The prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity

A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling

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Executive summary

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Executive summary

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for the treatment of pain (in particular musculoskeletal pain) and stiffness. All NSAID treatment carries some risk of gastrointestinal (GI) toxicity, ranging in severity from mild dyspepsia to GI haemorrhage and perforation. These last complications may lead to hospitalisation, surgery or death. A number of strategies exist to reduce the incidence and impact of NSAID-induced GI toxicity. These include the co-prescription of a histamine-2 receptor antagonist (H_2RA), proton pump inhibitor (PPI) or misoprostol; or the prescription of a Cox-2 preferential or specific NSAID rather than a conventional NSAID. It is unclear which of these strategies is more effective or cost-effective.

Objectives

The aim of this study was to assess the relative effectiveness, patient acceptability, costs and cost-effectiveness of four strategies for the prevention of NSAID induced GI toxicity:

1. Cox-1 NSAIDs plus H_2RAs
2. Cox-1 NSAIDs plus PPIs
3. Cox-1 NSAIDs plus misoprostol
4. Cox-2 NSAIDs (later expanded to 4a Cox-2 coxib NSAIDs and 4b Cox-2 preferential NSAIDs).

The primary outcomes were mortality, health-related quality of life, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness and side-effects. Serious GI complications were defined as a GI perforation, bleed (including melaena) or obstruction. A symptomatic ulcer was defined as an endoscopic ulcer which is discovered when a patient complains of dyspepsia or has experienced a GI bleed. Secondary outcomes included endoscopic ulcers. An endoscopic ulcer was defined as an ulcer at least 3 mm in diameter and/or that could be distinguished from erosions based on the author's description, for example lesions with unequivocal depth.

Methods

Data sources

The Cochrane Library, MEDLINE, EMBASE, Current Controlled Trials and SIGLE were searched to May 2002. Bibliographies and author contacts were used to identify further studies. Non-English language studies were included.

Study selection

Articles were selected if they were randomised controlled trials (RCTs), assessed a gastroprotective strategy vs placebo, studied adult patients (i.e. not healthy volunteers), had an NSAID exposure of at least 21 days and included at least one of the review outcome measures.

Data extraction

Trial selection, data extraction and quality assessment were performed independently in duplicate. Data on participants, interventions, outcomes and potential effect modifiers were extracted, using a data extraction form designed for this review, and tabulated.

Data synthesis

Where appropriate, the differences in the outcomes were combined across studies using relative risks or weighted mean differences in random effects meta-analysis on RevMan 4.2 software. Heterogeneity was examined visually and using Cochran's test (considered significant at $p < 0.1$). Meta-analysis was also carried out on StatsDirect software for the active gastroprotective agent versus placebo analyses in order to produce weighted relative risk ratios for the economic analysis. Adjusted indirect comparisons were also calculated using the relevant active treatment versus placebo analyses results.

Random effects meta-regression was performed in order to analyse the associations between treatment effect and the following study characteristics: length of follow-up, mean age of participants, and baseline GI status. Funnel plots and related inferential methods were used to assess for evidence of small study effects, including publication bias. As data for direct comparisons between active treatments were often sparse, adjusted indirect comparisons were also ▶

calculated, using the relevant active treatment versus placebo analyses results.

Economic evaluation

Pooled relative risk ratios from the systematic review were combined with up-to-date UK resource use and unit costs data in an incremental economic analysis. As outcome data for the direct comparisons between active treatments were often sparse, adjusted indirect comparisons were calculated using the relevant results from active treatment versus placebo analyses. The five strategies were evaluated from a UK NHS perspective, incorporating drug costs, GP visits and management of adverse events. Published estimates of resource use were used because no detailed resource data were reported in the clinical trials in the meta-analysis. A probabilistic decision-analytic model was designed and populated with data to carry out incremental economic analysis. Incremental cost-effectiveness ratios (ICERs) were generated for the outcome measure, endoscopic ulcer or serious GI event averted, against total cost, and non-parametric bootstrapping was used to simulate variance of these ICERs.

Results

Effectiveness

The electronic and bibliographic searches, plus replies from trial authors, identified 6417 potentially relevant titles and abstracts. From these, 505 full-text papers were collected for further examination. These included relevant systematic reviews, economic papers, cohorts and controlled trials. Once publications had been screened, 118 trials remained, including 125 relevant comparisons. These trials (which included 76,322 participants) reported only 138 deaths and 248 serious GI events. Seven comparisons were judged to be at low risk of bias.

Comparing the gastroprotective strategies against placebo, there was no evidence of effectiveness of H_2RAs against any primary outcomes (few events reported), PPIs may reduce the risk of symptomatic ulcers [relative risk (RR) 0.09, 95% confidence interval (CI) 0.02 to 0.47], misoprostol reduces the risk of serious GI complications (RR 0.57, 95% CI 0.36 to 0.91) and symptomatic ulcers (RR 0.36, 95% CI 0.20 to 0.67), Cox-2 'preferentials' reduce the risk of symptomatic ulcers (RR 0.41, 95% CI 0.26 to 0.65) and Cox-2 'coxibs' reduce the risk of symptomatic ulcers (RR 0.49, 95% CI 0.38 to 0.62) and possibly serious GI events (RR 0.55, 95% CI 0.38 to 0.80). All strategies except Cox-2 'preferentials' reduce the risk of endoscopic ulcers.

There were only 12 direct comparisons between gastroprotective strategies. All they suggest is that Cox-2 preferentials are better than misoprostol for preventing GI complications. Indirect comparisons suggested that PPIs may prevent symptomatic ulcers better than Cox-2 coxibs, but this is very weak evidence. For prevention of endoscopic ulcers PPIs and misoprostol appear more successful than H_2RAs and misoprostol is better than Cox-2 preferentials.

Economic modelling

There were no UK head-to-head published economic analyses with regard to the main gastroprotective strategies. There were generally insufficient data with regards to cardiac or renal outcomes, serious GI outcomes or life-years gained to populate the mode. Mean (2.5th and 97.5th percentile) costs per endoscopic ulcer averted compared with Cox-1 NSAIDs alone were as follows: Cox-1 plus H_2RAs, –£186 (–555 to 804); Cox-1 plus PPIs, £454 (251 to 877); Cox-1 plus misoprostol, £54 (–112 to 238); Cox-2 selective NSAIDs, £263 (–570 to 1280), or Cox-2 specific NSAIDs, £301 (189 to 418). With regard to the prevention of endoscopic ulcers, Cox-1 NSAID plus H_2RA is a dominant option. Cost-effectiveness acceptability analysis showed a 95% probability that this combination was less costly and more effective. Cost-effectiveness acceptability frontiers showed that if the decision-maker is willing to pay up to £750 to avoid an endoscopic ulcer, then Cox-1 plus H_2RA is the optimal strategy. If the decision-maker is willing to pay over £750, the optimal strategy is NSAID plus misoprostol. Between £1900 and £3750, Cox-2 selective inhibitors are optimal, and over £3750, Cox-2 specific inhibitors become optimal. NSAID plus PPI is never the optimal strategy. Sensitivity and subgroup analyses suggest that Cox-1 NSAID plus H_2RA and Cox-1 NSAID plus misoprostol become more cost-effective in the older age group. Some conclusions were associated with high levels of uncertainty.

Conclusions

Although there is a very large body of evidence comparing Cox-2 NSAIDs with Cox-1 NSAIDs, this is not matched by studies of the other types of gastroprotectors or by studies directly ▶

comparing active gastroprotective strategies. This lack of direct comparisons led to the use of indirect comparisons to help understand the relative efficacy of these strategies. Indirect evidence in itself is weak and was also hampered by lack of evidence in the underlying studies (where the gastroprotectors were compared with placebo).

Economic modelling suggests that Cox-1 NSAID plus H_2RA or Cox-1 NSAID plus misoprostol are the most cost-effective strategies for avoiding endoscopic ulcers in patients requiring long-term NSAID therapy.

Implications for healthcare

All strategies other than Cox-2 selective inhibitors reduce the rate of endoscopic ulcer compared with Cox-1 alone. The economic analysis suggests that there may be a case for prescribing H_2RAs in all patients requiring NSAIDs. Misoprostol is more effective, but is associated with a greater cost and GI side-effects which may be unacceptable for patients. However, when assessing serious GI events, the economic analysis is sufficiently weakened by the data available as to render clear practice recommendations impossible.

Recommendations for research

1. Major outcomes, and also important patient-centred outcomes such as quality of life, should be reported in trials even where individual trials may not be powered to evaluate them, collected centrally and be available for use in research synthesis.
2. There is a need for further large, independent RCTs directly comparing various gastroprotective strategies, in particular PPI plus Cox-1 NSAIDs with Cox-2 NSAIDs alone in patients at high risk of NSAID-induced GI toxicity.
3. Economic analyses should be based on primary data when they are available, rather than adding to the large number of modelling studies,
4. Increased follow-up of patients who experience adverse events with prescription medicines including Cox-2 inhibitors should be implemented to allow a clearer understanding of, and provide better quality data on, incidence rates and practice patterns after mild and major side-effects.
5. There should be an assessment of practice, such as the extent of use of H_2RAs and PPIs with specific Cox-2 inhibitors, willingness to use misoprostol, patient risk factors affecting individual prescribers' use of selective and specific Cox-2 inhibitors and recent events around rofecoxib affecting attitudes to specific Cox-2 inhibitors.
6. There is a need for exploration of patients' preferences around the optimal strategy, understanding of risks and benefits of NSAIDs and Cox-2 inhibitors, wish for involvement in decision-making and reaction to recent events around rofecoxib.

The recommendations from this study can only be tentative owing to the variable quality of research available. Clinical data need to be improved through greater use of head-to-head comparisons and major outcomes and patient-centred outcomes should be more rigorously reported.

Publication

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

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The research reported in this monograph was commissioned by the HTA Programme as project number 01/40/02. The contractual start date was in June 2002. The draft report began editorial review in December 2003 and was accepted for publication in August 2005. 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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