugammadex to be cost-effective for the reversal of short procedures or long procedures requiring profound blockade throughout than for the reversal of long procedures not requiring profound blockade throughout. All other things being equal, a higher baseline probability of mortality with succinylcholine is required for sugammadex to be cost-effective for 60-year-old patients than for 20-year-old patients, as fewer QALYs are gained through the avoidance of mortality in older patients. Similarly, a higher baseline probability of mortality with succinylcholine is required for sugammadex to be cost-effective where the relative risk of mortality with sugammadex is higher. Finally, as the probability of a 'cannot intubate–cannot ventilate' event increases, a higher baseline probability of mortality with succinylcholine is required for sugammadex to be cost-effective.

Chapter 5
Discussion

Statement of principal findings

Clinical assessment

There is evidence from randomised trials that sugammadex is more effective than neostigmine or placebo for the reversal (determined by monitoring of the TOF ratio) of moderate or profound NMB induced by rocuronium or vecuronium. The reversal of NMB by sugammadex appears to be both more rapid and generally more predictable (narrower range of recovery times) than placebo or neostigmine. The available data also suggest that reversal of moderate block when the NMBA–reversal agent combination is rocuronium–sugammadex may be faster than when other NMBA–reversal agent combinations are used. Administration of sugammadex (16 mg/kg) 3 minutes after rocuronium has been shown to result in more rapid recovery than with spontaneous recovery from succinylcholine. The available evidence on safety of sugammadex administered after rocuronium or vecuronium suggests that rates of adverse events are similar to those found with comparators (N&G or placebo). No direct evidence was found on resource use, costs or QoL.

Economic assessment

The evidence base for modelling cost-effectiveness is very limited and no published economic evaluation in this area was identified. In particular, no evidence appears to exist linking measures of clinical efficacy such as time to TOF 0.9 to patients' HRQoL and mortality risks. As a result, direct cost-effectiveness modelling was not considered feasible. Rather, a series of threshold analyses were undertaken, which essentially establish how effective sugammadex needs to be, relative to existing practice, to justify its acquisition cost.

In the routine setting, the analyses were undertaken on the assumption that sugammadex shortens patients' recovery time and reduces the rate of recurrence of blockade or residual blockade, resulting in resource savings to the NHS. The size of these resource savings depends on the extent to which the time saved due to more rapid recovery would allow clinicians to undertake other productive activities. Under the base-case assumptions, if sugammadex provides no reduction in recovery time then it is not cost-effective at the current list price. As the reduction in recovery time increases, the minimum value of each minute of saved recovery time required for sugammadex to be cost-effective falls. It appears that 2 mg/kg (4 mg/kg) sugammadex is cost-effective for the routine reversal of rocuronium-induced moderate (profound) blockade at the current list price, if all reductions in recovery time that are associated with sugammadex are achieved in the operating room, but does not appear cost-effective if all reductions in recovery time are achieved in the recovery room. Where savings in recovery time are achieved in both the operating room and the recovery room, or where there is additional value in reducing recovery times (e.g. in preventing operations from being delayed or forgone), the cost-effectiveness of sugammadex is highly dependent on the setting in which it is administered. The results are broadly similar for rocuronium-induced blockade and vecuronium-induced blockade. One scenario not modelled in the routine setting (due to the lack of available data) is that where a 'cannot intubate, cannot ventilate' event occurs. In current practice, such an event has potentially serious consequences (for both patient health and resource use) due to the inability to quickly reverse profound blockade with neostigmine. In the absence of modelling, it is not clear whether administering 16-mg/kg sugammadex is likely to be a cost-effective strategy in such circumstances, due to uncertainty over the time it would take to prepare such a high dose of sugammadex in a high-pressure situation and the cost associated with preparing such a dose beforehand for every patient list.

In the context of reversal of NMB used in the RSI setting, where sugammadex is assumed to be associated with a reduced risk of mortality, the decision over whether or not sugammadex is cost-effective depends upon the baseline probability of death from succinylcholine, the relative risk of mortality due to sugammadex compared with succinylcholine, the probability of a 'cannot intubate, cannot ventilate' event, the value of each minute of recovery time saved due to sugammadex

(should the procedure go ahead), whether sugammadex is required to reverse moderate or profound blockade and the age of the patient (and hence the discounted QALYs forgone in the case of mortality). It would appear that any reduction in morbidity from adopting sugammadex is unlikely to result in significant cost savings for the NHS.

Strengths and limitations of the assessment

Rigorous systematic review methods were used for the assessment of clinical effectiveness. We have attempted to make full use of the available evidence by including unpublished studies and by extracting data from regulatory documents, including the Organon submission to the US FDA and the EMEA assessment report for sugammadex. No other relevant systematic reviews of sugammadex were found. A Cochrane review[98] was published while this report was in the editorial process (October 2009). This review reached similar conclusions to ours.

The limitations of the assessment follow from the limitations of the evidence, including the fact that many trials of sugammadex have not been published as peer-reviewed articles, were not designed to assess efficacy and/or report only a limited range of outcomes. Our inability to obtain the relevant data to perform a MTC of rocuronium–vecuronium + sugammadex with other NMBA–reversal agent combinations means that only limited information is available for assessment of treatment options (e.g. atracurium + neostigmine–glycopyrrolate and mivacurium + neostigmine–glycopyrrolate) that have not been compared directly with options involving sugammadex.

It is possible that sugammadex results in further resource savings to those considered in the modelling by allowing additional operations to be fitted into the working day and/or by reducing the costs associated with serious adverse events; however, there are no suitable data to provide a basis for such modelling and so these are not formally considered. Similarly, there are no data to inform any possible differences between anaesthetic strategies in terms of HRQoL or to model differences in outcomes that might arise for different types of surgery given a particular anaesthetic strategy. This and other data weaknesses need to be considered when the results presented here are being interpreted.

One scenario not considered in the modelling due to a lack of suitable evidence was the rare possibility of an unexpected 'cannot intubate–cannot ventilate' situation occurring in the routine setting (following induction of NMB with 0.6 mg/kg of rocuronium). Without the possibility of the rapid reversal of blockade with 16-mg/kg sugammadex, this is potentially a situation with extremely serious consequences for the patient (including death). It is not clear whether a strategy of administering 16-mg/kg sugammadex in such circumstances would be cost-effective.

Given the limited evidence available on many aspects of the effects of sugammadex compared to alternative regimens (for example, the model considers none of the adverse events associated with succinylcholine, except death), the direct modelling of the cost-effectiveness of sugammadex is highly speculative. One alternative would have been to formally elicit the opinions of clinical experts to estimate uncertain parameters for the model. However, the time was not available to undertake such an elicitation study. Moreover, it is doubtful whether the key unknown parameters in the model (e.g. proportion of saved recovery time that could be used for productive purposes; the baseline mortality risk on the rapid induction setting) would be estimable by clinicians.

Although direct modelling has not been possible, the threshold analyses presented here will give decision-makers an idea of the magnitude of clinical outcomes that will need to be achieved for sugammadex to be considered cost-effective. If these are extremely low or high, compared with what would be clinically expected, it may be possible to conclude that sugammadex is highly likely or unlikely to be cost-effective. It may be that such a conclusion could be reached in patients with particular characteristics. The most obvious example is that the cost-effectiveness of sugammadex in the rapid intubation setting is, all other things equal, more likely in patients with a higher baseline mortality risk. Another use of the threshold analyses presented here is to help design research to reduce the uncertainties in the modelling. By indicating what values key variables need to take in order for sugammadex to be considered cost-effective, appropriate studies can be designed to more accurately estimate these values.

A possibility not considered in this report is that the use of remifentanil, a potent short-acting

opioid analgesic, may reduce the need to use NMBAs (and hence reversal agents) during surgery. The anaesthetist may use an NMBA to facilitate tracheal intubation, but infuse remifentanil during the operation without administering any further doses of NMBA. In this situation, reversal of blockade at the end of the operation might not be required or if required could easily be achieved with neostigmine and glycopyrrolate. This may be a valid approach for some types of surgery, particularly head and neck surgery, but many surgical procedures, for example abdominal or thoracic surgery, require NMB throughout and this is the type of procedure for which sugammadex is intended to be used.

Uncertainties

At the conclusion of this assessment several uncertainties remain:

- Sugammadex combinations should be formally compared with all commonly used NMBA–reversal agent combinations. This could be done through a MTC, subject to access to all data, and data being available from older trials that are comparable with those from the newer sugammadex trials.
- The benefits of sugammadex 16 mg/kg are difficult to assess fully until this dose has been used more widely in clinical practice – an analysis of the proportion of patients who do not recover within 5 minutes would be informative.
- The incidence and significance of rare but serious adverse effects, such as anaphylactic/allergic reactions, will become clearer when larger numbers of patients have been exposed to sugammadex.
- The patients in the sugammadex trials were mainly relatively young, and in ASA classes I–II, and may not be fully representative of those who would receive sugammadex in routine clinical practice.
- The reductions in recovery time with sugammadex seen in the clinical trials may represent the maximum that can be achieved and the benefits in normal clinical practice will remain uncertain pending wider adoption and evaluation of sugammadex.
- In the routine setting, the key economic uncertainties surround the productivity benefits to the NHS of reduced time in recovery, in particular the value of operating room staff time and the proportion of any reduction in recovery time that can be put to productive use.
- In the rapid induction and/or reversal setting, the key uncertainties surround the baseline rate of mortality due to succinylcholine, the relative risk of mortality due to sugammadex and the probability of a 'cannot intubate, cannot ventilate' event occurring.
- It is possible that sugammadex results in further resource savings than those considered by allowing additional operations to be fitted into the working day and/or by reducing the costs associated with serious adverse events; however, there are no suitable data to provide a basis for such modelling and so these are not considered.
- Similarly there are no data to inform any possible differences between anaesthetic strategies in HRQoL. These, and other data weaknesses, need to be considered when the results presented here are being interpreted.

Assessment of factors relevant to the NHS and other parties

If sugammadex were to be widely recommended for use in routine surgery in the NHS, it is likely that the overall cost of reversal agents would increase, as the more expensive sugammadex replaces a cheaper agent (N&G). The use of rocuronium and vecuronium for NMB would increase at the expense of other non-depolarising NMBAs and succinylcholine. There would be some requirement for training of staff during the initial period but this is not expected to involve significant costs.

The implications for use of objective monitoring in practice are uncertain. In the clinical trials, sugammadex was administered at specific points determined by TOF monitoring and if anaesthetists follow this practice, the use of monitoring would increase. However, because sugammadex appears effective at all levels of block, anaesthetists may feel able to reduce levels of monitoring as they become more confident and experienced in its use, especially bearing in mind resultant savings in equipment costs. There could be an overall deterioration in practice that is associated with decreased monitoring, although this would be difficult to quantify.

Increased use of sugammadex could lead to improvements in list management, which associated with reduced recovery times and benefits for patients in terms of quicker and easier recovery and fewer adverse effects (especially if rocuronium + sugammadex replaces succinylcholine).

These implications relate to UK practice and may not apply to other countries and different health-care systems.

An alternative scenario is for sugammadex to be reserved for use in rapid reversal of NMB following rapid sequence induction and intubation of patients considered at risk of aspiration of gastric contents, and for reversal of blockade when a 'cannot intubate–cannot ventilate' emergency occurs during preparation for routine surgery. This would primarily involve the 16-mg/kg dose of sugammadex. This scenario would require less expenditure on sugammadex, but would also bring fewer benefits. The availability of sugammadex in situations where there is currently no reversal agent available could be life-saving, but the evidence suggests that the number of lives likely to be saved could be very small. Furthermore, use of sugammadex in this limited role would still require that rocuronium (or possibly vecuronium) was used as the NMBA in most cases.

Chapter 6
Conclusions

Implications for service provision

Sugammadex produces a substantially faster and more predictable recovery from rocuronium- or vecuronium-induced moderate NMB than does neostigmine. Also, recovery from NMB is faster and more predictable when the NMBA–reversal agent combination is rocuronium + sugammadex than when it is cisatracurium + neostigmine. As sugammadex may be a cost-effective option compared with N&G for reversal of moderate NMB, then the use of rocuronium + sugammadex appears to be a realistic option for clinical practice. In addition, sugammadex can produce a rapid recovery from profound NMB, provided that the block was induced with rocuronium or vecuronium. Therefore, the choice of this combination of NMBA–reversal agent is further supported by the facility to recover patients from profound blockade, a facility not available with any other combination except, to a lesser extent, vecuronium + sugammadex.

Sugammadex 16 mg/kg can reverse blockade induced by high-dose rocuronium shortly after the block has been established. This cannot be achieved with any other available reversal agent. The availability of sugammadex 16 mg/kg to reverse immediately block induced with high-dose rocuronium means that rocuronium + sugammadex could be considered as a replacement for succinylcholine for rapid induction (and reversal) of NMB. This would avoid the morbidity associated with succinylcholine, although the economic assessment suggests that the cost-effectiveness of sugammadex will be highly sensitive to a given patient's underlying mortality risk during the procedure, so this may not be a cost-effective option in some types of patient at the current list prices for sugammadex. This option could be considered if a price reduction for sugammadex could be negotiated or, in the context of a clinical study, at a limited range of centres.

The adverse effect profile of sugammadex indicates it is well tolerated. However, the number of patients exposed to sugammadex is relatively small and further monitoring is required as the exposed patient population expands.

Sugammadex offers different ways of managing patients in anaesthesia, but its pharmacological benefits can only be achieved when rocuronium or possibly vecuronium is used to induce NMB. There are potential benefits of sugammadex in terms of increased patient safety, increased predictability of recovery from NMB, and more efficient use of theatre time and staff, but these have yet to be explored in clinical practice. New practices in anaesthesia may have to be adopted before the full benefits of sugammadex can be realised.

Suggested research priorities

- Evaluate the effects of replacing succinylcholine with rocuronium + sugammadex for rapid induction and reversal of NMB on morbidity, mortality, patient-reported outcomes and resource use.
- Collect data on the use of sugammadex in clinical practice to obtain better estimates of the incidence and implications of rare major adverse events, for example allergic/anaphylactic reactions.
- Evaluate outcomes of sugammadex use in routine surgery for which there is little information to date, for example patient-reported outcomes, clinical signs of recovery, resource use and costs.
- Evaluate the use of sugammadex in paediatric and obstetric practice.
- The need for further randomised trials of sugammadex should be evaluated following full publication of the trials considered in this report and in the light of trials currently in progress. Possible trials include further direct comparisons of rocuronium or vecuronium + sugammadex with other NMBA–reversal agent combinations; trials to assess the safety and efficacy of sugammadex for use in profound block and immediate reversal in special populations, and young and elderly patients, and further trials in special

populations for reversal of moderate block; and further trials to assess the relative efficacy of vecuronium + sugammadex as most trials to date have assessed rocuronium.
- Evaluate the use of a 4-mg/kg dose of sugammadex for immediate reversal of blockade induced by low-dose (0.6 mg/kg) rocuronium in the routine setting.
- Evaluate new theatre practices that could potentially make optimum use of the time savings afforded through the use of sugammadex. This would ideally involve a nationwide prospective study.
- Evaluate the effects of using different combinations of anaesthesia and analgesia with sugammadex, specifically in situations where potent inhalational agents have been used but discontinued.
- Further research is needed to quantify the mortality risk of patients with different clinical characteristics in the setting of rapid induction of NMB.

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Contribution of authors

Duncan Chambers was involved in all stages of the clinical review from development of the protocol, through screening studies and data extraction to analysis and synthesis and production of the final report. Michael Paulden was involved in all stages of the economic review from development of the protocol, study selection, development of the economic model and production of the final report. Fiona Paton was involved in all stages of the clinical review from development of the protocol, through screening studies and data extraction to analysis and synthesis and production of the final report. Morag Heirs was involved in all stages of the clinical review from development of the protocol, through screening studies and data extraction to analysis and synthesis and production of the final report. Steven Duffy devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report. Dawn Craig was involved in analysis of neuromuscular blocking agents and reversal agents (mixed-treatment comparison) and commented on the draft report. Jennifer Hunter provided clinical advice and commented on the draft report in detail. Jonathan Wilson provided clinical advice and commented on the draft report. Mark Sculpher provided input at all stages of the review, commented on drafts of the report and took overall responsibility for the economic section. Nerys Woolacott provided input at all stages of the review, commented on drafts of the report and took overall responsibility for the review.

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101. Flockton E, Scanni E, Gomar C, Shields M, Aguilera L. Sugammadex after rocuronium provides faster recovery from neuromuscular blockade than neostigmine after cisatracurium [abstract]. *Eur J Anaesthesiol* 2007;**24**:123.

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107. Organon. *A bridging trial comparing Org 25969 at reappearance of T2 in Japanese and Caucasian subjects. Part B: Caucasian subjects (19.4.208B)*. In: ClinicalTrials.gov (internet). Bethesda, MD: National Library of Medicine (US). 2005–2006. Accessed 30 May 2008. URL: http://clinicaltrials.gov/show/NCT00552617 NLM Identifier: NCT00552617

Appendix 1

Literature search strategies

Sugammadex search strategies

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OvidSP), 1950–2008/May week 3: 30 May 2008

50 records were retrieved in MEDLINE and 6 in MEDLINE In-Process & Other Non-Indexed Citations.

1. sugammadex.ti,ab,rn,nm.
2. (org 25969 or org25969).ti,ab,rn,nm.
3. bridion.ti,ab,rn,nm.
4. 343306–79–6.rn.
5. (selective adj3 relaxant$).ti,ab.
6. SRBA.ti,ab.
7. or/1–6
8. Animals/
9. Humans/
10. 8 not (8 and 9)
11. 7 not 10

EMBASE (OvidSP), 1980–2008/week 21: 30 May 2008

84 records were retrieved.

1. Sugammadex/
2. sugammadex.ti,ab,rn,mf,tn.
3. (org 25969 or org25969).ti,ab,rn,mf,tn.
4. bridion.ti,ab,rn,mf,tn.
5. 343306 79 6.rn.
6. (selective adj3 relaxant$).ti,ab.
7. SRBA.ti,ab.
8. or/1–7
9. Animal/or Animal Experiment/or Nonhuman/
10. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.
11. 9 or 10
12. exp Human/or Human Experiment/
13. 11 not (11 and 12)
14. 8 not 13

CINAHL (OvidSP), 1982–2008/May week 4: 30 May 2008

14 records were retrieved.

1. sugammadex.ti,ab.
2. (org 25969 or org25969).ti,ab.
3. bridion.ti,ab.
4. 343306–79–6.mp.
5. (selective adj3 relaxant$).ti,ab.
6. SRBA.ti,ab.
7. or/1–6

Science Citation Index (Web of Science), 1900–2008/29 May: 30 May 2008

48 records were retrieved.

#1 TS = (sugammadex)
#2 TS = (org 25969 or org25969)
#3 TS = (bridion)
#4 TS = ("selective relaxant binding agent*")
#5 #1 or #2 or #3 or #4

ISI Proceedings: Science & Technology (Web of Science), 1990–2008/23 May: 30 May 2008

4 records were retrieved.

#1 TS = (sugammadex)
#2 TS = (org 25969 or org25969)
#3 TS = (bridion)
#4 TS = ("selective relaxant binding agent*")
#5 #1 or #2 or #3 or #4

CDSR and CENTRAL (Cochrane Library), 2008 Issue 2: 30 May 2008

0 reviews were retrieved in CDSR and 9 records were retrieved in CENTRAL.

#1 (sugammadex)
#2 "org 25969" OR org25969
#3 (bridion)
#4 (343306–79–6 or "343306 79 6")
#5 (selective NEAR/3 relaxant*)
#6 (SRBA)
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

DARE and HTA (Cochrane Library), 2008 – Issue 2: 30 May 2008

0 records were retrieved in DARE and 1 record was retrieved in HTA.

#1 (sugammadex)
#2 "org 25969" OR org25969
#3 (bridion)
#4 (343306–79–6 or "343306 79 6")
#5 (selective NEAR/3 relaxant*)

#6 (SRBA)
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

BIOSIS (Dialog), 1926–2008/May week 4: 30 May 2008
24 records were retrieved.

- s sugammadex
- s org(w)25969 or org25969
- s bridion
- s selective(w)relaxant(w)binding(w)agent?
- s RN = 343306–79–6
- s s1:s5
- s s6/HUMAN

Inside Conferences (Dialog), 1993–2008/30 May 30: 30 May 2008
0 records were retrieved.

- s sugammadex
- s org(w)25969 or org25969
- s bridion
- s selective(w)relaxant(w)binding(w)agent?
- s RN = 343306–79–6
- s s1:s5
- s s6/HUMAN

TOXLINE (TOXNET – US National Library of Medicine), 2008/30 May: 30 May 2008
14 records were retrieved.

#1 sugammadex
#2 org 25969
#3 org25969
#4 bridion
#6 "selective relaxant binding agent"
#7 "selective relaxant binding agents"
#8 343306–79–6 [rn]
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

NHS EED (Cochrane Library) 2008 – Issue 2: 30 May 2008
0 records were retrieved.

#1 (sugammadex)
#2 "org 25969" OR org25969
#3 (bridion)
#4 (343306–79–6 or "343306 79 6")
#5 (selective NEAR/3 relaxant*)
#6 (SRBA)
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

HEED (Wiley online), 2008/April: 30 May 2008
0 records were retrieved.

- AX = (sugammadex)
- AX = (org 25969) or (org25969)
- AX = (bridion)
- AX = (selective relaxant binding agent) or (selective relaxant binding agents)
- CS = 1 or 2 or 3 or 4

ClinicalTrials.gov (US National Library of Medicine), 2008/May: 30 May 2008
20 records were retrieved.

Each line searched separately:

- sugammadex
- org 25969
- org25969
- bridion

Current Controlled Trials (mRCT), 2008/May: 30 May 2008
16 records were retrieved.

Each line searched separately:

- sugammadex
- org 25969
- org25969
- bridion

ClinicalStudyResults.org (Clinical Study Results website), 2008/May: 30 May 2008
0 records were retrieved.

Each line searched separately:

- sugammadex
- org 25969
- org25969
- bridion

ClinicalTrialResults.org (Clinical Trial Results website), 2008/May: 30 May 2008
0 records were retrieved.

Each line searched separately:

- sugammadex
- org 25969
- org25969
- bridion

ICTRP, 2008/May: 30 May 2008
20 records were retrieved.

Each line searched separately:

- sugammadex
- org 25969
- org25969
- bridion

Internet sites searched

Websites were browsed (publication and research sections) and searched using a variety of combinations of the following terms: sugammadex, org 25969, org25969, bridion

- *MedlinePlus* www.nlm.nih.gov/medlineplus/medlineplus.html
- *intute* www.intute.ac.uk/
- *Royal College of Anaesthetists* www.rcoa.ac.uk/
- *Association of Anaesthetists of Great Britain and Ireland* www.aagbi.org/
- *Anaesthesia Research Trust* www.anaesthesiaresearch.org.uk/
- *American Society of Anesthesiologists (ASA)* www.asahq.org/
- *European Society of Anaesthesiology (ESA)* www.euroanesthesia.org/
- *World Federation of Societies of Anaesthesiologists* www.anaesthesiologists.org/
- *National Library for Health (NLH): Surgery, Theatres & Anaesthesia Specialist Library* www.library.nhs.uk/theatres/

Conference proceedings searched

Annual Meeting of the European Society of Anaesthesiology (Euroanaesthesia Congress)

- www.euroanesthesia.org/
- 2008 Copenhagen, Denmark.
- Previous conference abstracts available in the European Journal of Anaesthesiology:
  - 2007;24(Suppl. 39). Munich, Germany, 9–12 June 2007
  - 2006;23(Suppl. 37). Madrid, Spain, 3–6 June 2006
  - 2005;22(Suppl. 34). Vienna, Austria, 28–31 May 2005
  - 2004;21(Suppl. 32). Lisbon, Portugal, 5–8 June 2004.

American Society of Anesthesiologists Annual Meeting (2001–8)

- www.asaabstracts.com/strands/asaabstracts/home.htm
- Searchable archive available for meetings 2001–8.

Association of Anaesthetists of Great Britain & Ireland Annual Congress (2004–7)

- www.aagbi.org/
- Congress programmes available online. 2005 and 2006 congress 'free' abstracts available in *Anaesthesia* 2006;**61**(1):80–94, 2005;**60**(3):302–17.

World Federation of Societies of Anaesthesiologists

- www.anaesthesiologists.org/
- 14th World Congress of Anaesthesiologists (WCA). 2008 Cape Town, South Africa, 2–7 March 2008.

Search alerts

Search alerts were set up in MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and EMBASE to run every time the databases were updated (weekly).

Search alerts were also created in the following journals:

- *Anaesthesia*
- *British Journal of Anaesthesia*
- *European Journal of Anaesthesiology*
- *Anesthesia and Analgesia*

NMBAs and reversal agents search strategies

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OvidSP), 1950–2008/July week 1: 11 July 2008

1038 records were retrieved in MEDLINE and 243 in MEDLINE In-Process & Other Non-Indexed Citations.

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1–8
10. humans.sh.
11. 9 and 10
12. (letter or comment or editorial).pt.
13. 11 not 12
14. exp Neuromuscular Nondepolarizing Agents/

15. ((neuromuscular or neuro muscular) adj2 (block$or agent$)).ti,ab.
16. (nondepolarizing or non-depolarizing or non depolarizing or nondepolarising or non-depolarising or non depolarising).ti,ab.
17. rocuronium$.ti,ab,rn.
18. (esmeron$or zemuron$).ti,ab,rn.
19. Vecuronium Bromide/
20. vecuronium$.ti,ab,rn.
21. norcuron$.ti,ab,rn.
22. Atracurium/
23. atracurium$.ti,ab,rn.
24. tracrium$.ti,ab,rn.
25. cisatracurium$.ti,ab,rn.
26. nimbex$.ti,ab,rn.
27. mivacurium$.ti,ab,rn.
28. mivacron$.ti,ab,rn.
29. or/14–28
30. exp Cholinesterase Inhibitors/
31. (cholinesterase$inhibitor$or anticholinesterase$or anti-cholinesterase$or ac etylcholinesterase$inhibitor$).ti,ab.
32. Neostigmine/
33. neostigmine$.ti,ab,rn.
34. prostigmin$.ti,ab,rn.
35. (proserine$or prozerin$or synstigmin$or polstigmine$or syntostigmine$).ti,ab,rn.
36. (reverse or reverses or reversal or reversed or reversing or reversible).ti,ab.
37. or/30–36
38. Anesthesia Recovery Period/
39. (recover$adj3 an?esthes$).ti,ab.
40. (recover$adj3 (neuromuscular or block$)).ti,ab.
41. (recover$adj3 spontaneous).ti,ab.
42. ((neuromuscular or neuro muscular) adj3 antago$).ti,ab.
43. (muscle relax$adj3 antago$).ti,ab.
44. (residual paralysis or residual paresis).ti,ab.
45. (residual adj2 (neuromuscular or neuro muscular)).ti,ab.
46. residual curari$.ti,ab.
47. or/38–46
48. 13 and 29 and (37 or 47)

Trials filter Lefebvre C, Manheimer E, Glanville J. Searching for studies. In Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.0.0 (updated February 2008). The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org

EMBASE (OvidSP). 1980–2008/week 28: 11 July 2008

1318 records were retrieved.

1. random.tw.
2. clinical trial.mp.
3. exp Health Care Quality/
4. or/1–3
5. Animal/or Animal Experiment/or Nonhuman/
6. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.
7. 5 or 6
8. exp Human/or Human Experiment/
9. 7 not (7 and 8)
10. 4 not 9
11. exp Neuromuscular Blocking Agent/
12. ((neuromuscular or neuro muscular) adj2 (block$or agent$)).ti,ab.
13. (nondepolarizing or non-depolarizing or non depolarizing or nondepolarising or non-depolarising or non depolarising).ti,ab.
14. Rocuronium/
15. rocuronium$.ti,ab,rn.
16. (esmeron$or zemuron$).ti,ab,rn.
17. Vecuronium/
18. vecuronium$.ti,ab,rn.
19. norcuron$.ti,ab,rn.
20. Atracurium/
21. atracurium$.ti,ab,rn.
22. tracrium$.ti,ab,rn.
23. Cisatracurium/
24. cisatracurium$.ti,ab,rn.
25. nimbex$.ti,ab,rn.
26. Mivacurium/
27. mivacurium$.ti,ab,rn.
28. mivacron$.ti,ab,rn.
29. or/11–28
30. Cholinesterase Inhibitor/
31. (cholinesterase$inhibitor$or anticholinesterase$or anti-cholinesterase$or ac etylcholinesterase$inhibitor$).ti,ab.
32. Neostigmine/
33. neostigmine$.ti,ab,rn.
34. prostigmin$.ti,ab,rn.
35. (proserine$or prozerin$or synstigmin$or polstigmine$or syntostigmine$).ti,ab,rn.
36. (reverse or reverses or reversal or reversed or reversing or reversible).ti,ab.
37. or/30–36
38. Anesthetic Recovery/
39. (recover$adj3 an?esthes$).ti,ab.
40. (recover$adj3 (neuromuscular or block$)).ti,ab.
41. (recover$adj3 spontaneous).ti,ab.
42. ((neuromuscular or neuro muscular) adj3 antago$).ti,ab.
43. (muscle relax$adj3 antago$).ti,ab.
44. (residual paralysis or residual paresis).ti,ab.

45. (residual adj2 (neuromuscular or neuro muscular)).ti,ab.
46. residual curari$.ti,ab.
47. or/38–46
48. 10 and 29 and (37 or 47)
49. (letter or editorial).pt.
50. 48 not 49

Trials filter Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *J Med Libr Assoc* 2006;94(1):41–7.

CINAHL (OvidSp), 1982–2008/July week 1: 11 July 2008

17 records were retrieved.

1. exp prognosis/
2. exp study design/
3. random.mp.
4. or/1–3
5. (commentary or editorial or letter).pt.
6. 4 not 5
7. exp Neuromuscular Nondepolarizing Agents/
8. ((neuromuscular or neuro muscular) adj2 (block$or agent$)).ti,ab.
9. (nondepolarizing or non-depolarizing or non depolarizing or nondepolarising or non-depolarising or non depolarising).ti,ab.
10. rocuronium$.ti,ab.
11. (esmeron$or zemuron$).ti,ab.
12. Vecuronium Bromide/
13. vecuronium$.ti,ab.
14. norcuron$.ti,ab.
15. ATRACURIUM/
16. atracurium$.ti,ab.
17. tracrium$.ti,ab.
18. cisatracurium$.ti,ab.
19. nimbex$.ti,ab.
20. mivacurium$.ti,ab.
21. mivacron$.ti,ab.
22. or/10–21
23. exp Cholinesterase Inhibitors/
24. (cholinesterase$inhibitor$or anticholinesterase$or anti-cholinesterase$or ac etylcholinesterase$inhibitor$).ti,ab.
25. NEOSTIGMINE/
26. neostigmine$.ti,ab.
27. prostigmin$.ti,ab.
28. (proserine$or prozerin$or synstigmin$or polstigmine$or syntostigmine$).ti,ab.
29. (reverse or reverses or reversal or reversed or reversing or reversible).ti,ab.
30. or/23–29
31. Anesthesia Recovery/
32. (recover$adj3 an?esthes$).ti,ab.
33. (recover$adj3 (neuromuscular or block$)).ti,ab.
34. (recover$adj3 spontaneous).ti,ab.
35. ((neuromuscular or neuro muscular) adj3 antago$).ti,ab.
36. (muscle relax$adj3 antago$).ti,ab.
37. (residual paralysis or residual paresis).ti,ab.
38. (residual adj2 (neuromuscular or neuro muscular)).ti,ab.
39. residual curari$.ti,ab.
40. or/31–39
41. 6 and 22 and (30 or 40)

Trials filter McMaster University. Health Information Research Unit (HiRU). Evidence-Based Informatics. Hedges Project. Search strategies for CINAHL: therapy. http://hiru.mcmaster.ca/hiru/HIRU_Hedges_CINAHL_Strategies.aspx

Science Citation Index (Web of Science), 1900–2008/10 July 10: 11 July 2008

257 records were retrieved.

#1 TS = (clinical* SAME trial*)
#2 TS = (controlled SAME trial*) OR TS = (controlled SAME stud*)
#3 TS = (random OR randomisation OR randomization OR randomized or randomised)
#4 TS = (singl* or doubl* or tripl* or trebl*) SAME TS = (mask* or blind*)
#5 TS = placebo*
#6 #1 or #2 or #3 or #4 or #5
#7 TS = (neuromuscular or "neuro muscular") SAME TS = (block* or agent*)
#8 TS = (nondepolarizing or non-depolarizing or "non depolarizing" or nondepolarising or non-depolarising or "non depolarising")
#9 TS = (rocuronium* or esmeron* or zemuron*)
#10 TS = (vecuronium* or norcuron*)
#11 TS = (atracurium* or tracrium*)
#12 TS = (cisatracurium* or nimbex*)
#13 TS = (mivacurium* or mivacron*)
#14 #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 TS = ("cholinesterase* inhibitor*" or anticholinesterase* or anti-cholinesterase* or "acetylcholinesterase* inhibitor*")
#16 TS = (neostigmine* or prostigmin* or proserine* or prozerin* or synstigmin* or polstigmine* or syntostigmine*)
#17 TS = (reverse or reverses or reversal or reversed or reversing or reversible)
#18 #15 or #16 or #17
#19 TS = (recover* SAME anesthes*) or TS = (recover* SAME anaesthes*)

#20 TS = (recover*) SAME TS = (neuromuscular or block*)
#21 TS = (recover* SAME spontaneous)
#22 TS = (neuromuscular or "neuro muscular") SAME TS = (antago*)
#23 TS = ("muscle relax*") SAME TS = (antago*)
#24 TS = ("residual paralysis" or "residual paresis")
#25 TS = (residual) SAME TS = (neuromuscular or "neuro muscular")
#26 TS = ("residual curari*")
#27 #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28 #6 and #14 and (#18 or #27)
#29 TS = (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys)
#30 #28 not #29

ISI Proceedings: Science & Technology (Web of Science), 1990–2008/11 July: 11 July 2008

31 records were retrieved.

#1 TS = (clinical* SAME trial*)
#2 TS = (controlled SAME trial*) OR TS = (controlled SAME stud*)
#3 TS = (random OR randomisation OR randomization OR randomized or randomised)
#4 TS = (singl* or doubl* or tripl* or trebl*) SAME TS = (mask* or blind*)
#5 TS = placebo*
#6 #1 or #2 or #3 or #4 or #5
#7 TS = (neuromuscular or "neuro muscular") SAME TS = (block* or agent*)
#8 TS = (nondepolarizing or non-depolarizing or "non depolarizing" or nondepolarising or non-depolarising or "non depolarising")
#9 TS = (rocuronium* or esmeron* or zemuron*)
#10 TS = (vecuronium* or norcuron*)
#11 TS = (atracurium* or tracrium*)
#12 TS = (cisatracurium* or nimbex*)
#13 TS = (mivacurium* or mivacron*)
#14 #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 TS = ("cholinesterase* inhibitor*" or anticholinesterase* or anti-cholinesterase* or "acetylcholinesterase* inhibitor*")
#16 TS = (neostigmine* or prostigmin* or proserine* or prozerin* or synstigmin* or polstigmine* or syntostigmine*)
#17 TS = (reverse or reverses or reversal or reversed or reversing or reversible)
#18 #15 or #16 or #17
#19 TS = (recover* SAME anesthes*) or TS = (recover* SAME anaesthes*)
#20 TS = (recover*) SAME TS = (neuromuscular or block*)
#21 TS = (recover* SAME spontaneous)
#22 TS = (neuromuscular or "neuro muscular") SAME TS = (antago*)
#23 TS = ("muscle relax*") SAME TS = (antago*)
#24 TS = ("residual paralysis" or "residual paresis")
#25 TS = (residual) SAME TS = (neuromuscular or "neuro muscular")
#26 TS = ("residual curari*")
#27 #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28 #6 and #14 and (#18 or #27)
#29 TS = (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys)
#30 #28 not #29

CDSR and CENTRAL (Cochrane Library), 2008 – Issue 2: 11 July 2008

1 review was retrieved in CDSR and 855 records were retrieved in CENTRAL.

#1 MeSH descriptor Neuromuscular Nondepolarizing Agents explode all trees
#2 (neuromuscular or "neuro muscular") NEAR/2 (block* or agent*):ti,ab,kw
#3 (nondepolarizing or non-depolarizing or "non depolarizing" or nondepolarising or non-depolarising or "non depolarising"):ti,ab,kw
#4 (rocuronium* or esmeron* or zemuron*):ti,ab,kw
#5 MeSH descriptor Vecuronium Bromide explode all trees
#6 (vecuronium* or norcuron*):ti,ab,kw
#7 MeSH descriptor Atracurium explode all trees
#8 (atracurium* or tracrium*):ti,ab,kw
#9 (cisatracurium* or nimbex*):ti,ab,kw
#10 (mivacurium* or mivacron):ti,ab,kw
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 MeSH descriptor Cholinesterase Inhibitors explode all trees
#13 "cholinesterase* inhibitor*" or anticholinesterase* or anti-cholinesterase* or "acetylcholinesterase* inhibitor*":ti,ab,kw

#14 MeSH descriptor Neostigmine explode all trees
#15 (neostigmine* or prostigmin* or proserine* or prozerin* or synstigmin* or polstigmine* or syntostigmine*):ti,ab,kw
#16 (reverse or reverses or reversal or reversed or reversing or reversible):ti,ab,kw
#17 (#12 OR #13 OR #14 OR #15 OR #16)
#18 MeSH descriptor Anesthesia Recovery Period explode all trees
#19 (recover* NEAR/3 anesthes*) or (recover* NEAR/3 anaesthes*):ti,ab,kw
#20 (recover* NEAR/3 (neuromuscular or block*)):ti,ab,kw
#21 (recover* NEAR/3 spontaneous):ti,ab,kw
#22 (neuromuscular or "neuro muscular") NEAR/3 antago*:ti,ab,kw
#23 "muscle relax*" NEAR/3 antago*:ti,ab,kw
#24 "residual paralysis" or "residual paresis":ti,ab,kw
#25 (residual NEAR/2 (neuromuscular or "neuro muscular")):ti,ab,kw
#26 "residual curari*":ti,ab,kw
#27 (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
#28 (#11 AND (#17 OR #27))

DARE and HTA (Cochrane Library), 2008 – Issue 2: 11 July 2008

2 records were retrieved in DARE and 1 record was retrieved in HTA.

#1 MeSH descriptor Neuromuscular Nondepolarizing Agents explode all trees
#2 (neuromuscular or "neuro muscular") NEAR/2 (block* or agent*):ti,ab,kw
#3 (nondepolarizing or non-depolarizing or "non depolarizing" or nondepolarising or non-depolarising or "non depolarising"):ti,ab,kw
#4 (rocuronium* or esmeron* or zemuron*):ti,ab,kw
#5 MeSH descriptor Vecuronium Bromide explode all trees
#6 (vecuronium* or norcuron*):ti,ab,kw
#7 MeSH descriptor Atracurium explode all trees
#8 (atracurium* or tracrium*):ti,ab,kw
#9 (cisatracurium* or nimbex*):ti,ab,kw
#10 (mivacurium* or mivacron):ti,ab,kw
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 MeSH descriptor Cholinesterase Inhibitors explode all trees
#13 "cholinesterase* inhibitor*" or anticholinesterase* or anti-cholinesterase* or "acetylcholinesterase* inhibitor*":ti,ab,kw
#14 MeSH descriptor Neostigmine explode all trees
#15 (neostigmine* or prostigmin* or proserine* or prozerin* or synstigmin* or polstigmine* or syntostigmine*):ti,ab,kw
#16 (reverse or reverses or reversal or reversed or reversing or reversible):ti,ab,kw
#17 (#12 OR #13 OR #14 OR #15 OR #16)
#18 MeSH descriptor Anesthesia Recovery Period explode all trees
#19 (recover* NEAR/3 anesthes*) or (recover* NEAR/3 anaesthes*):ti,ab,kw
#20 (recover* NEAR/3 (neuromuscular or block*)):ti,ab,kw
#21 (recover* NEAR/3 spontaneous):ti,ab,kw
#22 (neuromuscular or "neuro muscular") NEAR/3 antago*:ti,ab,kw
#23 "muscle relax*" NEAR/3 antago*:ti,ab,kw
#24 "residual paralysis" or "residual paresis":ti,ab,kw
#25 (residual NEAR/2 (neuromuscular or "neuro muscular")):ti,ab,kw
#26 "residual curari*":ti,ab,kw
#27 (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
#28 (#11 AND (#17 OR #27))

BIOSIS (Dialog), 1926–2008/July week 1: 11 July 2008

186 records were retrieved.

- s clinical(2w)trial?
- s controlled(2w)(trial? or stud?)
- s random or randomi?ation or randomi?ed
- s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)
- s placebo?
- s (prospective(2w)stud?) or (comparative(2w)stud?)
- s phase(w)4 or phase(w)four or phase(w)IV
- s post(w)market?(w)surveillance
- s s1:s8
- s rocuronium or vecuronium or atracurium or cisatracurium or mivacurium
- s neostigmine
- s reverse or reverses or reversal or reversed or reversing or reversible
- s s11:s12
- s recover?(w3)anesthes? or recover?(w3)anaesthes?
- s recover?(w3)(neuromuscular or block?)
- s recover?(w3)spontaneous

- s (neuromuscular or neuro(w)muscular)(w3) antago?
- s muscle(w)relax?(w3)antago?
- s residual(w)paralysis or residual(w)paresis
- s residual(w2)(neuromuscular or neuro(w) muscular)
- s residual(w)curari?
- s s14:s21
- s s9 and s10 and (s13 or s22)
- s s23/HUMAN

Inside Conferences (Dialog), 1993–2008/9 July: 11 July 2008
3 records were retrieved.

- s clinical(2w)trial?
- s controlled(2w)(trial? or stud?)
- s random or randomi?ation or randomi?ed
- s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)
- s placebo?
- s (prospective(2w)stud?) or (comparative(2w) stud?)
- s phase(w)4 or phase(w)four or phase(w)IV
- s post(w)market?(w)surveillance
- s s1:s8
- s rocuronium or vecuronium or atracurium or cisatracurium or mivacurium
- s neostigmine
- s reverse or reverses or reversal or reversed or reversing or reversible
- s s11:s12
- s recover?(w3)anesthes? or recover?(w3) anaesthes?
- s recover?(w3)(neuromuscular or block?)
- s recover?(w3)spontaneous
- s (neuromuscular or neuro(w)muscular)(w3) antago?
- s muscle(w)relax?(w3)antago?
- s residual(w)paralysis or residual(w)paresis
- s residual(w2)(neuromuscular or neuro(w) muscular)
- s residual(w)curari?
- s s14:s21
- s s9 and s10 and (s13 or s22)
- s s23/HUMAN

ClinicalTrials.gov (US National Library of Medicine), 2008/August: 11 September 2008
46 records were retrieved.

Each line searched separately:

- rocuronium, esmeron, zemuron
- vecuronium, norcuron
- atracurium, tracrium
- cisatracurium, nimbex
- mivacurium, mivacron
- neostigmine, prostigmine, prostigmin
- glycopyrrolate, glycopyrronium.

current Controlled Trials (MetaRegister of Current Controlled Trials – mRCT), 2008/August: 11 September 2008
65 records were retrieved.

Each line searched separately:

- rocuronium, esmeron, zemuron
- vecuronium, norcuron
- atracurium, tracrium
- cisatracurium, nimbex
- mivacurium, mivacron
- neostigmine, prostigmine, prostigmin
- glycopyrrolate, glycopyrronium.

ClinicalStudyResults.org (ClinicalStudyResults website), 2008/August: 11 September 2008
0 records were retrieved.

Each line searched separately:

- rocuronium, esmeron, zemuron
- vecuronium, norcuron
- atracurium, tracrium
- cisatracurium, nimbex
- mivacurium, mivacron
- neostigmine, prostigmine, prostigmin
- glycopyrrolate, glycopyrronium.

ClinicalTrialResults.org (Clinical Trial Results website), 2008/August: 11 September 2008
0 records were retrieved.

Each line searched separately:

- rocuronium, esmeron, zemuron
- vecuronium, norcuron
- atracurium, tracrium
- cisatracurium, nimbex
- mivacurium, mivacron
- neostigmine, prostigmine, prostigmin
- glycopyrrolate, glycopyrronium.

International Clinical Trials Registry Platform (ICTRP), 2008/August: 12 September 2008

46 records were retrieved.

Each line searched separately:

- rocuronium, esmeron, zemuron
- vecuronium, norcuron
- atracurium, tracrium
- cisatracurium, nimbex
- mivacurium, mivacron
- neostigmine, prostigmine, prostigmin
- glycopyrrolate, glycopyrronium.

Adverse event search strategies

Adverse event information sources

- US Food and Drug Administration, Center for Drug Evaluation and Research (CDER)
  - www.fda.gov/cder/index.html
  - Index to Drug-Specific Information www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm
  - Drugs@FDA www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
- European Medicines Agency (EMEA) www.emea.europa.eu/
  - European Public Assessment Reports (EPARs).
- www.emea.europa.eu/htms/human/epar/eparintro.htm
- *British National Formulary* (BNF) 2008;55
  - http://bnf.org/bnf/
  - Non-depolarising neuromuscular blocking drugs.
- *Meyler's Side Effects of Drugs: The Encyclopedia of Adverse Reactions and Interactions*
  - Chapter 12: Neuromuscular blocking agents and skeletal muscle relaxants
  - Chapter 13: Drugs affecting autonomic functions or the extrapyramidal system. Agents with cholinergic effects (inc. Neostigmine)
  - Chapter 14: Dermatological drugs, topical agents and cosmetics. (inc. glycopyrrolate).
- *Meyler's Side Effects of Drugs Annual 27*
  - Chapter 12. Neuromuscular blocking agents and skeletal muscle relaxants.
- *Meyler's Side Effects of Drugs used in Anesthesia*
  - Neuromuscular blocking drugs and muscle relaxants.
- *Martindale: The Complete Drug Reference*
  - Neuromuscular blockers.
  - Antimyasthenics. Neostigmine.
  - Glycopyrronium Bromide.
- Medicines Compendium 2008
  - www.medicines.org.uk
- American Society of Hospital Pharmacists (ASHP). American Hospital Formulary Service (AHFS) drug information. Bethesda, MD: ASHP; 2008.
  - Neuromuscular blocking agents 12:20.20
  - Neostigmine bromide, neostigmine methylsulfate
  - Glycopyrrolate.

Adverse-event information database searches

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OvidSP), 1998–2008/October week 3: 23 October 2008

895 records were retrieved in MEDLINE and 132 in MEDLINE In-Process & Other Non-Indexed Citations.

1. exp *Neuromuscular Blocking Agents/ae [Adverse Effects]
2. rocuronium.mp. and ae.fs.
3. Vecuronium Bromide/ae [Adverse Effects]
4. Atracurium/ae [Adverse Effects]
5. cisatracurium.mp. and ae.fs.
6. mivacurium.mp. and ae.fs.
7. Neostigmine/ae [Adverse Effects]
8. Glycopyrrolate/ae [Adverse Effects]
9. Succinylcholine/ae [Adverse Effects]
10. or/1–9
11. exp *Neuromuscular Blocking Agents/
12. rocuronium.mp.
13. *Vecuronium Bromide/
14. *Atracurium/
15. cisatracurium.mp.
16. mivacurium.mp.
17. *Neostigmine/
18. glycopyrrolate.mp.
19. (succinylcholine or suxamethonium).mp.
20. or/11–19
21. (adverse or side effect$).ti,ab.
22. Flushing/or skin flush.ti,ab.
23. Erythema/or erythema$.ti,ab.
24. Pruritis/or (pruritis or pruritus or itching).ti,ab.
25. Urticaria/or (urticaria$or hives).ti,ab.
26. Respiratory Sounds/or Wheezing.ti,ab.
27. Hypotension/or hypotensi$.ti,ab.
28. Bronchial Spasm/or (bronchospasm$or bronchial spasm$).ti,ab.
29. Cyanosis/or (cyanosis or cyanoses).ti,ab.
30. Hypersensitivity/or (hypersensitivit$or allergy or allergies or allergic).ti,ab.
31. Heart Arrest/or (cardiac arrest or heart arrest or cardiopulmonary arrest or asystole$).ti,ab.

32. Seizures/or seizure$.ti,ab.
33. Anaphylaxis/or (anaphylaxis or anaphylactic or anaphylactoid).ti,ab.
34. Paralysis/or paralysis.ti,ab.
35. muscle pain.ti,ab.
36. (prolong$adj2 block$).ti,ab.
37. Intraocular Pressure/or (intraocular pressure$or ocular tension$).ti,ab.
38. Malignant Hyperthermia/or (malignant hyperthermia$or malignant hyperpyrexia$).ti,ab.
39. Hyperkalemia/or (hyperkalaemia$or hyperkalemia$or hyperpotassemia$).ti,ab.
40. Rhabdomyolysis/or (rhabdomyolysis or rhabdomyolyses).ti,ab.
41. Bradycardia/or (bradycardia$or bradyarrhythmia$).ti,ab.
42. "Postoperative Nausea and Vomiting"/or (postoperative adj (nausea or vomiting or emesis or emeses)).ti,ab.
43. or/21–42
44. 20 and 43
45. 10 or 44
46. humans/
47. 45 and 46
48. limit 47 to (english language and yr = "1998 – 2008")
49. (comment or news or editorial or letter).pt.
50. 48 not 49

MEDLINE In-Process & Other Non-Indexed Citations search strategy

1. (neuromuscular block$).mp
2. rocuronium.mp.
3. vecuronium.mp.
4. atracurium.mp.
5. cisatracurium.mp.
6. mivacurium.mp.
7. neostigmine.mp.
8. glycopyrrolate.mp.
9. (succinylcholine or suxamethonium).mp.
10. or/1–9
11. (adverse or side effect$).mp
12. (flushing or skin flush).mp
13. erythema$.mp
14. (pruritis or pruritus or itching).mp
15. (urticaria$or hives).mp
16. wheezing.mp
17. hypotensi$.mp
18. (bronchospasm$or bronchial spasm$).mp
19. (cyanosis or cyanoses).mp
20. (hypersensitivit$or allergy or allergies or allergic).mp
21. (cardiac arrest or heart arrest or cardiopulmonary arrest or asystole$).mp
22. seizure$.mp
23. (anaphylaxis or anaphylactic or anaphylactoid).mp
24. muscle pain.mp
25. (prolong$adj2 block$).mp
26. paralysis.mp
27. (intraocular pressure$or ocular tension$).mp
28. (malignant hyperthermia$or malignant hyperpyrexia$).mp
29. (hyperkalaemia$or hyperkalemia$or hyperpotassemia$).mp
30. (rhabdomyolysis or rhabdomyolyses).mp
31. (bradycardia$or bradyarrhythmia$).mp
32. (postoperative adj (nausea or vomiting or emesis or emeses)).mp
33. or/11–32
34. 10 and 33

EMBASE (OvidSP), 1998–2008/week 42: 23 October 2008

800 records were retrieved.

1. *Neuromuscular Blocking Agent/ae [Adverse Drug Reaction]
2. *ROCURONIUM/ae [Adverse Drug Reaction]
3. *VECURONIUM/ae [Adverse Drug Reaction]
4. *ATRACURIUM/ae [Adverse Drug Reaction]
5. *CISATRACURIUM/ae [Adverse Drug Reaction]
6. *MIVACURIUM/ae [Adverse Drug Reaction]
7. *NEOSTIGMINE/ae [Adverse Drug Reaction]
8. *Glycopyrronium Bromide/ae [Adverse Drug Reaction]
9. *Suxamethonium/ae [Adverse Drug Reaction]
10. or/1–9
11. exp *Neuromuscular Blocking Agent/
12. *ROCURONIUM/
13. *VECURONIUM/
14. *ATRACURIUM/
15. *CISATRACURIUM/
16. *MIVACURIUM/
17. *NEOSTIGMINE/
18. *Glycopyrronium Bromide/
19. *Suxamethonium/
20. or/11–19
21. Side Effect/or (adverse or side effect$).ti,ab.
22. Flushing/or skin flush.ti,ab.
23. Erythema/or erythema$.ti,ab.
24. Pruritis/or (pruritis or pruritus or itching).ti,ab.
25. Urticaria/or (urticaria$or hives).ti,ab.
26. Wheezing/or wheezing.ti,ab.
27. Hypotension/or hypotensi$.ti,ab.
28. Bronchospasm/or (bronchospasm$or bronchial spasm$).ti,ab.
29. Cyanosis/or (cyanosis or cyanoses).ti,ab.
30. Allergy/or (hypersensitivit$or allergy or allergies or allergic).ti,ab.

31. Heart Arrest/or (cardiac arrest or heart arrest or cardiopulmonary arrest or asystole$).ti,ab.
32. Seizures/
33. Seizure/or seizure$.ti,ab.
34. Anaphylaxis/or (anaphylaxis or anaphylactic or anaphylactoid).ti,ab.
35. muscle pain.ti,ab.
36. (prolong$adj2 block$).ti,ab.
37. Paralysis/or paralysis.ti,ab.
38. Intraocular Pressure/or (intraocular pressure$or ocular tension$).ti,ab.
39. Malignant Hyperthermia/or (malignant hyperthermia$or malignant hyperpyrexia$).ti,ab.
40. Hyperkalemia/or (hyperkalaemia$or hyperkalemia$or hyperpotassemia$).ti,ab.
41. Rhabdomyolysis/or (rhabdomyolysis or rhabdomyolyses).ti,ab.
42. Bradycardia/or (bradycardia$or bradyarrhythmia$).ti,ab.
43. Postoperative Nausea/or (postoperative adj (nausea or vomiting or emesis or emeses)).ti,ab.
44. or/21–43
45. 20 and 44
46. 10 or 45
47. Animal/or Animal Experiment/or Nonhuman/
48. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.
49. 47 or 48
50. exp Human/or Human Experiment/
51. 49 not (49 and 50)
52. 46 not 51
53. limit 52 to (english language and yr = "1998 – 2008")
54. (editorial or letter).pt.
55. 53 not 54

TOXLINE (TOXNET – US National Library of Medicine), 2008/23 October: 23 October 2008

559 records were retrieved.

#1 "neuromuscular blocking agents" [ti] AND 1998:2008 [yr] AND (eng [la])
#2 (rocuronium OR zemuron)[ti] AND 1998:2008 [yr] AND (eng [la])
#3 vecuronium [ti] AND 1998:2008 [yr] AND (eng [la])
#4 (atracurium)[ti] AND 1998:2008 [yr] AND (eng [la])
#5 (cisatracurium)[ti] AND 1998:2008 [yr] AND (eng [la])
#6 (mivacurium) [ti] AND 1998:2008 [yr] AND (eng [la])
#7 (neostigmine OR prostigmine OR prostigmin OR eustigmine OR eustigmin) [ti] AND 1998:2008 [yr] AND (eng [la])
#8 (glycopyrrolate OR robinul OR "robinul forte" OR "glycopyrronium bromide") [ti] AND 1998:2008 [yr] AND (eng [la])
#9 (succinylcholine OR "succinylcholine chloride" OR anectine OR quelicin OR "suxamethonium chloride" OR 71–27–2 [rn]) OR (suxamethonium OR 55–94–7 [rn])) [ti] AND 1998:2008 [yr] AND (eng [la])
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)

Economics search strategies

NMBA economic searches

NHS EED (Cochrane Library), 2008 – Issue 2: 14 August 2008

35 records were retrieved.

#1 MeSH descriptor Neuromuscular Nondepolarizing Agents explode all trees
#2 (neuromuscular or "neuro muscular") NEAR/2 (block* or agent*):ti,ab,kw
#3 (nondepolarizing or non-depolarizing or "non depolarizing" or nondepolarising or non-depolarising or "non depolarising"):ti,ab,kw
#4 (rocuronium* or esmeron* or zemuron*):ti,ab,kw
#5 MeSH descriptor Vecuronium Bromide explode all trees
#6 (vecuronium* or norcuron*):ti,ab,kw
#7 MeSH descriptor Atracurium explode all trees
#8 (atracurium* or tracrium*):ti,ab,kw
#9 (cisatracurium* or nimbex*):ti,ab,kw
#10 (mivacurium* or mivacron):ti,ab,kw
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)

HEED (Wiley online), 2008/July: 14 August 2008

39 records were retrieved.

- AX = (neuromuscular block) or (neuromuscular blocking) or (neuromuscular agent) or neuromuscular agents) or (neuro muscular block) or (neuro muscular blocking) or (neuro muscular agent) or (neuro muscular agents)
- AX = (nondepolarizing) or (non-depolarizing) or (non depolarizing) or (nondepolarising) or (non-depolarising) or (non depolarising)

- AX = (rocuronium or vecuronium or atracurium or cisatracurium or mivacurium)
- CS = 1 or 2 or 3

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OvidSP), 1950–2008/August week 1: 14 August 2008

176 records were retrieved in MEDLINE and 9 in MEDLINE In-Process & Other Non-Indexed Citations.

1. economics/
2. exp "costs and cost analysis"/
3. economics, dental/
4. exp "economics, hospital"/
5. economics, medical/
6. economics, nursing/
7. economics, pharmaceutical/
8. (economic$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.
9. (expenditure$not energy).tw.
10. (value adj1 money).tw.
11. budget$.tw.
12. or/1–11
13. ((energy or oxygen) adj cost).ti,ab.
14. (metabolic adj cost).ti,ab.
15. ((energy or oxygen) adj expenditure).ti,ab.
16. or/13–15
17. 12 not 16
18. humans.sh.
19. 17 and 18
20. (letter or comment or editorial).pt.
21. 19 not 20
22. exp Neuromuscular Nondepolarizing Agents/
23. ((neuromuscular or neuro muscular) adj2 (block$or agent$)).ti,ab.
24. (nondepolarizing or non-depolarizing or non depolarizing or nondepolarising or non-depolarising or non depolarising).ti,ab.
25. rocuronium$.ti,ab,rn.
26. (esmeron$or zemuron$).ti,ab,rn.
27. Vecuronium Bromide/
28. vecuronium$.ti,ab,rn.
29. norcuron$.ti,ab,rn.
30. Atracurium/
31. atracurium$.ti,ab,rn.
32. tracrium$.ti,ab,rn.
33. cisatracurium$.ti,ab,rn.
34. nimbex$.ti,ab,rn.
35. mivacurium$.ti,ab,rn.
36. mivacron$.ti,ab,rn.
37. or/22–36
38. 21 and 37

EMBASE (OvidSP), 1980–2008/week 32: 14 August 2008

179 records were retrieved.

1. Health Economics/
2. exp Economic Evaluation/
3. exp Health Care Cost/
4. exp PHARMACOECONOMICS/
5. or/1–4
6. (econom$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
7. (expenditure$not energy).ti,ab.
8. (value adj2 money).ti,ab.
9. budget$.ti,ab.
10. or/6–9
11. 5 or 10
12. (metabolic adj cost).ti,ab.
13. ((energy or oxygen) adj cost).ti,ab.
14. ((energy or oxygen) adj expenditure).ti,ab.
15. or/12–14
16. 11 not 15
17. editorial.pt.
18. note.pt.
19. letter.pt.
20. or/17–19
21. 16 not 20
22. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
23. exp animal/
24. Nonhuman/
25. or/22–24
26. exp human/
27. exp human experiment/
28. 26 or 27
29. 25 not (25 and 28)
30. 21 not 29
31. exp Neuromuscular Blocking Agent/
32. ((neuromuscular or neuro muscular) adj2 (block$or agent$)).ti,ab.
33. (nondepolarizing or non-depolarizing or non depolarizing or nondepolarising or non-depolarising or non depolarising).ti,ab.
34. Rocuronium/
35. rocuronium$.ti,ab,rn.
36. (esmeron$or zemuron$).ti,ab,rn.
37. Vecuronium/
38. vecuronium$.ti,ab,rn.
39. norcuron$.ti,ab,rn.
40. Atracurium/
41. atracurium$.ti,ab,rn.
42. tracrium$.ti,ab,rn.
43. Cisatracurium/
44. cisatracurium$.ti,ab,rn.
45. nimbex$.ti,ab,rn.

46. Mivacurium/
47. mivacurium$.ti,ab,rn.
48. mivacron$.ti,ab,rn.
49. or/31–48
50. Cholinesterase Inhibitor/
51. (cholinesterase$inhibitor$or anticholinesterase$or anti-cholinesterase$or ac etylcholinesterase$inhibitor$).ti,ab.
52. Neostigmine/
53. neostigmine$.ti,ab,rn.
54. prostigmin$.ti,ab,rn.
55. (proserine$or prozerin$or synstigmin$or polstigmine$or syntostigmine$).ti,ab,rn.
56. (reverse or reverses or reversal or reversed or reversing or reversible).ti,ab.
57. or/50–56
58. Anesthetic Recovery/
59. (recover$adj3 an?esthes$).ti,ab.
60. (recover$adj3 (neuromuscular or block$)).ti,ab.
61. (recover$adj3 spontaneous).ti,ab.
62. ((neuromuscular or neuro muscular) adj3 antago$).ti,ab.
63. (muscle relax$adj3 antago$).ti,ab.
64. (residual paralysis or residual paresis).ti,ab.
65. (residual adj2 (neuromuscular or neuro muscular)).ti,ab.
66. residual curari$.ti,ab.
67. or/58–66
68. 30 and 49 and (57 or 67)

CINAHL (OvidSP), 1982–2008/August week 2: 14 August 2008
4 records were retrieved.

1. exp "costs and cost analysis"/or "economic aspects of illness"/or "economic value of life"/or economics, pharmaceutical/
2. ((cost or costs or costed or costly or costing) adj (utilit$or benefit$or effective$or stud$or minimi$or analys$)).ti,ab.
3. (economic$or pharmacoeconomic$or price$or pricing).ti,ab.
4. (expenditure$not energy).ti,ab.
5. (value adj1 money).ti,ab.
6. budget$.ti,ab.
7. or/1–6
8. exp Neuromuscular Nondepolarizing Agents/
9. ((neuromuscular or neuro muscular) adj2 (block$or agent$)).ti,ab.
10. (nondepolarizing or non-depolarizing or non depolarizing or nondepolarising or non-depolarising or non depolarising).ti,ab.
11. rocuronium$.ti,ab.
12. (esmeron$or zemuron$).ti,ab.
13. Vecuronium Bromide/
14. vecuronium$.ti,ab.
15. norcuron$.ti,ab.
16. ATRACURIUM/
17. atracurium$.ti,ab.
18. tracrium$.ti,ab.
19. cisatracurium$.ti,ab.
20. nimbex$.ti,ab.
21. mivacurium$.ti,ab.
22. mivacron$.ti,ab.
23. or/11–22
24. 7 and 23

Science Citation Index (Web of Science), 1900–2008/9 August: 14 August 2008
163 records were retrieved.

#1 TS = (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
#2 TS = (value SAME money)
#3 TS = budget*
#4 TS = (expenditure* NOT energy)
#5 #1 OR #2 OR #3 OR #4
#6 TS = (neuromuscular or "neuro muscular") SAME TS = (block* or agent*)
#7 TS = (nondepolarizing or non-depolarizing or "non depolarizing" or nondepolarising or non-depolarising or "non depolarising")
#8 TS = (rocuronium* or esmeron* or zemuron*)
#9 TS = (vecuronium* or norcuron*)
#10 TS = (atracurium* or tracrium*)
#11 TS = (cisatracurium* or nimbex*)
#12 TS = (mivacurium* or mivacron*)
#13 #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 #5 AND #13

CENTRAL (Cochrane Library), 2008 – Issue 3: 14 August 2008
90 records were retrieved.

#1 MeSH descriptor Neuromuscular Nondepolarizing Agents explode all trees
#2 (neuromuscular or "neuro muscular") NEAR/2 (block* or agent*):ti,ab,kw
#3 (nondepolarizing or non-depolarizing or "non depolarizing" or nondepolarising or non-depolarising or "non depolarising"):ti,ab,kw
#4 (rocuronium* or esmeron* or zemuron*):ti,ab,kw
#5 MeSH descriptor Vecuronium Bromide explode all trees
#6 (vecuronium* or norcuron*):ti,ab,kw
#7 MeSH descriptor Atracurium explode all trees
#8 (atracurium* or tracrium*):ti,ab,kw
#9 (cisatracurium* or nimbex*):ti,ab,kw
#10 (mivacurium* or mivacron):ti,ab,kw

#11 (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
#12 MeSH descriptor Economics, this term only
#13 MeSH descriptor Costs and Cost Analysis explode all trees
#14 MeSH descriptor Economics, Medical explode all trees
#15 MeSH descriptor Economics, Pharmaceutical explode all trees
#16 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*):ti,ab,kw
#17 (expenditure* not energy):ti,ab,kw
#18 (value NEAR/3 money):ti,ab,kw
#19 (budget*):ti,ab,kw
#20 (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#11 AND #20)

ISI Proceedings: Science & Technology (Web of Science), 1990–2008/9 August: 14 August 2008
22 records were retrieved.

#1 TS = (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
#2 TS = (value SAME money)
#3 TS = budget*
#4 TS = (expenditure* NOT energy)
#5 #1 OR #2 OR #3 OR #4
#6 TS = (neuromuscular or "neuro muscular") SAME TS = (block* or agent*)
#7 TS = (nondepolarizing or non-depolarizing or "non depolarizing" or nondepolarising or non-depolarising or "non depolarising")
#8 TS = (rocuronium* or esmeron* or zemuron*)
#9 TS = (vecuronium* or norcuron*)
#10 TS = (atracurium* or tracrium*)
#11 TS = (cisatracurium* or nimbex*)
#12 TS = (mivacurium* or mivacron*)
#13 #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 #5 AND #13

Economic model: MEDLINE search strategies

Anaesthesia-controlled time: UK specific studies (line 20) and non-UK economic studies (line 38)

1. exp anesthesia/
2. Anesthesiology/
3. 1 or 2
4. "time and motion studies"/
5. Time Management/
6. "Appointments and Schedules"/
7. Workload/
8. or/4–7
9. 3 and 8
10. (an?esth$adj3 (time$or duration or schedul$)).ti,ab.
11. (an?esth$adj3 (turnover$or throughput or quick$or fast$or rapid$or short$)).ti,ab.
12. (an?esth$adj3 (workload or work load or productivity)).ti,ab.
13. or/10–12
14. 9 or 13
15. humans/
16. 14 and 15
17. exp Great Britain/
18. (united kingdom or great britain or uk or england or wales or Scotland or Ireland).ti,ab,in.
19. 17 or 18
20. 16 and 19
21. economics/
22. exp "costs and cost analysis"/
23. economics, dental/
24. exp "economics, hospital"/
25. economics, medical/
26. economics, nursing/
27. economics, pharmaceutical/
28. (economic$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
29. (expenditure$not energy).ti,ab.
30. (value adj1 money).ti,ab.
31. budget$.ti,ab.
32. or/25–31
33. ((energy or oxygen) adj cost).ti,ab.
34. (metabolic adj cost).ti,ab.
35. ((energy or oxygen) adj expenditure).ti,ab.
36. or/33–35
37. 32 not 36
38. 16 and 37

TOF/NMBAs and utility values

1. exp Neuromuscular Nondepolarizing Agents/
2. ((neuromuscular or neuro muscular) adj2 (block$or agent$)).ti,ab.
3. (nondepolarizing or non-depolarizing or non depolarizing or nondepolarising or non-depolarising or non depolarising).ti,ab.
4. rocuronium$.ti,ab,rn.
5. (esmeron$or zemuron$).ti,ab,rn.
6. Vecuronium Bromide/
7. vecuronium$.ti,ab,rn.
8. norcuron$.ti,ab,rn.
9. Atracurium/
10. atracurium$.ti,ab,rn.
11. tracrium$.ti,ab,rn.
12. cisatracurium$.ti,ab,rn.
13. nimbex$.ti,ab,rn.

14. mivacurium$.ti,ab,rn.
15. mivacron$.ti,ab,rn.
16. or/1–15
17. Anesthesia Recovery Period/
18. (recover$adj3 an?esthes$).ti,ab.
19. (recover$adj3 (neuromuscular or block$)).ti,ab.
20. (recover$adj3 spontaneous).ti,ab.
21. (residual adj2 block$).ti,ab.
22. (residual paralysis or residual paresis).ti,ab.
23. (residual adj2 (neuromuscular or neuro muscular)).ti,ab.
24. residual curari$.ti,ab.
25. or/17–24
26. train-of-four.ti,ab.
27. TOF.ti,ab.
28. 27 or 26
29. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
30. (multiattribute$health or multi attribute$health).ti,ab.
31. (health utilit$index or health utilit$indices).ti,ab.
32. (multiattribute$theor$or multi attribute$theor$or multiattribute$analys$or multi attribute$analys$).ti,ab.
33. (health utilit$scale$or classification of illness state$).ti,ab.
34. health state$utilit$.ti,ab.
35. (multiattribute$utilit$or multi attribute$utilit$).ti,ab.
36. health utilit$scale$.ti,ab.
37. (euro qual or eruo qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
38. (sf36 or sf 36).ti,ab.
39. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
40. (sf 6d or sf6d or short form 6d or shortform 6d or sf six$or shortform six$or short form six$).ti,ab.
41. hrqol.ti,ab.
42. hrql.ti,ab.
43. (health related quality adj2 life$).ti,ab.
44. or/29–43
45. 25 or 28 or 16
46. 45 and 44

Overlapping induction

1. (overlap$adj3 induction$).ti,ab.
2. (overlap$adj3 an?esth$).ti,ab.
3. 1 or 2
4. exp Great Britain/
5. (united kingdom or great britain or uk or england or wales or Scotland or Ireland).ti,ab,in.
6. 4 or 5
7. 6 and 3

Rapid intubation mortality rates

1. Intubation, Intratracheal/mo
2. Intubation, Intratracheal/and (Mortality/or Death/)
3. 1 or 2
4. (rapid intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
5. (rapid sequence intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
6. (rapid induction and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
7. (rapid sequence induction and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
8. (RSI and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
9. (emergency intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
10. (emergency sequence intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
11. (emergency induction and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
12. (emergency sequence induction and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
13. (early intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
14. (early sequence intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
15. (early induction and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
16. (early sequence induction and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
17. (crash intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
18. (crash sequence intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
19. (crash induction and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
20. (crash sequence induction and (mortality or mortalities or death or fatality or fatalities)).ti,ab.

21. (emergency airway manag$and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
22. (emergency tracheal intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
23. (rapid tracheal intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
24. (emergency endotracheal intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
25. (rapid endotracheal intubation and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
26. (emergency tracheostomy and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
27. (rapid tracheostomy and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
28. (early tracheostomy and (mortality or mortalities or death or fatality or fatalities)).ti,ab.
29. or/3–28
30. Humans/
31. 29 and 30
32. (letter or comment or editorial).pt.
33. 31 not 32
34. exp Anesthesia/mo [Mortality]
35. Succinylcholine/and (exp Mortality/or exp Death/)
36. 30 and (34 or 35)
37. 36 not 32
38. 33 or 37

Appendix 2
Excluded studies

Excluded sugammadex studies – no relevant comparison

- Study 19.4.203.
- Study 19.4.204.
- Study 19.4.210.
- Study 19.4.311.
- Study 19.4.312.

Not a randomised trial or sugammadex study

Abeysekera A, Bergman IJ, Kluger MT, Short TG. (2005) Drug error in anaesthetic practice: A review of 896 reports from the Australian Incident Monitoring Study database. *Anaesthesia*, 60, 220–7.

Baillard C, Gehan G, Reboul-Marty J, Larmignat P, Samama CM, Cupa M. (2000) Residual curarization in the recovery room after vecuronium. *British Journal of Anaesthesia*, 84, 394–5.

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Balcioglu YO, Bilgin TE, Kocaoglu Y, Unlugenc H, Isik G. (1999) [The neuromuscular effects of rocuronium. Vecuronium and succinylcholine in cesarean section patients.] *Turk Anesteziyoloji ve Reanimasyon*, 27, 474–9.

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Baxter MR, Bevan JC, Samuel J, Donati F, Bevan DR. (1991) Postoperative neuromuscular function in pediatric day-care patients. *Anesthesia & Analgesia*, 72, 504–8.

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Choi WW, Mehta MP, Murray DJ, Sokoll MD, Forbes RB, Gergis SD, Abou-Donia M, Kirchner J. (1989) Neuromuscular and cardiovascular effects of mivacurium chloride in surgical patients receiving nitrous oxide-narcotic or nitrous oxide-isoflurane anaesthesia. *Canadian Journal of Anaesthesia*, 36, 641–50.

Claudius C, Skovgaard LT, Viby-Mogensen, J. A comparison of acceleromyography and mechanomyography for establishing dose response relationships [abstract].

Debaene B, Plaud B, Dilly M, Donati F. (2003) Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. *Anesthesiology*, 98, 1042–8.

D'Honneur G, Guignard B, Slavov V, Ruggier R, Duvaldestin P. (1995) Comparison of the neuromuscular blocking effect of atracurium and vecuronium on the adductor pollicis and the geniohyoid muscle in humans. *Anesthesiology*, 82, 649–54.

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Hunter JM, Jones RS, Utting JE. (1984) Comparison of vecuronium, atracurium and tubocurarine in normal patients and in patients with no renal function. *British Journal of Anaesthesia*, 56, 941–51.

Jones JE, Parker CJ, Hunter JM. (1988) Antagonism of blockade produced by atracurium or vecuronium with low doses of neostigmine. *British Journal of Anaesthesia*, 61, 560–4.

Khuenl-Brady KS, Pomaroli A, Puhringer F, Mitterschiffthaler G, Koller J. (1993) The use of rocuronium (ORG 9426) in patients with chronic renal failure. *Anaesthesia*, 48, 873–5.

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Study 19.4.208A – author not found.

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Appendix 3
Data extraction tables

Appendix 3.1 Sugammadex trials

Amao (2007): Sugammadex safely reverses rocuronium-induced blockade in patients with pulmonary disease (abstract)[53]	
Study publications	Amao 2007;[53] Muendel 2007[99]
Country	USA
Indication(s)	Reversal of moderate block
Number of patients	86 patients randomised
Age of population	Not reported (all patients aged 18 years or more)
Gender	Not reported
ASA Physical Status	Not reported (all patients were in ASA classes II–III)
Weight	Not reported
Comorbid disease	Other (all patients had a diagnosis or known history of pulmonary disease)
Type of surgical procedure	Not reported
Type of anaesthesia (induction)	Other (not specified to allow for routine anaesthetic practices)
Type of anaesthesia (maintenance)	Other (not specified to allow for routine anaesthetic practices)
Nitrous oxide	Not reported
Type of analgesic	Not reported
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	Not reported
Number of patients treated	39
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	Not reported
Number of patients treated	38
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo was administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable

From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	Yes (AEs reported)
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Clinical evidence of residual blockade or recurrence of blockade
Numbers with residual paralysis per group	None
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No (all patients had pulmonary disease)
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Not reported
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	Unclear
Were treatment groups comparable?	Unclear
Were all patients accounted for at the end of the study?	Unclear

Blobner (2007): Sugammadex (2.0 mg/kg) significantly faster reverses shallow rocuronium-induced neuromuscular blockade compared with neostigmine (50 μg/kg) (abstract)[30,56]	
Study publications	Blobner 2007;[30] Alvarez-Gomez 2007[56]
Country	Multinational
Indication(s)	Reversal of moderate block
Number of patients	196 (196 randomised, 189 treated, 185 completed) EMEA report has 198 randomised, 189 treated, 189 in ITT group, 177 in per-protocol group
Age of population	Mean 49–50 years (range 18–83 years)
Gender	102/189 (54%) male
ASA Physical Status	Not reported (all were ASA classes I–III)
Weight	Not reported
Comorbid disease	Not reported
Type of surgical procedure	Not reported (surgery in a supine position)
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Sevoflurane
Nitrous oxide	Not reported
Type of analgesic	Not reported
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	49
Number of patients treated	48
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	49
Number of patients treated	48
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.05 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Glycopyrrolate: 0.01 mg/kg
Treatment group 3	
Number of patients randomised	51
Number of patients treated	48
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable

Treatment group 4	
Number of patients randomised	49
Number of patients treated	45
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.05 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Glycopyrrolate: 0.01 mg/kg
From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	Yes (AEs reported)
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Clinical signs of residual or recurarisation
Numbers with residual paralysis per group	None
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	ITT ITT population comprised all patients who received sugammadex or neostigmine and had at least one efficacy assessment
Was allocation of treatment concealed?	Yes (central randomisation system)
Was the method used to assign participants to treatment groups truly random?	Yes (numbers assigned via central randomisation system)
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear (person who administered study drug was unblinded; safety assessors during anaesthesia were 'kept blind as long as possible')
Was power calculation reported?	Yes (sample size of 46 per group to have 95% power to detect a 5-minute difference in mean recovery time between sugammadex and neostigmine)
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Dahl (2007): Reversal of rocuronium-induced neuromuscular blockade by sugammadex in cardiac patients (abstract)[54]	
Study publication	Dahl 2007[54]
Country	Multinational (Europe)
Indication(s)	Reversal of moderate block
Number of patients	121
Age of population	Range 36–90 years
Gender	Not reported
ASA Physical Status	Not reported (patients were in ASA classes II–IV)
Weight	Not reported
Comorbid disease	All patients had cardiac disease
Type of surgical procedure	Elective non-cardiac surgery
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	Not reported
Type of analgesic	Not reported
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	Not reported
Number of patients treated	38
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	Not reported
Number of patients treated	38
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	Not reported
Number of patients treated	40
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Reappearance of T2

What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	Yes (AEs reported)
Was residual paralysis reported?	No
How was residual paralysis defined?	Not applicable
Numbers with residual paralysis per group	Not applicable
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No All patients had cardiac disease
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Not reported
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	Unclear
Were treatment groups comparable?	Unclear
Were all patients accounted for at the end of the study?	Unclear

De Boer (2007): Reversal of rocuronium-induced (1.2 mg/kg) profound neuromuscular block by sugammadex: a multicenter, dose-finding and safety study[40,100]	
Study publications	de Boer 2007;[40] de Boer 2005[99]
Country	The Netherlands
Indication(s)	Reversal of deep block Immediate/rapid reversal
Number of patients	45 (43 treated patients in FDA submission[23])
Age of population	Mean 42 years (SD 15) (43 patients)
Gender	22/43 (51%) male
ASA Physical Status	ASA I: 32/43 (74%) ASA II: 11/43 (26%)
Weight	Mean 76 kg (SD 18)
Comorbid disease	Not reported
Type of surgical procedure	Surgery in the supine position, lasting 90 minutes or longer
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	Not reported
Type of analgesic	Remifentanil Opioid (unspecified)
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	5
Number of patients treated	5
NMBA used and dose	Rocuronium: 1.2 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 2mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA 5 minutes after administration of rocuronium
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	5
Number of patients treated	5
NMBA used and dose	Rocuronium: 1.2 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA 5 minutes after administration of rocuronium
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	12
Number of patients treated	12
NMBA used and dose	Rocuronium: 1.2 mg/kg
Mode of administration	Bolus

Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 8 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA 5 minutes after administration of rocuronium
Antimuscarinic agent used	Not applicable
Treatment group 4	
Number of patients randomised	8
Number of patients treated	7
NMBA used and dose	Rocuronium: 1.2 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 16 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA 5 minutes after administration of rocuronium
Antimuscarinic agent used	Not applicable
Treatment group 5	
Number of patients randomised	6
Number of patients treated	4
NMBA used and dose	Rocuronium: 1.2 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Placebo: 0.9% saline
When was reversal agent or placebo administered?	Set time after administration of NMBA 5 minutes after administration of rocuronium
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Start of administration of sugammadex or placebo
What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	Yes: AEs reported
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Residual NMB and recurrence of NMB, defined as a relapse into a lower TOF ratio, or as deterioration in clinical signs attributed to NMB
Numbers with residual paralysis per group	None
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Per protocol
Was allocation of treatment concealed?	Yes

Was the method used to assign participants to treatment groups truly random?	Yes
Was the assessment of outcomes conducted blind to treatment allocation?	Yes, safety assessor blinded
Was power calculation reported?	No
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Duvaldestin (2007): Sugammadex achieves fast recovery from profound neuromuscular blockade induced by rocuronium or vecuronium: a dose-response study (abstract)[35]	
Study publication	Duvaldestin 2007[35]
Country	France
Indication(s)	Reversal of deep block
Number of patients	102 (101 treated patients in FDA submission[23])
Age of population	Range 21–64 years
Gender	Not reported
ASA Physical Status	Not reported (all were ASA classes I–III)
Weight	Not reported
Comorbid disease	Not reported
Type of surgical procedure	Not reported
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Sevoflurane
Nitrous oxide	Not reported
Type of analgesic	Not reported
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	Not reported
Number of patients treated	10
NMBA used and dose	Rocuronium: 0.9 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	PTC 1–2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	Not reported
Number of patients treated	10
NMBA used and dose	Rocuronium: 0.9 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	PTC 1–2
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	Not reported
Number of patients treated	11
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	PTC 1–2
Antimuscarinic agent used	Not applicable

Treatment group 4	
Number of patients randomised	Not reported
Number of patients treated	8
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	PTC 1–2
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	PTC 1–2
What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	Yes (AEs reported)
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Decrease of TOF ratio from >0.9 to <0.8
Numbers with residual paralysis per group	None in licensed-dose groups (4 in patients treated with sugammadex 0.5 or 1 mg/kg)
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Per protocol
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	Unclear
Were treatment groups comparable?	Unclear
Were all patients accounted for at the end of the study?	Unclear

Flockton (2008): Reversal of rocuronium-induced neuromuscular block with sugammadex is faster than reversal of cisatracurium-induced block with neostigmine[29]	
Study publications	Flockton 2008;[29] Flockton 2007[101]
Country	Multinational (Europe)
Indication(s)	Reversal of moderate block
Number of patients	84
Age of population	Mean 45 years (calculated)
Gender	37/73 (41%) male
ASA Physical Status	ASA I: 34/73 (47%) ASA II: 36/73 (49%) ASA III: 3/73 (4%)
Weight	Mean 75 kg (calculated)
Comorbid disease	Not reported
Type of surgical procedure	Surgery in the supine position, requiring muscle relaxation
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	Not reported
Type of analgesic	Remifentanil, fentanyl, sufentanil
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	40
Number of patients treated	34
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	44
Number of patients treated	39
NMBA used and dose	Cisatracurium: 0.15 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.05 mg/kg (maximum of 5 mg)
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Glycopyrrolate: 0.01 mg/kg
From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.9 Time to recovery of TOF 0.8 Time to recovery of TOF 0.7
Were clinical outcomes reported?	Yes [clinical signs of recovery (level of consciousness, cooperative, able to perform 5-second head-lift, general muscle weakness) and AEs reported]
Was residual paralysis reported?	Yes

How was residual paralysis defined?	Inadequate recovery or re-occurrence of block (a decrease in TOF to < 0.8) until the end of anaesthesia
Numbers with residual paralysis per group	None
Was mortality reported?	Yes
Numbers of deaths per group	None
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	ITT
Was allocation of treatment concealed?	Yes
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Yes
Was power calculation reported?	Yes
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Jones (2007): Faster reversal of profound rocuronium-induced neuromuscular blockade with sugammadex vs neostigmine (abstract)[36–38]	
Study publications	Jones 2007;[36] Lemmens 2007;[37] Jones 2008[38]
Country	USA
Indication(s)	Reversal of deep block
Number of patients	187 (187 randomised, 157 treated)
Age of population	Not reported (adults aged ≥ 18 years)
Gender	Not reported
ASA Physical Status	Not reported (all were ASA classes I–III)
Weight	Not reported
Comorbid disease	Not reported
Type of surgical procedure	Not reported (surgery in the supine position)
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Sevoflurane
Nitrous oxide	Not reported
Type of analgesic	Intravenous opioid (not specified)
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	48
Number of patients treated	37
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	1–2 PTC
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	40
Number of patients treated	37
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.07 mg/kg
When was reversal agent or placebo administered?	1–2 PTC
Antimuscarinic agent used	Glycopyrrolate: 0.014 mg/kg
Treatment group 3	
Number of patients randomised	Not reported
Number of patients treated	47
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	1–2 PTC
Antimuscarinic agent used	Not applicable

Treatment group 4	
Number of patients randomised	Not reported
Number of patients treated	36
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.07 mg/kg
When was reversal agent or placebo administered?	1–2 PTC
Antimuscarinic agent used	Glycopyrrolate: 0.014 mg/kg
From when were outcomes measured?	1–2 PTC
What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	Yes (AEs reported)
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Clinical evidence of residual blockade or recurrence of blockade
Numbers with residual paralysis per group	None
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	ITT
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	No (safety assessors were blinded)
Was power calculation reported?	Yes
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Lee (2007): Reversal of profound rocuronium NMB with sugammadex is faster than recovery from succinylcholine (abstract)[41] Subsequently published in full by Lee *et al.* 2009[58]	
Study publication	Lee 2007[41]
Country	USA
Indication(s)	Immediate/rapid reversal
Number of patients	115 randomised
Age of population	Mean 42 years (range 18–65 years)
Gender	42% male (46/110 calculated)
ASA Physical Status	ASA II: 40/110 calculated (41% rocuronium + sugammadex group; 31% succinylcholine group)
Weight	Not reported [mean BMI 25 kg/m^2 (SD 3)]
Comorbid disease	Not reported
Type of surgical procedure	Surgical procedure Elective surgery requiring short duration of muscle relaxation
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	Not reported
Type of analgesic	Not reported
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	57
Number of patients treated	56 (55 included in ITT analysis according to randomised treatment group) One patient randomised to rocuronium + sugammadex received succinylcholine, and two patients randomised to succinylcholine received rocuronium + sugammadex
NMBA used and dose	Rocuronium: 1.2 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 16 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA 3 minutes after start of rocuronium administration
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	58
Number of patients treated	54 (55 included in ITT analysis according to randomised treatment group) One patient randomised to rocuronium + sugammadex received succinylcholine, and two patients randomised to succinylcholine received rocuronium + sugammadex
NMBA used and dose	Succinylcholine 1 mg/kg
Mode of administration	Not reported
Maintenance doses allowed/used	No
Reversal agent used and dose	None (spontaneous recovery)
When was reversal agent or placebo administered?	Not applicable
Antimuscarinic agent used	Not applicable

Outcomes (Recovery of TOF)	
From when were outcomes measured?	Other [start of NMBA administration (both groups); start of reversal agent administration (sugammadex group only)]
What outcomes were reported?	Time to recovery of TOF 0.9 (sugammadex group only) Time to recovery of TOF 0.8 (sugammadex group only) Time to recovery of TOF 0.7 (sugammadex group only) Time to recovery of T1 0.1 Time to recovery of T1 0.9
Were clinical outcomes reported?	Yes [AEs reported (clinical signs of recovery reported in FDA document)]
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Clinical evidence or decline of T4/T1 ratio
Numbers with residual paralysis per group	None in either group with clinical evidence of recurarisation or residual curarisation; one patient in the rocuronium + sugammadex group had recurarisation based on TOF monitoring
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Quality of Recovery questionnaire (no results reported)[12]
Baseline scores	Not reported
Follow-up scores	Not reported
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	ITT Included all randomised patients with at least one post-baseline efficacy evaluation. The three patients who received the wrong trial medication were included under the treatment group to which they were randomised[10].
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear (some of the other phase III trials used a central randomisation system but this was not explicitly reported for study 19.4.303)
Was the assessment of outcomes conducted blind to treatment allocation?	Yes [safety assessors blinded (the person who prepared the medication was not to perform any subjective safety assessments and the safety assessor was not allowed to witness the preparation of the study medication)[10]]
Was power calculation reported?	Yes (described in EMEA assessment report[10])
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

McDonagh (2007): Efficacy and safety of sugammadex for reversal of rocuronium-induced blockade in elderly patients (abstract)[55]	
Study publication	McDonagh 2007[55]
Country	USA
Indication(s)	Reversal of moderate block
Number of patients	162
Age of population	Range 18 to >75 years
Gender	Not reported
ASA Physical Status	Not reported (ASA classes I–III, no further details)
Weight	Not reported
Comorbid disease	Not reported
Type of surgical procedure	Surgery with general anaesthesia requiring the use of rocuronium
Type of anaesthesia (induction)	Other (not specified to allow for routine anaesthetic practice)
Type of anaesthesia (maintenance)	Other (not specified to allow for routine anaesthetic practice)
Nitrous oxide	Not reported
Type of analgesic	Not reported
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	Not applicable
Number of patients treated	150 [48 adults (aged 18–64), 62 elderly (aged 65–74), 40 old elderly (aged 75 years or older)]
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	Yes (AEs reported)
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Clinical evidence of recurarisation or residual curarisation
Numbers with residual paralysis per group	0/150
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable

Subgroup analyses reported	Other (analysis by age group)
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	ITT (defined as patients who were treated and had at least one post-baseline efficacy assessment)
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	Unclear
Were treatment groups comparable?	Unclear
Were all patients accounted for at the end of the study?	Unclear

Plaud (2007). Reversal of rocuronium-induced neuromuscular blockade with sugammadex in paediatric and adult patients (abstract)[52]	
Study publication	Plaud 2007[52]
Country	France
Indication(s)	Reversal of moderate block
Number of patients	91 (8 infants, 24 children, 31 adolescents, 28 adults)
Age of population	Not reported
Gender	Not reported
ASA Physical Status	Not reported (all were ASA classes I–II)
Weight	Not reported
Comorbid disease	Not reported
Type of surgical procedure	Not reported
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	Not reported
Type of analgesic	Other [opioids (unspecified) or caudal analgesia (infants)]
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	Not reported
Number of patients treated	16 (1 infant, 4 children, 6 adolescents, 5 adults)
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Not reported
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	Not reported
Number of patients treated	16 (1 infant, 4 children, 6 adolescents, 5 adults)
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Not reported
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	Not reported
Number of patients treated	13 (2 infants, 4 children, 5 adolescents, 2 adults)
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Not reported
Maintenance doses allowed/used	No
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	Reappearance of T2

Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	Yes (AEs reported)
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Recurrence of NMB (not defined)
Numbers with residual paralysis per group	None
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	Other (outcomes reported by age group)
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Per protocol
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	Unclear
Were treatment groups comparable?	Unclear
Were all patients accounted for at the end of the study?	Unclear

Puhringer (2007): Sugammadex achieves fast recovery from shallow neuromuscular blockade induced by rocuronium or vecuronium: dose–response studies (abstract)[50]	
Study publication	Puhringer 2007[50]
Country	Not reported
Indication(s)	Reversal of moderate block
Number of patients	100 (98 treated patients in FDA submission[23])
Age of population	Not reported
Gender	Not reported
ASA Physical Status	Not reported
Weight	Not reported
Comorbid disease	Not reported
Type of surgical procedure	Not reported
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Sevoflurane
Nitrous oxide	Not reported
Type of analgesic	Fentanyl
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	10?
Number of patients treated	9
NMBA used and dose	Rocuronium: 0.9 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	10?
Number of patients treated	8
NMBA used and dose	Rocuronium: 0.9 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	10?
Number of patients treated	7
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 4	
Number of patients randomised	10?
Number of patients treated	9

NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 5	
Number of patients randomised	10
Number of patients treated	7
NMBA used and dose	Rocuronium: 0.9 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 6	
Number of patients randomised	10?
Number of patients treated	8
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	Yes (AEs reported)
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Recurarisation (decrease of TOF ratio from >0.9 to <0.8) or residual curarisation
Numbers with residual paralysis per group	Total 7/83 participants (unclear which groups – mainly in the 0.5-mg/kg group)
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	Unclear
Were treatment groups comparable?	Unclear
Were all patients accounted for at the end of the study?	Unclear

Puhringer (2008): Reversal of profound, high-dose rocuronium-induced neuromuscular blockade by sugammadex at two different time points: an international, multicenter, randomized, dose-finding, safety assessor-blinded, phase II trial[34,102,103]	
Study publications	Puhringer 2008;[34] Rex 2005;[103] Khuenl-Brady 2005[102]
Country	Multinational
Indication(s)	Reversal of deep block Immediate/rapid reversal
Number of patients	176 (173 treated patients in FDA submission[23])
Age of population	Mean 50 years (SD 16)
Gender	93/173 males (54%)
ASA Physical Status	ASA I: 66/173 (38%) ASA II: 88/173 (51%) ASA III: 19/173 (11%)
Weight	Mean 77 kg (SD 15)
Comorbid disease	Not reported
Type of surgical procedure	Surgery lasting for 120 minutes or more in the supine position
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	Not reported
Type of analgesic	Intravenous opioid (selected by anaesthetist)
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	32?
Number of patients treated	31
NMBA used and dose	Rocuronium: 1 mg/kg and 1.2 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA At 3 or 15 minutes after administration of rocuronium
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	32?
Number of patients treated	28
NMBA used and dose	Rocuronium: 1.0 or 1.2 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA At 3 or 15 minutes after administration of rocuronium
Antimuscarinic agent used	Not applicable

Treatment group 3	
Number of patients randomised	32?
Number of patients treated	32
NMBA used and dose	Rocuronium: 1 or 1.2 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 8 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA
	At 3 and 15 minutes after administration of rocuronium
Antimuscarinic agent used	Not applicable
Treatment group 4	
Number of patients randomised	32?
Number of patients treated	31
NMBA used and dose	Rocuronium: 1 or 1.2 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 16 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA
	At 3 or 15 minutes after administration of rocuronium
Antimuscarinic agent used	Not applicable
Treatment group 5	
Number of patients randomised	16?
Number of patients treated	16
NMBA used and dose	Rocuronium: 1 or 1.2 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	Set time after administration of NMBA
	At 3 or 15 minutes after administration of rocuronium
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Set time after administration of NMBA
	At 3 or 15 minutes after administration of NMBA
What outcomes were reported?	Time to recovery of TOF 0.9
	Time to recovery of TOF 0.7
Were clinical outcomes reported?	Yes (AEs reported)
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Residual NMB, defined as a decrease in the TOF ratio to < 0.8 for three consecutive measurements within 30 minutes of achieving sufficient recovery to a TOF ratio of 0.9 first, or reoccurrence of NMB, defined as a final TOF ratio of < 0.9

Numbers with residual paralysis per group	None
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Not reported
Was allocation of treatment concealed?	Yes
Was the method used to assign participants to treatment groups truly random?	Yes
Was the assessment of outcomes conducted blind to treatment allocation?	Yes: safety assessor blinded
Was power calculation reported?	No
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Sorgenfrei (2006) Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex[16,104]	
Study publications	Sorgenfrei 2006;[16] Sorgenfrei 2004[104]
Country	Denmark
Indication(s)	Reversal of moderate block
Number of patients	29 (27 treated patients in FDA submission[23])
Age of population	Mean 40 years (SD 13)
Gender	29 male (100%)
ASA Physical Status	ASA I: 22/27 (81%) ASA II: 5/27 (19%)
Weight	Mean 80 kg (SD 12)
Comorbid disease	Not reported
Type of surgical procedure	Surgery lasting at least 60 minutes and requiring muscle relaxation to facilitate only tracheal intubation
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	No
Type of analgesic	Fentanyl
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	4
Number of patients treated	4
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	3
Number of patients treated	3
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	5
Number of patients treated	5

NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.7, 0.8 and 0.9
Were clinical outcomes reported?	Yes (AEs reported)
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Recurarisation or residual curarisation (e.g. respiratory problems, respiratory rate, oxygen saturation)
Numbers with residual paralysis per group	None
Was mortality reported?	Yes
Numbers of deaths per group	None
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	ITT: [105] 27 patients Per protocol[16]: 24 patients
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Yes for safety outcomes Unclear for TOF
Was power calculation reported?	No
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Sparr (2007): Early reversal of profound rocuronium-induced neuromuscular blockade by sugammadex in a randomized multicenter study: efficacy, safety, and pharmacokinetics[32,105]	
Study publications	Sparr 2007;[32] Vermeyen 2004[105]
Country	Multinational
Indication(s)	Reversal of deep block Immediate/rapid reversal
Number of patients	99
Age of population	Mean 38.8 years (calculated) (range 19–63)
Gender	99 male (100%)
ASA Physical Status	ASA I: 77/98 (79%) ASA II: 21/98 (21%)
Weight	Mean 81.8 kg (calculated)
Comorbid disease	Not reported
Type of surgical procedure	Elective surgery lasting at least 75 minutes and requiring muscle relaxation to facilitate only tracheal intubation
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	No
Type of analgesic	Fentanyl
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	16
Number of patients treated	16
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA 3, 5 or 15 minutes after administration of NMBA
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	18
Number of patients treated	18
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA 3, 5 or 15 minutes after administration of NMBA
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	18
Number of patients treated	18
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No

Reversal agent used and dose	Sugammadex: 8 mg/kg
When was reversal agent or placebo administered?	Set time after administration of NMBA 3, 5 or 15 minutes after administration of NMBA
Antimuscarinic agent used	Not applicable
Treatment group 4	
Number of patients randomised	10
Number of patients treated	10
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	Set time after administration of NMBA 3, 5 or 15 minutes after administration of NMBA
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Set time after administration of NMBA 3, 5 or 15 min after administration of NMBA
What outcomes were reported?	Time to recovery of TOF 0.9 Time to recovery of TOF 0.8 Time to recovery of TOF 0.7
Were clinical outcomes reported?	Yes: AEs reported
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Signs of residual curarisation or recurarisation
Numbers with residual paralysis per group	Not applicable
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Per protocol 99 patients enrolled and randomised. One patient withdrew before receiving study medication and was excluded from the ITT population. In 4 patients, non-compliance with the protocol was observed that might have affected study end points; therefore the per-protocol population included 94 patients
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to Treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Yes: safety assessors blinded
Was power calculation reported?	No
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Staals (2008): Multicentre, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function[51]	
Study publications	Staals 2008;[51] Staals 2007[59]
Country	Multinational
Indication(s)	Reversal of moderate block
Number of patients	30 patients (15 uraemic; 15 healthy)
Age of population	Mean 57.5 years (calculated)
Gender	14/30 (47%) male
ASA Physical Status	ASA I: 5/30 (17%)
	ASA II: 11/30 (37%)
	ASA III: 14/30 (46%)
Weight	Mean 80 kg (calculated)
Comorbid disease	Renal disease
	15 patients
Type of surgical procedure	Elective surgical procedures where it was anticipated that only one dose of rocuronium would be required
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	No
Type of analgesic	Other (opiates)
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	15 (uraemic patients)
Number of patients treated	15
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	15 (healthy patients)
Number of patients treated	14
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.9
	Time to recovery of TOF 0.8
	Time to recovery of TOF 0.7
Were clinical outcomes reported?	Yes (clinical signs of recovery and AEs reported)
Was residual paralysis reported?	Yes

How was residual paralysis defined?	Recurrence of NMB (a decrease in the TOF ratio to <0.9) after full recovery had been detected, or a deterioration in the clinical signs of recovery from block
Numbers with residual paralysis per group	None
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	Renal status
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Not reported
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	Yes
Were treatment groups comparable?	No (renal failure)
Were all patients accounted for at the end of the study?	Yes

Suy (2007): Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent[49,106]	
Study publications	Suy 2007;[49] Suy 2005[106]
Country	Belgium
Indication(s)	Reversal of moderate block
Number of patients	80 (98 treated patients in FDA submission,[23] probably includes pancuronium arm)
Age of population	Mean 55 years (calculated)
Gender	43/80 male (54%)
ASA Physical Status	ASA I: 37/80 (47%)
	ASA II: 42/80 (53%)
Weight	Mean 75 kg (calculated)
Comorbid disease	Not reported
Type of surgical procedure	Surgery lasting 60 minutes or more and requiring muscle relaxation only for intubation
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	Not reported
Type of analgesic	Remifentanil
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	8
Number of patients treated	8
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	8
Number of patients treated	8
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	8
Number of patients treated	8
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No

Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 4	
Number of patients randomised	8
Number of patients treated	7
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 5	
Number of patients randomised	4
Number of patients treated	4
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Sugammadex: 8 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 5	
Number of patients randomised	3
Number of patients treated	3
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 6	
Number of patients randomised	4
Number of patients treated	4
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Placebo

When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.9 Time to recovery of TOF 0.8 Time to recovery of TOF 0.7
Were clinical outcomes reported?	Yes: AEs reported
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Clinical signs of residual NMB or decrease in TOF ratio after recovery to 0.9
Numbers with residual paralysis per group	None
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Per protocol
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	No: partially random using a step-up/step-down design
Was the assessment of outcomes conducted blind to treatment allocation?	Yes: safety assessor blinded
Was power calculation reported?	No
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

No published paper or abstract available[23,107]	
Study publications	No published paper or abstract available, data extracted from Organon Schering-Plough submission 2008;[23] clinical trials website[107]
Country	Japan
Indication(s)	Reversal of moderate block
Number of patients	98
Age of population	Not reported (ages ranged between 20 and 65 years)
Gender	Not reported (males and females)
ASA Physical Status	Not reported (all patients in ASA classes I–III)
Weight	Not reported
Comorbid disease	Not reported
Type of surgical procedure	Elective surgery in the supine position, lasting approximately 1.5 to 3 hours
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Sevoflurane
Nitrous oxide	Not reported
Type of analgesic	Not reported
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	Unclear
Number of patients treated	7
NMBA used and dose	Rocuronium: 0.9 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	Unclear
Number of patients treated	6
NMBA used and dose	Rocuronium: 0.9 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	Unclear
Number of patients treated	6
NMBA used and dose	Vecuronium
0.1 mg/kg	
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 2 mg/kg

When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
Treatment group 4	
Number of patients randomised	Unclear
Number of patients treated	7
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	No
Was residual paralysis reported?	No
How was residual paralysis defined?	Not applicable
Numbers with residual paralysis per group	Not applicable
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Per protocol
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	No
Was power calculation reported?	No
Were treatment groups comparable?	Unclear
Were all patients accounted for at the end of the study?	Unclear

No published paper or abstract available[66]	
Study publications	No study publications; data extracted from FDA submission[66] and ClinicalTrials.gov
Country	Japan
Indication(s)	Reversal of deep block Reversal at PTC 1–2
Number of patients	21
Age of population	Not reported
Gender	Not reported
ASA Physical Status	Not reported
Weight	Not reported
Comorbid disease	Not reported
Type of surgical procedure	Elective surgery in the supine position, with a duration of approximately 1.5–3 hours
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Sevoflurane
Nitrous oxide	Not reported
Type of analgesic	Not reported
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	Unclear
Number of patients treated	11
NMBA used and dose	Rocuronium: 0.9 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	PTC 1–2
Antimuscarinic agent used	Not applicable
Treatment group 2	
Number of patients randomised	Unclear
Number of patients treated	10
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Sugammadex: 4 mg/kg
When was reversal agent or placebo administered?	PTC 1–2
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	PTC 1–2
What outcomes were reported?	Time to recovery of TOF 0.9 Time to recovery of TOF 0.8
Were clinical outcomes reported?	No
Was residual paralysis reported?	No

How was residual paralysis defined?	Not applicable
Numbers with residual paralysis per group	Not applicable
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not reported
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Not reported
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	No
Were treatment groups comparable?	Unclear
Were all patients accounted for at the end of the study?	Unclear

Appendix 3.2 Non-sugammadex trials

Adamus (2006): Cisatracurium vs. rocuronium: a prospective, comparative, randomized study in adult patients under total intravenous anaesthesia[42]	
Study publications	Adamus 2006[42]
Country	Czech Republic
Indication(s)	Reversal of moderate block
Number of patients	120
Age of population	Mean 51.1 years (calculated)
Gender	59/120 (49%) male
ASA Physical Status	ASA I: 41/120 (34%) ASA II: 67/120 (56%) ASA III: 12/120 (10%)
Weight	Mean 75.05 kg (calculated)
Comorbid disease	Not reported
Type of surgical procedure	Elective general surgery under total intravenous anaesthesia
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	Not reported
Type of analgesic	Sufentanil
Monitoring equipment	Electromyography
Treatment group 1	
Number of patients randomised	15
Number of patients treated	15
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Neostigmine: 0.04 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Atropine: 0.015 mg/kg
Treatment group 2	
Number of patients randomised	15
Number of patients treated	15
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	None (spontaneous recovery)
When was reversal agent or placebo administered?	Not applicable
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	15
Number of patients treated	15
NMBA used and dose	Rocuronium: 0.9 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No

Reversal agent used and dose	Neostigmine: 0.04 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Atropine: 0.015 mg/kg
Treatment group 4	
Number of patients randomised	15
Number of patients treated	15
NMBA used and dose	Rocuronium: 0.9 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	None (spontaneous recovery)
When was reversal agent or placebo administered?	Not applicable
Antimuscarinic agent used	Not applicable
Treatment group 5	
Number of patients randomised	15
Number of patients treated	15
NMBA used and dose	Cisatracurium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Neostigmine: 0.04 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Atropine: 0.015 mg/kg
Treatment group 6	
Number of patients randomised	15
Number of patients treated	15
NMBA used and dose	Cisatracurium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	None (spontaneous recovery)
When was reversal agent or placebo administered?	Not applicable
Antimuscarinic agent used	Not applicable
Treatment group 7	
Number of patients randomised	15
Number of patients treated	15
NMBA used and dose	Cisatracurium: 0.15 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Neostigmine: 0.04 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Atropine: 0.015 mg/kg
Treatment group 8	
Number of patients randomised	15
Number of patients treated	15

NMBA used and dose	Cisatracurium: 0.15 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	None (spontaneous recovery)
When was reversal agent administered?	Not applicable
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	T1 25%
What outcomes were reported?	Time to recovery of TOF 0.9
Were clinical outcomes reported?	No
Was residual paralysis reported?	No
How was residual paralysis defined?	Not applicable
Numbers with residual paralysis per group	Not applicable
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Not reported (however, it appears that all patients were analysed in their randomised groups)
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Yes
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	Yes [however, power calculation was for comparison of NMBAs (not neostigmine vs spontaneous recovery) and for onset time not recovery time]
Were treatment groups comparable?	Yes [data given are for NMBA dose groups (not neostigmine/spontaneous recovery subgroups)]
Were all patients accounted for at the end of the study?	Yes

Bailey (1988): Comparison of atracurium and vecuronium during anaesthesia for laparoscopy[43]	
Study publication	Bailey 1988[43]
Country	UK
Indication(s)	Reversal of moderate block
Number of patients	60
Age of population	Mean 29.5 years (calculated)
Gender	100% female
ASA Physical Status	Not reported
Weight	Mean 58.7 kg (calculated)
Comorbid disease	Not reported
Type of surgical procedure	Laparoscopy for sterilisation or for investigation of infertility
Type of anaesthesia (induction)	Thiopental
Type of anaesthesia (maintenance)	Thiopental
	Other
	Enflurane
Nitrous oxide	Yes
Type of analgesic	Not reported
Monitoring equipment	Electromyography
Treatment group 1	
Number of patients randomised	30?
Number of patients treated	29
NMBA used and dose	Vecuronium: 0.06 mg/kg
Mode of administration	Not reported
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.04 mg/kg
When was reversal agent or placebo administered?	T1 20%
Antimuscarinic agent used	Atropine: 0.02 mg/kg
Treatment group 2	
Number of patients randomised	30?
Number of patients treated	28
NMBA used and dose	Atracurium: 0.3 mg/kg
Mode of administration	Not reported
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.04 mg/kg
When was reversal agent or placebo administered?	T1 20%
Antimuscarinic agent used	Atropine: 0.02 mg/kg
From when were outcomes measured?	T1 20%
What outcomes were reported?	Time to recovery of TOF 0.7
Were clinical outcomes reported?	Yes (AEs and muscle weakness reported).
Was residual paralysis reported?	No
How was residual paralysis defined?	Not applicable
Numbers with residual paralysis per group	Not applicable
Was mortality reported?	No
Numbers of deaths per group	Not applicable

Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Not reported
Was allocation of treatment concealed?	Yes
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Yes
Was power calculation reported?	No
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Barrio (2007): [Influence of neostigmine on the course of neuromuscular blockade with rocuronium or cisatracurium: a randomized, double-blind trial.][44]	
Study publication	Barrio 2007[44]
Country	Spain
Indication(s)	Reversal of moderate block
Number of patients	60
Age of population	Mean 44 years (calculated)
Gender	22/60 male (37%)
ASA Physical Status	ASA I: 39/60 (65%) ASA II: 21/60 (35%)
Weight	Mean 71 kg (calculated)
Comorbid disease	Not reported
Type of surgical procedure	Procedures with an expected duration of more than 90 minutes Saphenectomy 31/60 (52%); ruptured anterior cruciate ligament 10/60 (17%); arthroscopy 6/60 (10%); other procedures 13/60 (21%)
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	Yes
Type of analgesic	Remifentanil
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	10
Number of patients treated	10
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Neostigmine: 0.03 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Atropine: 0.01 mg/kg
Treatment group 2	
Number of patients randomised	10
Number of patients treated	9
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	10
Number of patients treated	10
NMBA used and dose	Cisatracurium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Neostigmine: 0.03 mg/kg

When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Atropine: 0.01 mg/kg
Treatment group 4	
Number of patients randomised	10
Number of patients treated	9
NMBA used and dose	Cisatracurium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	No
Reversal agent used and dose	Placebo
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	T1 25%
What outcomes were reported?	Time to recovery of TOF 0.8
Were clinical outcomes reported?	No
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Failure to reach TOF 0.8 by 60 or 90 minutes after administration of NMBA
Numbers with residual paralysis per group	Rocuronium + neostigmine, none; rocuronium + placebo, 6/10 at 60 minutes, 2/10 at 90 minutes; cisatracurium + neostigmine, 1/10 at 60 minutes, 0/10 at 90 minutes; cisatracurium + placebo, 8/10 at 60 minutes, 4/10 at 90 minutes
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Not reported
Was allocation of treatment concealed?	Yes
Was the method used to assign participants to treatment groups truly random?	Yes (table of random numbers)
Was the assessment of outcomes conducted blind to treatment allocation?	Yes
Was power calculation reported?	Yes [power calculation mentioned (last paragraph of Methods) but no other information reported]
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Berg (1997): Residual neuromuscular block is a risk factor for postoperative pulmonary complications: a prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium[45]	
Study publication	Berg 1997[45]
Country	Denmark
Indication(s)	Reversal of moderate block
Number of patients	693
Age of population	Mean 52 years (calculated)
Gender	Not reported
ASA Physical Status	Not reported ASA I–III [131 (19%) patients ASA II or III]
Weight	Mean 66 kg (calculated)
Comorbid disease	Preoperative pulmonary disease: 48 (7%) patients
Type of surgical procedure	Elective surgery lasting 60 minutes or more, including major surgery of the lower extremities, gynaecological operations or breast surgery, and major abdominal surgery
Type of anaesthesia (induction)	Thiopental: 98.3% patients Midazolam, diazepam, droperidol or etomidate
Type of anaesthesia (maintenance)	Diazepam, inhalational anaesthetic (unspecified), droperidol, midazolam, etomidate or nothing
Nitrous oxide	Yes
Type of analgesic	Fentanyl Epidural analgesia: morphine + bupivacaine
Monitoring equipment	Mechanomyography
Treatment group 1	
Number of patients randomised	230
Number of patients treated	230
NMBA used and dose	Vecuronium: 0.08–0.1 mg/kg If succinylcholine used, first dose was 0.05–0.06 mg/kg
Mode of administration	Not reported
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 2.5 mg Reversal induced with neostigmine 2.5 mg, and supplementary doses of 1.25 mg could be administered – up to 5 mg if judged necessary by the anaesthetist
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Glycopyrrolate: 0.6 mg Atropine: 1 mg
Treatment group 2	
Number of patients randomised	231
Number of patients treated	231
NMBA used and dose	Atracurium: 0.4–0.5 mg/kg If succinylcholine used, first dose was 0.3 mg/kg
Mode of administration	Not reported
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 2.5 mg Reversal induced with neostigmine 2.5 mg, and supplementary doses of 1.25 mg could be administered – up to 5 mg if judged necessary by the anaesthetist

When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Glycopyrrolate: 0.6 mg Atropine: 1 mg
Treatment group 3	
Number of patients randomised	230
Number of patients treated	230
NMBA used and dose	Pancuronium: 0.08–0.1 mg/kg If succinylcholine used, first dose was 0.05–0.06 mg/kg
Mode of administration	Not reported
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 2.5 mg Reversal induced with neostigmine 2.5 mg, and supplementary doses of 1.25 mg could be administered – up to 5 mg if judged necessary by the anaesthetist
When was reversal agent or placebo administered?	Reappearance of T2
Antimuscarinic agent used	Glycopyrrolate: 0.6 mg Atropine: 1 mg
From when were outcomes measured?	Reappearance of T2
What outcomes were reported?	Time to recovery of TOF 0.8
Were clinical outcomes reported?	Yes (5-second head-lift, tongue protrusion, sustained eye opening, and arm lift above and across the body)
Was residual paralysis reported?	Yes
How was residual paralysis defined?	Significant residual paralysis defined as a TOF ratio < 0.7
Numbers with residual paralysis per group	Pancuronium: 59/226 (26%) Atracurium or vecuronium: 24/450 (5%)
Was mortality reported?	Yes [8 patients died within the observation period (6 days) of causes unrelated to anaesthesia, but the number per treatment group was not stated]
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	Postoperative pulmonary complications
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Not reported
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Yes
Was the assessment of outcomes conducted blind to treatment allocation?	Yes
Was power calculation reported?	Yes But power calculation was for postoperative pulmonary complications, not TOF outcomes
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Bevan (1999): Early and late reversal of rocuronium and vecuronium with neostigmine in adults and children[46]	
Study publication	Bevan 1999[46]
Country	Canada
Indication(s)	Reversal of moderate block
Number of patients	176 (88 children and 88 adult women)
Age of population	Adults mean 40 years (calculated); children mean 4.6 years (calculated)
Gender	Adults: 88 women (100%); children: 39 girls (44%)
ASA Physical Status	Not reported (all patients were ASA class I or II)
Weight	Adults: mean 61 kg (calculated); children: mean 19 kg (calculated)
Comorbid disease	Not reported
Type of surgical procedure	Adults gynaecological surgery; children dental surgery; all scheduled for surgery of at least 1 hour's duration
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Propofol
Nitrous oxide	Yes
Type of analgesic	Fentanyl
Monitoring equipment	Electromyography
Treatment group 1	
Number of patients randomised	40 adults and 40 children for NMBA; not reported for reversal agent
Number of patients treated	40 adults and 40 children for NMBA; not reported for reversal agent
NMBA used and dose	Rocuronium: 0.45 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Not reported
Reversal agent used and dose	Neostigmine: 0.07 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Glycopyrrolate: 0.1 mg/kg
Treatment group 2	
Number of patients randomised	40 adults and 40 children for NMBA; not reported for reversal agent
Number of patients treated	40 adults and 40 children for NMBA; not reported for reversal agent
NMBA used and dose	Rocuronium: 0.45 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Not reported
Reversal agent used and dose	None (spontaneous recovery)
When was reversal agent or placebo administered?	Not applicable
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	40 adults and 40 children for NMBA; not reported for reversal agent
Number of patients treated	40 adults and 40 children for NMBA; not reported for reversal agent
NMBA used and dose	Vecuronium: 0.075 mg/kg
Mode of administration	Bolus

Maintenance doses allowed/used	Not reported
Reversal agent used and dose	Neostigmine: 0.07 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Glycopyrrolate: 0.1 mg/kg
Treatment group 4	
Number of patients randomised	40 adults and 40 children for NMBA; not reported for reversal agent
Number of patients treated	40 adults and 40 children for NMBA; not reported for reversal agent
NMBA used and dose	Vecuronium: 0.075 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Not reported
Reversal agent used and dose	None (spontaneous recovery)
When was reversal agent or placebo administered?	Not applicable
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	T1 25% (neostigmine groups only) Other [from administration of NMBA (neostigmine and spontaneous recovery groups)]
What outcomes were reported?	Time to recovery of TOF 0.9 Time to recovery of TOF 0.7
Were clinical outcomes reported?	No
Was residual paralysis reported?	No
How was residual paralysis defined?	Not applicable
Numbers with residual paralysis per group	Not applicable
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not reported
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	ITT
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Yes
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	No
Were treatment groups comparable?	Yes NMBA treatment groups comparable within age categories
Were all patients accounted for at the end of the study?	Yes

Carroll (1998): A comparison of the neuromuscular blocking effects and reversibility of cisatracurium and atracurium[47]	
Study publication	Carroll 1998[47]
Country	UK
Indication(s)	Reversal of moderate block
Number of patients	90
Age of population	Overall age Mean 31 years (calculated)
Gender	Not reported
ASA Physical Status	Not reported
Weight	Overall weight Mean 69 kg (calculated)
Comorbid disease	Not reported
Type of surgical procedure	Elective otorhinolaryngological or orthopaedic surgery
Type of anaesthesia (induction)	Propofol
Type of anaesthesia (maintenance)	Isoflurane
Nitrous oxide	Yes
Type of analgesic	Fentanyl
Monitoring equipment	Mechanomyography
Treatment group 1	
Number of patients randomised	10
Number of patients treated	10
NMBA used and dose	Cisatracurium: 0.1 mg/kg
Mode of administration	Infusion
Maintenance doses allowed/used	Not reported
Reversal agent used and dose	Neostigmine: 0.05 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Glycopyrrolate: 0.01 mg/kg
Treatment group 2	
Number of patients randomised	10
Number of patients treated	10
NMBA used and dose	Cisatracurium: 0.1 mg/kg
Mode of administration	Infusion
Maintenance doses allowed/used	Not reported
Reversal agent used and dose	None (spontaneous recovery)
When was reversal agent or placebo administered?	Not applicable
Antimuscarinic agent used	Not applicable
Treatment group 3	
Number of patients randomised	10
Number of patients treated	10
NMBA used and dose	Cisatracurium: 0.15 mg/kg
Mode of administration	Infusion
Maintenance doses allowed/used	Not reported
Reversal agent used and dose	Neostigmine: 0.05 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Glycopyrrolate: 0.01 mg/kg

Treatment group 4	
Number of patients randomised	10
Number of patients treated	10
NMBA used and dose	Cisatracurium: 0.15 mg/kg
Mode of administration	Infusion
Maintenance doses allowed/used	Not reported
Reversal agent used and dose	None (spontaneous recovery)
When was reversal agent or placebo administered?	Not applicable
Antimuscarinic agent used	Not applicable
Treatment group 5	
Number of patients randomised	10
Number of patients treated	10
NMBA used and dose	Atracurium: 0.5 mg/kg
Mode of administration	Infusion
Maintenance doses allowed/used	Not reported
Reversal agent used and dose	Neostigmine: 0.05 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Glycopyrrolate: 0.01 mg/kg
Treatment group 6	
Number of patients randomised	10
Number of patients treated	10
NMBA used and dose	Atracurium: 0.5 mg/kg
Mode of administration	Infusion
Maintenance doses allowed/used	Not reported
Reversal agent used and dose	None (spontaneous recovery)
When was reversal agent or placebo administered?	Not applicable
Antimuscarinic agent used	Not applicable
From when were outcomes measured?	T1 25% (also, time from the administration of neostigmine to achieving a TOF ratio of 0.8 recorded for groups receiving neostigmine) Other (measured from administration of NMBA)
What outcomes were reported?	Time to recovery of TOF 0.8
Were clinical outcomes reported?	No
Was residual paralysis reported?	No
How was residual paralysis defined?	Not applicable
Numbers with residual paralysis per group	Not applicable
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	No
Time in recovery room	Not reported

Costs	Not reported
ITT or per protocol	Not reported
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	No
Were treatment groups comparable?	Yes
Were all patients accounted for at the end of the study?	Yes

Della Rocca (2003): Atracurium, cisatracurium, vecuronium and rocuronium in patients with renal failure Sugammadex comparator RCTs[48]	
Study publication	Della Rocca 2003[48]
Country	Italy
Indication(s)	Reversal of moderate block
Number of patients	126
Age of population	Mean 47 years (calculated)
Gender	Not reported [67/126 male (53%)]
ASA Physical Status	Not reported (all patients were ASA I or II)
Weight	Mean 62.5 kg (calculated)
Comorbid disease	Renal disease [64 patients (51%)]
Type of surgical procedure	Anepheric patients undergoing renal transplantation and healthy patients undergoing abdominal surgery
Type of anaesthesia (induction)	Thiopental
Type of anaesthesia (maintenance)	Fentanyl
Nitrous oxide	Yes
Type of analgesic	Fentanyl
Monitoring equipment	Acceleromyography
Treatment group 1	
Number of patients randomised	31 (15 uraemic; 16 healthy)
Number of patients treated	31 (15 uraemic; 16 healthy)
NMBA used and dose	Atracurium: 0.5 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.05 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Atropine: 0.02 mg/kg
Treatment group 2	
Number of patients randomised	31 (16 uraemic; 15 healthy)
Number of patients treated	31 (16 uraemic; 15 healthy)
NMBA used and dose	Cisatracurium: 0.15 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.05 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Atropine: 0.02 mg/kg
Treatment group 3	
Number of patients randomised	30 (16 uraemic; 14 healthy)
Number of patients treated	30 (16 uraemic; 14 healthy)
NMBA used and dose	Vecuronium: 0.1 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.05 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Atropine: 0.02 mg/kg

Treatment group 4	
Number of patients randomised	32 (17 uraemic; 15 healthy)
Number of patients treated	32 (17 uraemic; 15 healthy)
NMBA used and dose	Rocuronium: 0.6 mg/kg
Mode of administration	Bolus
Maintenance doses allowed/used	Yes
Reversal agent used and dose	Neostigmine: 0.05 mg/kg
When was reversal agent or placebo administered?	T1 25%
Antimuscarinic agent used	Atropine: 0.02 mg/kg
From when were outcomes measured?	T1 25%
What outcomes were reported?	Time to recovery of TOF 0.8 Reported separately for healthy and uraemic subgroups
Were clinical outcomes reported?	No
Was residual paralysis reported?	No
How was residual paralysis defined?	Not applicable
Numbers with residual paralysis per group	Not applicable
Was mortality reported?	No
Numbers of deaths per group	Not applicable
Outcomes (patient experience/QoL)	
Measure used	Not applicable
Baseline scores	Not applicable
Follow-up scores	Not applicable
Subgroup analyses reported	Renal status
Time in recovery room	Not reported
Costs	Not reported
ITT or per protocol	Not reported
Was allocation of treatment concealed?	Unclear
Was the method used to assign participants to treatment groups truly random?	Unclear
Was the assessment of outcomes conducted blind to treatment allocation?	Unclear
Was power calculation reported?	No
Were treatment groups comparable?	No (no details provided, but lack of comparability appears to be between the renal and 'healthy' patients rather then between randomised groups)
Were all patients accounted for at the end of the study?	Yes

Appendix 3.3 Adverse events

Baillard (2000): Residual curarisation in the recovery room after vecuronium[63]	
Study publication	Baillard 2000[63]
Country	France
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	Single-centre survey
Drug(s) evaluated	Vecuronium
	Reversal agents not routinely used
Adverse effect(s) evaluated	Prolonged blockade
	Defined as TOF ratio < 0.7 on arrival in the recovery room
Rates of adverse effects reported by drug	Vecuronium
	Residual paralysis 42% (239/568); reversal agents not routinely used
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	Yes
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

Bhananker (2005): The risk of anaphylactic reactions to rocuronium in the United States is comparable to that of vecuronium: an analysis of food and drug administration reporting of adverse events[64]	
Study publication	Bhanaker 2005[64]
Country	USA
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	National survey
	Examined reports of anaphylaxis to FDA (1999–2002)
Drug(s) evaluated	Rocuronium and vecuronium
Adverse effect(s) evaluated	Anaphylactic reactions
Rates of adverse effects reported by drug	Rocuronium (33 reports of AEs with 'anaphylaxis' term)
	Rate per number of vials sold = 1/1,008,000
	Vecuronium (20 reports of AEs with 'anaphylaxis' term)
	Rate per number of vials sold = 1/1,107,250
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	No
Was nature of 'anaphylactic reactions' established by immunological testing?	No (any term that could indicate anaphylaxis: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction)

Cammu (2006): Postoperative residual paralysis in outpatients versus inpatients[65]	
Study publication	Cammu 2006[65]
Country	Belgium
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	Single-centre survey
Drug(s) evaluated	Rocuronium (reversal agent use not reported) Atracurium (reversal agent use not reported) Cisatracurium (reversal agent use not reported) Mivacurium (reversal agent use not reported) Succinylcholine
Adverse effect(s) evaluated	Prolonged blockade: defined as TOF ratio < 0.9 on arrival in the postanaesthetic care unit
Rates of adverse effects reported by drug	*Rocuronium* Residual paralysis: outpatients 39% (28/71); inpatients 48% (67/141) Reversal agents used in 26% of outpatients and 25% of inpatients *Atracurium* Residual paralysis: outpatients 51% (38/75); inpatients 43% (49/114) Reversal agents used in 26% of outpatients and 25% of inpatients *Cisatracurium* Residual paralysis: outpatients 33% (2/6); inpatients 62% (5/8) Reversal agents used in 26% of outpatients and 25% of inpatients *Mivacurium* Residual paralysis: outpatients 23% (37/160); inpatients 35% (17/48) Reversal agents used in 26% of outpatients and 25% of inpatients *Succinylcholine* Residual paralysis: outpatients 17% (1/6); inpatients 50% (1/2)
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	Yes
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

Cheng *et al*. (2005): Does neostigmine administration produce a clinically important increase in postoperative nausea and vomiting?[77]	
Study publication	Cheng 2005[77]
Country	USA
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	Systematic review 5 trials of neostigmine and glycopyrrolate pooled in meta-analysis
Drug(s) evaluated	Neostigmine–glycopyrrolate combination
Adverse effect(s) evaluated	Nausea/vomiting
Rates of adverse effects reported by drug	Neostigmine–glycopyrrolate combination *The combination of N&G effect on*: Vomiting (0–24 hours): relative risk 0.95 (95% CI: 0.72–1.25); $p = 0.72$ Nausea (0-24 hours): relative risk 1.26 (95% CI: 0.98–1.62); $p = 0.07$ Meta-regression found no association between dose of neostigmine and risk of vomiting
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	Yes
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

Dexter (2001): Cost identification for succinylcholine[74]	
Study publication	Dexter 2001[74]
Country	USA
Focus of data source	Study of NMBA(s)
Type of data source	Non-systematic review
Drug(s) evaluated	Succinylcholine
Adverse effect(s) evaluated	Cardiac arrest Malignant hyperthermia
Rates of adverse effects reported by drug	Succinylcholine *Cardiac arrest* From 3 large observational studies there were 21 cases of cardiac arrest in 457,609 anaesthesias. Therefore, rate is 1:21,790 (upper and lower limits taken to be 0 and 1:11,930 because all observed cardiac arrests occurred in one study, $n = 250,541$) *Malignant hyperthermia* Risk of hyperthermia calculated as 1: 96,046 (95% CI –1:302,755 to 1:41,442)
Population rates of adverse effects reported	Butyrylcholinesterase deficiency (associated with risk of prolonged NMB by succinylcholine) 1:2886 (95% CI 1:4327 to 1:1967)
Was the denominator based on actual patient data?	Yes
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

European Medicines Agency (2008): Assessment report for Bridion[10]	
Study publication	European Medicines Agency 2008[10]
Country	Multinational
Focus of data source	Study of reversal agent(s): sugammadex
Type of data source	Regulatory agency assessment report
Drug(s) evaluated	Sugammadex, standard doses of 2, 4 and 16 mg/kg
Adverse effect(s) evaluated	Allergic reactions Cardiac rhythm disturbances Hypotension Nausea/vomiting Prolonged blockade Airway complications and anaesthetic complications
Rates of adverse effects reported by drug	*Sugammadex* EMEA document data based on 29 clinical trials of sugammadex (n = 1833); of these there were 24 trials (n = 1713) where a NMBA had been administered as well as sugammadex or placebo Most of the patients included were aged 18–64 years, white or Asian, and almost none were ASA class IV Further subsets were also identified: trials of sugammadex vs neostigmine (2 trials, sugammadex n = 179, neostigmine n = 167); and sugammadex vs placebo (10 trials, sugammadex n = 640, placebo n = 140) Overall 80% of all patients exposed to any dose of sugammadex experienced at least one AE; by dose, the rates were: 2 mg/kg 79%; 4 mg/kg 89% and 16 mg/kg 81% Sugammadex vs neostigmine (2 trials with sugammadex n = 179, neostigmine n = 167) Total of at least one AE (%) Total sugammadex = 88 (157/179), total neostigmine = 89 (149/167) Rocuronium + sugammadex = 91 Rocuronium + neostigmine = 93 Vecuronium + sugammadex = 85% Vecuronium + neostigmine = 85% AEs that occurred in at least 2% of sugammadex patients and at least twice as frequently as with neostigmine were flatulence and post-operative GI disorder Serious adverse events: SAEs (regardless of NMBA used) occurred in: sugammadex (3%), neostigmine (4%) Sugammadex vs placebo (10 trials): sugammadex n = 640, placebo n = 140 Incidence of at least one AE Sugammadex = 68% (435/640) Placebo = 72% (101/140) Rocuronium + sugammadex = 67% (352/526) Rocuronium + placebo = 70% (81/116) Vecuronium + sugammadex = 75% (86/114) Vecuronium + placebo = 83% (20/24)

	Adverse events that occurred in at least 2% of patients receiving sugammadex and at least twice as frequently as with placebo were anaesthetic complication and cough Treatment-related AEs that occurred in at least 2% of sugammadex patients and at least twice as frequently as with placebo were dysgeusia, nausea, abdominal pain, dry mouth, dizziness and salivary hypersecretion Serious adverse events: SAEs (regardless of NMBA used) occurred in: sugammadex (6%), placebo (4%) Specific adverse events: Anaesthetic complications: reported in 3% of patients but most were related to the immediate reversal of NMB associated with sugammadex; such complications included airways complications, such as bucking and spontaneous breathing (1% sugammadex, 2.4% neostigmine, 0% placebo), moving or coughing (8% sugammadex, 1% placebo), unwanted awareness in anaesthesia (< 1%) and delayed recovery from anaesthetic (1%) Allergic reactions: no specific rate was reported; from all the clinical trials there were 7 cases that were possibly indicative of a hypersensitivity reaction to sugammadex Cardiac rhythm disturbances: prolongation of QTc interval seen in all phase I–III studies, especially with sevoflurane. No torsades des pointes arrhythmia was reported. The report noted that QTc prolongation is a concern in the clinical situation where many other drugs affecting the QT interval are used together Prolonged blockade: 2% in pooled phase I–III studies (0% with placebo); < 1% overall (0% placebo, 5% vecuronium + neostigmine in phase III controlled studies)
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	Yes (actual numbers were often not reported)
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

Laake (2001): Rocuronium and anaphylaxis – a statistical challenge[66]	
Study publication	Laake 2001[66]
Country	Scandinavia
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	National Survey [data from Norwegian Medicines Agency (1997–2000) and other data sources]
Drug(s) evaluated	Rocuronium and vecuronium
Adverse effect(s) evaluated	Anaphylactic reactions
Rates of adverse effects reported by drug	*Rocuronium* Norwegian data: 29 cases of anaphylaxis (95% CI 19 to 42) per 150,000 patients exposed to rocuronium Rate estimated to be 1/5000, 95% CI 1/3600 to 1/7700 Sweden data: 3 cases of anaphylaxis (95% CI 0 to 9) per 250,000 patients exposed to rocuronium Rate estimated to be 95% CI 1/28,000 to 0 Denmark data: 0 cases of anaphylaxis (95% CI 0 to 4) per 180,000 patients exposed to rocuronium Rate estimated to be 95% CI 1/45,000 to 0 Finland data: 4 cases of anaphylaxis (95% CI 1 to 11) per 350,000 patients exposed to rocuronium Rate estimated to be 95% CI 1/32,000 to 1/350,000 Differences in rates believed to be due to biased reporting (high rates in Norway, low rates in other countries) *Vecuronium* Norwegian data: 3 cases of anaphylaxis per 65,000 patients exposed to vecuronium Rate estimated to be 1/22,000 (95% CI 1/7400 to 1/105,000)
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	No (number of exposed patients was estimated from sales data)
Was nature of 'anaphylactic reactions' established by immunological testing?	No

Laxenaire and Groupe d'Etudes des Réactions Anaphylactoides (2001) Anaphylaxis during anaesthesia: results of a two-year survey in France[67]	
Study publication	Laxenaire 2001[67]
Country	France
Focus of data source	Study of specific adverse effects (general focus) Anaphylaxis
Type of data source	National survey (survey January 1997–December 1998)
Drug(s) evaluated	Rocuronium Vecuronium Atracurium Cisatracurium Mivacurium Succinylcholine
Adverse effect(s) evaluated	Anaphylactic reactions
Rates of adverse effects reported by drug	*Rocuronium* Total number of anaphylactic reactions to NMB = 336 % of these reactions attributed = 29.2% (98/336) % market share (vials) = 10.0% Ratio % reactions to % market share* = 2.92 *Calculated on data extraction for comparison with Mertes[70] *Vecuronium* Total number of anaphylactic reactions to NMB = 336 % of these reactions attributed = 17.6% (59/336) % market share (vials) = 17.5% Ratio % reactions to % market share* = 1.0 *Calculated on data extraction for comparison with Mertes[70] *Atracurium* Total number of anaphylactic reactions to NMB = 336 % of these reactions attributed = 21.1% (71/336) % market share (vials) = 51.2% Ratio % reactions to % market share* = 0.41 *Calculated on data extraction for comparison with Mertes[70] *Cisatracurium* Total number of anaphylactic reactions to NMB = 336 % of these reactions attributed = 0.3% (1/336) % market share (vials) = 1.4% Ratio % reactions to % market share* = 0.21 *Calculated on data extraction for comparison with Mertes[70]

	Mivacurium Total number of anaphylactic reactions to NMB = 336 % of these reactions attributed = 2.7% (9/336) % market share (vials) = 7% Ratio % reactions to % market share* = 0.39 *Calculated on data extraction for comparison with Mertes[70] *Succinylcholine* Total number of anaphylactic reactions to NMB = 336 % of these reactions attributed = 23.2% (78/336) % market share (vials) = 7.6% Ratio % reactions to % market share* = 3.05 *Calculated on data extraction for comparison with Mertes[70]
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	No (size of population exposed to drug was estimated from market share of individual NMBAs; no attempt was made to calculate actual number of patients, only percentage reported; comparison between agents based on ratio of percentage reaction to percentage market share)
Was nature of 'anaphylactic reactions' established by immunological testing?	Yes

Light (2006): Adverse effects of neuromuscular blocking agents based on yellow card reporting in the UK: are there differences between males and females?[62]	
Study publication	Light 2006[62]
Country	UK
Focus of data source	Study of NMBA(s)
Type of data source	National survey (1967–2000 yellow card reporting data)
Drug(s) evaluated	Vecuronium Atracurium Mivacurium Pancuronium Succinylcholine
Adverse effect(s) evaluated	Allergic reactions – no details given in paper Cardiac arrest Cardiac rhythm disturbances Malignant hyperthermia Prolonged blockade Also recorded information on: bronchospasm, apnoea, paralysis and ineffective neuromuscular block
Rates of adverse effects reported by drug	*Vecuronium* Total number fatalities = 4 Number allergic reactions = 45 *Atracurium* Total number fatalities = 19 Number allergic reactions = 151 Non-allergic reactions = 146 (bronchospasm 31, cardiac arrest/dysrhythmia 45, convulsion 4, increased NMB/ apnoea 11, ineffective NMB 7) *Mivacurium* Total number fatalities = 0 Number allergic reactions = 45 *Pancuronium* Total number fatalities = 5 Number allergic reactions = 16 *Succinylcholine* Total number fatalities = 44 Number allergic reactions = 165 Non-allergic reactions = 157 (bronchospasm 26, cardiac arrest/dysrhythmia 31, convulsion 3, increased NMB/ apnoea 19, ineffective NMB 15) NMBAs not specified *Alcuronium* Total number fatalities = 7 Number allergic reactions = 62 *Tubocurarine* Total number fatalities = 1 Number allergic reactions = 13
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	No
Was nature of 'anaphylactic reactions' established by immunological testing?	No

Malinovsky (2008): Systematic follow-up increases incidence of anaphylaxis during adverse reactions in anesthetized patients[68]	
Study publication	Malinovsky 2008[68]
Country	France
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	Single-centre survey [2-year prospective study (May 2001–April 2003) of 70,000 anaesthesias]
Drug(s) evaluated	NMBAs not specified
Adverse effect(s) evaluated	Anaphylactic reactions
Rates of adverse effects reported by drug	NMBAs not specified Six cases of anaphylaxis (IgE-mediated hypersensitivity reactions) with NMBAs as main causative agent from approximately 70,000 anaesthesias
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	Yes (study was prospective and number of anaesthesias was 'nearly 70,000')
Was nature of 'anaphylactic reactions' established by immunological testing?	Yes

Maybauer (2007) Incidence and duration of residual paralysis at the end of surgery after multiple administrations of cisatracurium and rocuronium[69]	
Study publication	Maybauer 2007[69]
Country	Germany
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	RCT
Drug(s) evaluated	Rocuronium (no reversal agent) Cisatracurium (no reversal agent)
Adverse effect(s) evaluated	Prolonged blockade Residual paralysis defined as TOF ratio < 0.9 at time of scheduled extubation (skin closure)
Rates of adverse effects reported by drug	Rocuronium [residual paralysis 44% (62/142); reversal agents not used] Cisatracurium [residual paralysis 57% (99/175); reversal agents not used]
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	Yes
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

Mertes (2003): Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000[70]	
Study publication	Mertes 2003[70]
Country	France
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents) Anaphylaxis
Type of data source	National survey (survey January 1999–December 2001)
Drug(s) evaluated	Rocuronium Vecuronium Atracurium Cisatracurium Mivacurium Succinylcholine
Adverse effect(s) evaluated	Anaphylactic reactions
Rates of adverse effects reported by drug	*Rocuronium* Total number of anaphylactic reactions to NMB = 306 % of these reactions attributed = 43.1% (132/306) % market share (vials) = 8.8% Ratio % reactions to % market share* = 4.9 *Calculated on data extraction for comparison with Laxenaire[67] *Vecuronium* Total number of anaphylactic reactions to NMB = 306 % of these reactions attributed = 8.5% (26/306) % market share (vials) = 11.3% Ratio % reactions to % market share* = 0.75 *Calculated on data extraction for comparison with Laxenaire[67] *Atracurium* Total number of anaphylactic reactions to NMB = 306 % of these reactions attributed = 19.0% (58/306) % market share (vials) = 54.1% Ratio % reactions to % market share* = 0.35 *Calculated on data extraction for comparison with Laxenaire[67] *Cisatracurium* Total number of anaphylactic reactions to NMB = 306 % of these reactions attributed = 0.6% (2/306) % market share (vials) = 4.1% Ratio % reactions to % market share* = 0.15 *Calculated on data extraction for comparison with Laxenaire[67]

	Mivacurium Total number of anaphylactic reactions to NMB = 306 % of these reactions attributed = 2.6% (8/306) % market share (vials) = 5.5% Ratio % reactions to % market share* = 0.47 *Calculated on data extraction for comparison with Laxenaire[67] *Succinylcholine* Total number of anaphylactic reactions to NMB = 306 % of these reactions attributed = 22.6% (69/306) % market share (vials) = 6.7% Ratio % reactions to % market share* = 3.37 *Calculated on data extraction for comparison with Laxenaire[67]
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	No Ratio calculated of % of all reactions to % market share
Was nature of 'anaphylactic reactions' established by immunological testing?	Yes

Murphy (2004): Postanesthesia care unit recovery times and neuromuscular blocking drugs[71]	
Study publication	Murphy 2004 [71]
Country	USA
Focus of data source	Study of specific adverse effects (focus on NMBAs or reveresal agents)
Type of data source	RCT
Drug(s) evaluated	Rocuronium: all patients received N&G on completion of surgical wound closure
	Pancuronium: all patients received N&G on completion of surgical wound closure
Adverse effect(s) evaluated	Nausea/vomiting
	Prolonged blockade: defined as TOF ratio < 0.7 on arrival in the post-anaesthesia care unit
Rates of adverse effects reported by drug	*Rocuronium*
	Residual paralysis 5.9% (2/34).
	Nausea 8.8% (3/34); vomiting 8.8% (3/34)
	Pancuronium
	Residual paralysis 40% (14/35)
	Nausea 17.1% (6/35); vomiting 8.6% (3/35)
	Not applicable
	Overall, patients with postoperative TOF ratio < 0.9 were significantly more likely to spend > 60 minutes in the postanaesthesia care unit than those with a TOF ratio > 0.9 (23/39 vs 7/30, $p = 0.004$)
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	Yes
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

Murphy (2008): Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit[72]	
Study publication	Murphy 2008[72]
Country	USA
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	Single-centre survey: case–control study ($n = 7459$)
Drug(s) evaluated	Not applicable
Adverse effect(s) evaluated	Prolonged blockade: defined as TOF ratio < 0.7 on arrival in the postanesthesia care unit
	Critical respiratory events occurring in the postanesthesia care unit
Rates of adverse effects reported by drug	Not applicable
	Critical respiratory events in patients receiving general anaesthesia 0.8% (61/7459); 8 patients required emergency reintubation
	When 42 patients with a critical respiratory event (cases) were compared with matched control patients, 73.8% (31/42) of cases had a TOF ratio < 0.7 compared with 0% of control patients
Population rates of adverse effects reported	Other
Was the denominator based on actual patient data?	Yes
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

Organon, Schering-Plough (2008): FDA briefing document[23]	
Study publication	Organon, Schering-Plough 2008[23]
Country	Multinational
Focus of data source	Study of reversal agent(s)
Type of data source	Manufacturer's report for regulatory authority
Drug(s) evaluated	Sugammadex
Adverse effect(s) evaluated	Allergic reactions Cardiac rhythm disturbances Nausea/vomiting Prolonged blockade Anaesthetic complications: AEs related to ventilation
Rates of adverse effects reported by drug	*Sugammadex* Submission to FDA by Organon. Data based on pooled phase I–III trials (n = 1926 patients exposed to sugammadex). Most of the patients included were aged 18–64 years, were white or Asian, and in ASA class I or II Subsets were: trials of sugammadex vs neostigmine [2 trials (19.4.301 and 19.4.302), sugammadex n = 179, neostigmine n = 167]; and sugammadex vs placebo (10 trials, sugammadex n = 640, placebo n = 140). Overall, 76.3% of all patients exposed to any dose of NMBA and sugammadex experienced at least one AE. By dose, the rates were: 2 mg/kg 78.9%; 4 mg/kg 88.7% and 16 mg/kg 80.8% Overall, 5.1% of patients exposed to sugammadex plus a NMBA experienced at least one SAE. Of these 8 (0.4%) were considered possibly related to treatment by the investigator: QTc interval prolongation (3 cases); bronchospasm (2 cases); respiratory failure (one case); hypotension (one case); and atrial fibrillation (one case). None of these was considered treatment related by the sponsor. There were no deaths attributed to sugammadex Sugammadex vs neostigmine (2 trials with sugammadex n = 179, neostigmine n = 167) Total of at least one AE % Total sugammadex= 88% (157/179), total neostigmine = 89% (149/167) AEs that occurred in at least 2% of sugammadex patients and at least twice as frequently as with neostigmine were flatulence and postoperative gastrointestinal disorder AEs considered related to treatment by the investigator sugammadex 18.4%; neostigmine 25.1%. Vomiting was the only related AE that was twice as common with sugammadex (4%) as it was with neostigmine Serious adverse events: SAEs (regardless of NMBA used) occurred in: sugammadex (3.4%), neostigmine (3.6%) Sugammadex vs placebo (10 trials), sugammadex n = 640, placebo n = 140 Incidence of at least one AE: Sugammadex= 68.3% (437/640) Placebo = 72.1% (101/140) AEs that occurred in at least 2% of sugammadex patients and at least twice as frequently as with placebo were anaesthetic complication and cough

	AEs considered related to treatment by the investigator: sugammadex 13.3%; placebo 7.9% *Serious adverse events:* SAEs (regardless of NMBA used) occurred in: sugammadex (5.8%), placebo (4.3%) *Specific adverse events*: Anaesthetic complications reported in 3% (57/1926) of patients but most were related to the immediate reversal of NMB associated with sugammadex and occurred mostly in trials where sugammadex was administered early (i.e. not reflective of balanced anaesthesia). Anaesthetic complications were more common with the 16-mg/kg dose (9.1%) than with the 2-mg/kg (2.0%) or 4-mg/kg (1.5%) doses Allergic or hypersensitivity reactions < 1% in pooled phase I–III trials (n = 1926); 7 cases of possible hypersensitivity reactions, 6 of which were in response to 32-mg/kg dose. Dysgeusia 12.6% (although most cases occurred at 32-mg/kg dose) Nausea 23.2% (447/1926) Vomiting 10.5% (202/1926) Prolonged blockade or recurrence of blockade during monitoring 1.2% (24/1926). Of these cases 20 were following subtherapeutic dose (< 2 mg/kg) of sugammadex. In placebo controlled trials the rates were 1.7 and 0 with sugammadex and placebo, respectively; 6/1926 patients (0.3%) had clinical signs of residual or recurrent block. AEs representative of residual or recurrent block occurred in 0.4% (7/1926) sugammadex patients, 2.4% (4/167) neostigmine patients and none with placebo patients Adverse events related to ventilation: dyspnoea 1.5%; oxygen saturation decreased 1%; bronchospasm, wheezing and obstructive airways disorder 0.5% (10/1926) Cardiac rhythm disturbances: prolongation of QTc interval examined in two specific trials. Administration of sugammadex at doses of 4 mg/kg and 32 mg/kg (with or without an NMBA) did not lead to QTc interval prolongations of regulatory concern (i.e. the one-sided upper confidence limit of the largest time-matched mean difference in QTc change compared with placebo did not exceed 10 ms), i.e. both trials found negative results according to the criteria of the ICH E14 guideline
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	Yes
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

Rosenberg (2007) Malignant hyperthermia[75]	
Study publication	Rosenberg 2007[75]
Country	USA
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	Non-systematic review
Drug(s) evaluated	Succinylcholine
Adverse effect(s) evaluated	Malignant hyperthermia
Rates of adverse effects reported by drug	*Succinylcholine* No real incidence data reported. Overall rate of malignant Hyperthermia with anaesthesia is between 1/5000 and 1/50,000 – 100,000 cases Genetic susceptibility to developing malignant hyperthermia estimated at 1/3000–1/8500 Masseter muscle rigidity also associated with succinylcholine and halothane or sevoflurane (which is used). Severe masseter muscle rigidity may be linked to development of malignant hyperthermia
Population rates of adverse effects reported	*Malignant hyperthermia* No real incidence data reported. Overall rate of malignant hyperthermia with anaesthesia is between 1/5000 and 1/50,000 – 100,000 cases Genetic susceptibility to developing Malignant Hyperthermia estimated at 1/3000 – 1/8500 Masseter muscle rigidity also associated with succinylcholine and halothane or sevoflurane (which is used). Severe masseter muscle rigidity may be linked to development of malignant hyperthermia
Was the denominator based on actual patient data?	Not applicable
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

Neal *et al.* (2000): Histaminoid reactions associated with rocuronium[73]	
Study publication	Neal 2000[73]
Country	UK
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	Single-centre survey
Drug(s) evaluated	Rocuronium
Adverse effect(s) evaluated	Anaphylactic reactions
Rates of adverse effects reported by drug	*Rocuronium* 3 cases reported Estimated 8800 patients received rocuronium over 2 years; estimated rate 1/3000
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	No
Was nature of 'anaphylactic reactions' established by immunological testing?	Yes

Schreiber (2005): Prevention of succinylcholine-induced fasciculation and myalgia[76]	
Study publication	Schreiber 2005[76]
Country	Germany
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	Systematic review Review was of interventions to prevent succinylcholine induced myalgia. As comparator in review was placebo or no treatment the results from the control arm should provide some useful data on rate of myalgia with succinylcholine.
Drug(s) evaluated	Succinylcholine
Adverse effect(s) evaluated	Myalgia and fasciculation
Rates of adverse effects reported by drug	*Succinylcholine* Data from 35 trials the incidence of fasciculation was 94% (range 73–100%) and of myalgia at 24 hours was 51% (range 10–83%) When divided into dose of succinylcholine, incidences were significantly higher with the higher dose: Fasciculation: 1 mg/kg 98.3%; 1.5 mg/kg 92.0% (relative risk 1.07, 95% CI 1.04 to 1.1) Myalgia at 24 hours: 1 mg/kg 62.8%; 1.5 mg/kg 44.6% (relative risk 1.41, 95% CI 1.23 to 1.61)
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	Yes, but *n* not reported
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

Tramer and Fuchs-Buder (1999): Omitting antagonism of neuromuscular block: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review[78]	
Study publication	Tramer 1999[78]
Country	Germany
Focus of data source	Study of specific adverse effects (focus on NMBAs or reversal agents)
Type of data source	Systematic review
Drug(s) evaluated	*Neostigmine–glycopyrrolate combination* Only 3 of the 8 trials in the systematic review were of neostigmine and glycopyrrolate NMBAs not specified
Adverse effect(s) evaluated	Nausea/vomiting Prolonged blockade
Rates of adverse effects reported by drug	*Neostigmine–glycopyrrolate combination* The presence or absence of neostigmine or edrophonium (1 trial) plus an antimuscarinic agent did not alter the relative risk for nausea and vomiting – relative risk remained near 1 and CIs included 1 NMBAs not specified From two trials of mivacurium and vecuronium, respectively, rates of residual blockade associated with no reversal agent were 3/90 compared with 0/90 following use of reversal agent (relative risk 4.00, 95% CI 0.46 to 35.1)
Population rates of adverse effects reported	Not applicable
Was the denominator based on actual patient data?	Yes: for residual blockade (muscle weakness)
Was nature of 'anaphylactic reactions' established by immunological testing?	Not applicable

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We look forward to hearing from you.

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