Acute pancreatitis and the role of histamine-2 receptor antagonists: a meta-analysis of randomized controlled trials of cimetidine

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Authors' objectives
To assess the efficacy of histamine type-2-receptor antagonists (H2RAs) in patients with acute pancreatitis.

Searching
MEDLINE and the Cochrane Library were searched for articles published in the English language from January 1966 to April 2001. The following MeSH terms were used in combination with terms indicating the type of publication: 'pancreatitis', 'random allocation', 'double-blind method', 'single blind method', 'randomized controlled trials', 'controlled clinical trials' and 'histamine H2 antagonists'. In addition, the following free textwords were used: 'acute pancreatitis', 'random*', 'burimamide', 'cimetidine', 'famotidine', 'nizatidine', 'ranitidine' and 'roxatine'. The bibliographies of the retrieved studies were reviewed and colleagues were consulted. Only full-length original journal articles were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible. Studies that did not provide standard deviations or standard errors were excluded from the meta-analysis.

Specific interventions included in the review
Comparisons of H2RAs with a concurrent placebo control were eligible. Studies that used only nasogastric tube suction as a control intervention were excluded. Only comparisons of parenteral cimetidine (1,200 to 2,000 mg/day, usually in divided doses every 4 to 6 hours) with placebo or fasting were included. The cointerventions, used in both groups as needed, included: nil by mouth, intravenous hydration, analgesia, antibiotics, and nasogastric tube.

Participants included in the review
The inclusion criteria were not defined in terms of the participants. Patients with alcoholic, biliary, idiopathic, and miscellaneous-cause pancreatitis were included. Most of the participants were male (40 to 96% across the studies), with a mean age ranging from 40 to 55 years across the studies. The mean baseline initial serum amylase was 2.5 to 5.6 times higher than the normal upper limit.

Outcomes assessed in the review
Studies that reported preplanned outcomes measures or the number of patients who died, developed complications or dropped out, were eligible. The duration of abdominal pain was also assessed. The authors intended to assess fever, leucocytosis and the dose of analgesia used, but insufficient data were reported in primary studies.

How were decisions on the relevance of primary studies made?
Two investigators independently screened the titles and abstracts of the identified studies, and any disagreements were resolved by a third investigator. The agreement between the reviewers for the study selection process was 100%.

Assessment of study quality
The included studies were restricted to placebo-controlled RCTs but no formal validity assessment was performed.

Data extraction
Two authors independently extracted the following data onto a standardised form: study design; sample size; characteristics of the participants or severity classification or similar information; the type and dose of H2RAs; and clinical outcomes. Any disagreements were resolved by discussion and consensus was reached.
Methods of synthesis

How were the studies combined?
Weighted descriptive means, along with the confidence intervals (CIs), and the mean values for a variety of study characteristics were calculated. For binary data, an odds ratio (OR) and 95% CI was calculated using the fixed-effect model weighted by the Mantel-Haenszel method. For continuous data, the treatment effect was calculated as the difference between the treatment and the placebo groups, and the data were pooled using the general variance-based method (see Other Publications of Related Interest no.1). Where the standard deviation was not reported, it was calculated from the standard error, 't' value or 'P' value (divided by two).

How were differences between studies investigated?
Statistical homogeneity for binary and continuous data was assessed using the chi-squared test Q statistic (see Other Publications of Related Interest no.2). Where there was evidence of heterogeneity, the random-effects method of DerSimonian and Laird (see Other Publications of Related Interest no.3) was used to combine the data. Sensitivity analyses were conducted for the two main outcomes (complications and duration of pain) by recalculating the weighted pooled estimated after excluding each individual study in turn.

Results of the review

Five placebo-controlled RCTs (285 patients) were included.

No RCTs reported the results of case-severity classification or other information to characterise the severity of the patients.

Mortality: only one death was reported so a pooled OR was not calculated.

Complications: some studies sought exhaustively for complications while other studies did not. There was no statistically-significant difference in complication rates between cimetidine and placebo. The OR was 1.64 (95% CI: 0.92, 2.92). There was no evidence of heterogeneity (P=0.477).

Duration of pain: there was no statistically-significant difference in the mean duration of pain between cimetidine and placebo. The weighted mean difference for cimetidine minus placebo was 6.96 hours (95% CI: -2.50, +16.43). There was no evidence of heterogeneity (P=0.145).

Only two studies reported the dose of analgesia but the names of the analgesics were not specified. No more than two studies reported the duration of fever, leucocytosis or hospitalisation.

Deleting the studies one at a time did not alter the results for complications (ORs ranged from 1.35 to 1.94) or duration of pain (weighted mean differences ranged from 2.99 to 10.07).

Authors’ conclusions

Cimetidine was not more effective than placebo in reducing acute pancreatitis-related complications and the duration of pain; rather, the use of cimetidine for acute pancreatitis could be associated with higher rates of complications and pain. Until the results of a large randomised trial show otherwise, H2RAs should not be used in the absence of specific clinical indications.

CRD commentary

The aims were stated and the inclusion criteria were defined in terms of the intervention, study design and outcomes. Several relevant sources were searched and the methods used to select the studies were described. Restricting the eligible studies to English language articles published in full, as identified in a limited number of databases, may have resulted in the omission of other relevant studies. In addition, the lack of an attempt to locate unpublished material raises the possibility of publication bias.

The included studies were restricted to placebo-controlled randomised trials but their validity was not formally assessed. Relevant data were extracted and tabulated, and details of the methods used to extract the data were reported. The
characteristics of participants across the studies were described in the text. Statistical heterogeneity was assessed, the
data were appropriately combined in a meta-analysis, and the influence of each study on the results was explored.

The evidence presented supports the authors' conclusions with respect to the lack of evidence of effectiveness for
cimetidine in acute pancreatitis. However, the results do not support the assertion that cimetidine may increase pain and
complications.

Implications of the review for practice and research
Practice: The authors state that the routine use of cimetidine should be abandoned until the safety and efficacy of
H2RAs are proven.

Research: The authors state that further randomised trials are required to assess the efficacy of a variety of H2RAs on
acute pancreatitis.

Bibliographic details
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Other publications of related interest

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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.