The cost-effectiveness of high-dose oral proton pump inhibition after endoscopy in the acute treatment of peptic ulcer bleeding

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of high-dose oral and intravenous (i.v.) proton-pump inhibitors (PPIs) for the treatment of selected patients with acute gastro-duodenal ulcer bleeding following successful endoscopic therapy for high-risk lesions. High-dose oral PPI consisted of pantoprazole 40 mg, taken orally twice daily for the first 5 days of the hospitalisation, followed by 40 mg/day oral pantoprazole for the remainder of their hospital stay (when applicable). High-dose i.v. PPI consisted of an 80-mg bolus of pantoprazole within 12 hours of endoscopy, followed by 8 mg/hour intravenously for 3 days and oral PPI (pantoprazole 40 mg/day) for the remainder of their hospital stay (when applicable).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with high-risk ulcer lesions having had endoscopic therapy. Patients who failed endoscopic haemostatic therapy were excluded.

Setting
The setting was secondary care. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness data were derived from studies published between 1978 and 2002. The costs and resource use were obtained from a database published in 2002. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies.

Modelling
A decision tree model was constructed to examine the effectiveness and costs of the interventions examined in the study. The structure of the tree was reported. The model considered only the probability of re-bleeding. A 30-day time horizon was considered to be an appropriate follow-up period for the capture of all relevant clinical and economic end points.

Outcomes assessed in the review
The outcomes estimated were the probabilities of re-bleeding associated with each treatment strategy.

**Study designs and other criteria for inclusion in the review**
A review of the literature was undertaken to identify relevant clinical trials on the efficacy of PPI treatments. Studies from which point estimates of re-bleeding rates for this patient population could not be estimated were not included in the review. Also excluded were studies reporting lower dosage regimens, including intermittent bolus administration, and those in patients without high-risk endoscopic lesions.

**Sources searched to identify primary studies**
MEDLINE was searched up to December 2002 to identify relevant studies. The search terms were "acid suppression", "ulcer bleeding or haemorrhage", or "proton pump". Published narrative reviews were also evaluated and handsearches were performed from relevant articles.

**Criteria used to ensure the validity of primary studies**
The validity of the primary studies was ensured by selecting only randomised clinical trials and studies from which the point estimates of re-bleeding rates could be estimated.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
Four primary studies were included in the review.

**Methods of combining primary studies**
The primary estimates were pooled and 95% confidence intervals (CIs) were calculated using the standard approximation of the binomial distribution.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The probability of re-bleeding was 0.1176 (range: 0.07 - 0.18) with high-dose oral PPI, 0.0588 (range: 0.02 - 0.11) with high-dose i.v. PPI, and 0.2716 (range: 0.02 - 0.35) with placebo.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the effectiveness of high-dose PPI therapy. This was defined as the rate of patients not experiencing re-bleeding. The rate was derived using the decision model.

**Direct costs**
Discounting was not relevant because of the short time horizon of the model. A detailed breakdown of the cost items was not provided. The quantities of resources used were presented separately from the costs, although the costs were presented as macro-categories. The health services included in the economic evaluation were hospital stay and drugs. The cost/resource boundary of the third-party payer was adopted. The estimation of both the costs and quantities of resources used was based on a published database, the Nationwide Inpatient Sample 2000. Only relevant Medicare cases were considered. All of the costs were inflated to 2001 values, which was the price year.
Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
One- and two-way sensitivity analyses were performed to investigate the robustness of the estimated cost-effectiveness ratios to variations in all model inputs (probability and costs). The ranges of values used were either derived from the literature or arbitrarily set by the authors.

Estimated benefits used in the economic analysis
The effectiveness rates were 94% with high-dose i.v. PPI, 88% with high-dose oral PPI, and 72% with placebo.

Cost results
The costs per patient were $8,576 with high-dose i.v. PPI, $8,712 with high-dose oral PPI, and $9,256 with placebo.

Synthesis of costs and benefits
Average and incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative treatment strategies. The average cost per re-bleeding rate averted was $9,111 with high-dose i.v. PPI, $9,874 with high-dose oral PPI, and $12,707 with placebo. The incremental analysis revealed that high-dose i.v. PPI dominated high-dose oral PPI, which was both more costly and less effective. In turn, high-dose oral PPI was less costly and more effective than placebo, which was dominated.

The base case results were robust to variations in the model inputs in the one-way sensitivity analysis. The two-way sensitivity analysis identified some clinical settings in which the base-case results changed. For example, if the re-bleeding rate for high-dose oral PPI dropped to the lower bound, the cost-effectiveness ratio of high-dose i.v. PPI was no longer the lowest when the re-bleeding rate for high-dose i.v. PPI exceeded 6.3%. Conversely, the cost-effectiveness ratio of high-dose i.v. PPI was no longer the lowest if the re-bleeding rate of high-dose i.v. PPI increased to the upper bound and the re-bleeding rate of high-dose oral PPI dropped below 11.4%. Finally, high-dose oral PPI dominated placebo under all scenarios considered in the sensitivity analysis.

Authors’ conclusions
In patients undergoing endoscopic haemostasis for high-risk ulcer lesions, high-dose intravenous (i.v.) proton-pump inhibitor (PPI) dominated high-dose oral PPI over a variety of assumptions.

CRD COMMENTARY - Selection of comparators
The selection of the comparators reflected the objective of the study, which compared different high-dose PPI administration options. The authors justified the choice of the comparators. The less effective high-dose PPI strategy was also compared with no PPI therapy (placebo). You should decide whether they are valid comparators in your own setting.
Validity of estimate of measure of effectiveness
A systematic review of the literature was undertaken to identify relevant primary studies. Only clinical trials were included in the review, which ensured the validity of the sources used. The issue of the comparability of the primary studies was not addressed. The search methods and the approach used to combine the primary estimates were reported. Uncertainty in the efficacy data was investigated in the sensitivity analysis. The authors noted that limited trials were identified in the literature, and oral PPI data were derived from Asian patients. In fact, there were no head-to-head comparisons of i.v. versus oral PPI.

Validity of estimate of measure of benefit
The summary benefit measure was derived from the decision model and was specific to the interventions considered in the study. The use of a more comparable measure would have been helpful.

Validity of estimate of costs
The authors reported explicitly the perspective that was adopted in the study. Only the hospitalisation and drug costs were considered in the analysis. The use of a broader prospective and the inclusion of patient (indirect) costs would have been interesting. The costs were presented as macro-categories and the items included in the "hospital stay" categories were not reported. The price year was given, which aids reflation exercises in other settings. The source of the data was reported. The authors noted the uncertainty around some cost estimates. Sensitivity analyses of the cost estimates were carried out.

Other issues
The authors reported the results of published studies that showed, in part, the superiority of i.v. high-dose PPI. The issue of the generalisability of the study results to other settings was not explicitly addressed, but extensive sensitivity analyses were performed. This enhances the external validity of the analysis. The study referred to patients who had undergone endoscopic haemostasis for high-risk ulcer lesions, and this was reflected in the authors' conclusions.

Implications of the study
The study results supported the use of high-dose i.v. PPI in patients undergoing endoscopic haemostasis for high-risk ulcer lesions. However, the conclusions of the study should be corroborated using data from studies carried out in Western populations. The authors stated that the findings of their study should be used to support and guide future prospective trials.

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Other publications of related interest
Spiegel BM, Ofman JJ, Woods K, Vakil NB. Minimizing recurrent peptic ulcer hemorrhage after endoscopic


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