Proton pump inhibitors for the prevention of stress-related mucosal disease in critically-ill patients: a meta-analysis
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CRD summary
The review found a significantly lower rate of clinically important bleeding when using proton pump inhibitors rather than histamine-2 receptor antagonists in the prevention of stress-related mucosal disease in critically ill patients. Rates of nosocomial pneumonia were similar. The reliability of the authors’ conclusions is unclear due to some methodological weaknesses and differences between the small number of studies.

Authors' objectives
To evaluate the effectiveness of proton pump inhibitors compared to histamine-2 receptor antagonists in the prevention of stress-related mucosal disease in critically ill patients.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Cochrane Database of Abstracts of Reviews of Effectiveness were searched from 1950 to January 2008 for publications in English. American College of Physicians journal club was searched. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA) in critically ill adult patients with either of two risk factors (mechanical ventilation for more than 48 hours or coagulopathy) were eligible for inclusion. The primary outcome was clinically important bleeding. The secondary outcome was nosocomial pneumonia. Studies were excluded if there was a history of aspirin or non-steroidal anti-inflammatory drug (NSAID) use, active gastrointestinal bleeding or post-endoscopic treatment, or if there was no relevant outcome. Follow up was until discharge or death in all the included studies.

The intervention in all of the included RCTs was 40mg omeprazole per day given orally, intravenously or via a nasogastric tube. For one study the dose was doubled on the first day. The drugs used for comparison were ranitidine, famotidine or cimetidine. Details of the dosage and frequency of the specific drugs used were given in the review. All of the included patients were intensive care unit patients, most of whom required mechanical ventilation for 48 or more hours. No details were provided of the age or sex of the patients in the included studies. Details of the underlying diseases in all the included patients were provided. The incidence of clinically important bleeding and nosocomial pneumonia were measured in all the included RCTs.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed by three reviewers independently. Any disagreements were resolved by consensus. The criteria used were: patient selection; patient characteristics; randomisation; blinding; and definitions of bleeding and pneumonia. A scale of 0, 1 or 2 was used for each of the five items (maximum score was 10).

Data extraction
The number of events for each outcome were extracted in order to calculate odds ratios (OR) with 95% confidence intervals (CIs). The number needed to treat was calculated.

Two reviewers independently performed the extraction. Any disagreements were resolved by consensus.

Methods of synthesis
ORs and 95% CIs were calculated for each study, followed by calculation of pooled ORs and 95% CIs. Between-study
heterogeneity was determined using the X² test.

**Results of the review**

Three relevant RCTs were identified (n=569). All three studies had a high quality rating of 9 or 10.

Treatment with proton pump inhibitors was associated with significantly less clinically important bleeding than treatment with histamine-2 receptor antagonists (OR 0.42, 95% CI 0.20 to 0.91, number needed to treat was 22). There were no significant differences in the incidence of nosocomial pneumonia for treatment with proton pump inhibitors and treatment with histamine-2 receptor antagonists. Significant heterogeneity was found for clinically important bleeding (p=0).

**Authors’ conclusions**

The use of proton pump inhibitors for stress-related mucosal disease prophylaxis was associated with a significantly lower rate of clinically important bleeding than with histamine-2 receptor antagonists and similar rates of nosocomial pneumonia.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched, but it appeared that unpublished studies were not considered and publication bias was not assessed. Only studies published in English were identified, which implied that studies published in other languages were excluded. Study quality was assessed using suitable criteria. Validity assessment and data extraction were carried out with efforts to reduce error and bias; it was unclear whether this applied to other aspects of the review process. Relevant study and patient details were reported, but no details of the age or sex of the patients were given. Little detail was given of the method used for meta-analysis. Statistical heterogeneity was assessed and there was evidence for heterogeneity with the primary outcome. The reliability of the authors’ conclusions are uncertain due to lack of reporting of some review methods, the small number and small sizes of included studies and differences between the studies.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors identified a need for further large well-conducted RCTs to confirm that proton pump inhibitors were superior to histamine-2 receptor antagonists for stress-related mucosal disease prophylaxis. The authors identified a need for studies that compared proton pump inhibitors or histamine-2 receptor antagonists with placebo, but suggested that using a placebo might lead to ethical issues.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.