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

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Executive summary

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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.

Publication

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

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Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

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Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/10/01. The contractual start date was in October 2008. The draft report began editorial review in February 2009 and was accepted for publication in November 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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