Treatment of acute pancreatitis with protease inhibitors: a meta-analysis
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CRD summary
This review assessed whether the treatment of acute pancreatitis with protease inhibitors reduces overall mortality or morbidity. The authors concluded that mortality may be reduced in patients with moderate to severe pancreatitis, but not in acute or mild forms of the disease. These conclusions are based on a post hoc analysis using an arbitrary definition of moderate to severe disease and, therefore, should be interpreted with caution.

Authors' objectives
To determine whether the treatment of acute pancreatitis with protease inhibitors reduces overall mortality or morbidity.

Searching
MEDLINE and the Cochrane Library were searched from 1966 to December 2003 for papers written in English, German or Japanese, or with an abstract in any of these languages. In addition to full papers, articles available in abstract form only were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing protease inhibitors administered by intravenous infusion with placebo were eligible for inclusion. The protease inhibitors used in the included studies were gabexate mesilate (600 to 4,000 mg/day) and aprotinin (275,000 to 800,000 units/day).

Participants included in the review
Studies of individuals with acute pancreatitis were eligible for inclusion. Just over half of the included studies specified a definition of acute pancreatitis. The definition used varied from 'an elevated urine or serum amylase level' to 'upper abdominal pain with a serum amylase level of more than four times the upper limit of normal'. The mortality rate in the control group, which was used to define case severity in individual studies, ranged from 0 to 31%.

Outcomes assessed in the review
The studies had to report relevant outcomes. However, these were not specified. The outcomes of interest were death, pancreatic pseudocyst formation, intra-abdominal abscess formation related to acute pancreatitis, and surgical treatment.

How were decisions on the relevance of primary studies made?
Five researchers independently assessed studies for inclusion, with any disagreements resolved by consensus.

Assessment of study quality
Study quality was assessed for appropriateness of randomisation, double-blinding, and withdrawals or drop-outs using the Jadad scale. The authors did not state who performed the quality assessment.

Data extraction
Five researchers independently extracted the data, with any disagreements resolved through discussion. The risk difference (RD) and 95% confidence interval (CI) were estimated for individual studies for the outcomes of interest.
Case severity was calculated on the basis of the mortality rate in the control group, with moderate to severe pancreatitis defined as a control group mortality rate greater than 10%.

**Methods of synthesis**
How were the studies combined?
The pooled RD and 95% CI were calculated using the Mantel-Haenszel fixed-effect model where there was no evidence of statistical heterogeneity, and the DerSimonian and Laird random-effects model if there was evidence of statistical heterogeneity. Publication bias was investigated using a funnel plot and the methods of Begg and Mazumdar and Egger et al.

How were differences between studies investigated?
Heterogeneity was investigated using the chi-squared statistic (P<0.05). Studies of gabexate mesilate and aprotinin were pooled separately, and a subgroup analysis and meta-regression was conducted based on disease severity. Differences between the studies were also discussed in the text.

**Results of the review**
Ten RCTs (n=1,036) were included: 6 of gabexate mesilate and 4 of aprotinin.

Based on the Jadad scale (minimum score 0, maximum score 5), the average quality score was 3.6 with a range of 2 to 4 points.

Mortality (10 RCTs).

There was no statistically significant difference in mortality between the protease inhibitors and placebo, either for gabexate mesilate and aprotinin pooled together (overall: RD -0.03, 95% CI: -0.07, 0.01) or separately (gabexate mesilate: RD -0.03, 95% CI: -0.09, 0.03; aprotinin: RD -0.04, 95% CI: -0.13, 0.05). There was evidence of statistical heterogeneity (P=0.015) in the aprotinin group of studies. The subgroup analysis found that there was a significantly lower mortality rate with protease inhibitors than with placebo in patients with moderate to severe pancreatitis but not mild pancreatitis (RD -0.07, 95% CI: -0.13, -0.01), as did the meta-regression (P=0.017).

Pancreatic pseudocysts (3 RCTs; 2 gabexate mesilate and 1 aprotinin).

There was no statistically significant difference between protease inhibitors and placebo in the formation of pancreatic pseudocysts (RD -0.03, 95% CI: -0.08, 0.03).

Intra-abdominal abscess (3 RCTs; 2 gabexate mesilate and 1 aprotinin).

There was no statistically significant difference between protease inhibitors and placebo in the formation of intra-abdominal abscess (RD -0.02, 95% CI: -0.05, 0.02).

Surgical treatment (3 RCTs of gabexate mesilate).

There was no statistically significant difference between protease inhibitors and placebo in the need for surgical treatment of acute pancreatitis (RD -0.10, 95% CI: -0.25, 0.04).

The authors reported that the funnel plot did not show an asymmetric pattern. Begg's and Egger's tests for publication bias were not statistically significant.

**Authors’ conclusions**
In patients with acute or mild pancreatitis, treatment with protease inhibitors did not significantly reduce mortality. However, mortality may be reduced in patients with moderate to severe pancreatitis.
CRD commentary
The review addressed a clear research question using defined inclusion criteria for the intervention, participants and study design. Two relevant databases were searched with some language restrictions. Relevant studies might have been missed as there were no specific attempts to identify unpublished studies, although the authors did investigate the possibility of publication bias and concluded that there was no evidence for this. The review methodology was described: this included measures to avoid the introduction of bias, though it was unclear whether the measures were applied to the quality assessment.

There was evidence of statistical heterogeneity in the aprotinin group of studies and pooling might have been inappropriate in this instance. It was not possible to fully assess clinical heterogeneity because of the limited information available on the primary study populations. The subgroup analysis according to disease severity appeared to be post hoc and the cut-off threshold used to define moderate to severe pancreatitis was arbitrary. In addition, the results of a statistical test for heterogeneity were not reported for this analysis. The authors’ conclusions about the effectiveness of protease inhibitors in reducing mortality in patients with moderate to severe pancreatitis should, therefore, be viewed with caution.

Implications of the review for practice and research
Practice: The authors suggested that the severity of pancreatitis should be assessed using the APACHE II score, with protease inhibitors being considered in patients with a score of 6 or more. However, APACHE II was not used in the review.

Research: The authors stated that RCTs are required to evaluate the efficacy of protease inhibitors for patients with severe pancreatitis.

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