Systematic review: rebound acid hypersecretion after therapy with proton pump inhibitors

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CRD summary
This review evaluated the incidence of rebound acid hypersecretion after the discontinuation of proton-pump inhibitors (PPIs). The authors concluded that the available evidence is too limited to confirm a clinically relevant acid hypersecretion after the withdrawal of PPIs. This review has some methodological weaknesses, but the authors' cautious conclusions seem to reflect the limited evidence presented and are likely to be reliable.

Authors' objectives
To evaluate the incidence of rebound acid hypersecretion after the discontinuation of proton-pump inhibitors (PPIs).

Searching
PubMed, EMBASE and the Cochrane CENTRAL Register were searched to October 2005 for published trials; the search terms were reported. Abstracts were excluded.

Study selection
Study designs of evaluations included in the review
No inclusion criteria were specified for study design.

Specific interventions included in the review
Studies evaluating the withdrawal of PPIs were eligible for inclusion. Most of the included studies evaluated oral omeprazole (40 mg daily); other studies evaluated different doses of omeprazole (20 to 60 mg) or lansoprazole (30 mg daily). Control treatments, where these existed, included placebo and ranitidine (300 mg daily). PPI treatment duration varied from 1 to 90 days. In one study, patients were also treated with Helicobacter pylori (H. pylori) eradication therapy.

Participants included in the review
Inclusion criteria were not specified with respect to participants. The included participants were most often healthy, but some studies of patients with duodenal ulcer or reflux oesophagitis were also included. Two-thirds of the included patients were men.

Outcomes assessed in the review
Studies that evaluated rebound acid hypersecretion, measured by nasogastric acid aspiration or intragastric pH monitoring, were eligible for inclusion. The included studies evaluated hypersecretion at different time points after PPI withdrawal and measured basal levels, maximal or peak secretory levels and levels after stimulation with various methods. Follow-up was for a maximum of 5 to 56 days after PPI withdrawal.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Reviews and trials, were rated according to study design as A1 (highest quality) to D (lowest quality; expert opinion). The level of evidence was graded from level 1 (strong evidence) to level 4 (evidence supported only by expert opinion).

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
Methods of synthesis
How were the studies combined?
The studies were grouped by the method used to measure outcomes and described in a narrative.

How were differences between studies investigated?
Differences in study interventions and outcomes were discussed in the text and tabulated. Studies reporting results by the patients' H. pylori status were discussed separately.

Results of the review
Eight studies (n=138) were included in the review: 4 randomised controlled trials (RCTs; n=60) and 4 open studies (n=78).

Study quality was considered good in three studies, moderate in three and low in two.

Aspiration studies with determination of basal, maximal or peak secretory capacity. Two small RCTs (n=22 healthy participants) did not find a higher gastric acid production, while an open trial of patients with reflux oesophagitis (n=9) showed a significant increase in basal and pentagastrin-stimulated acid secretion, after the cessation of PPIs. The influence of H. pylori on gastric acid secretion after PPI was assessed in 2 open studies of healthy participants. In the first trial (n=21), basal and maximal secretory capacity at day 15 were significantly higher compared with baseline among H. pylori-negative patients, while no significant variation was observed in H. pylori-positive patients. In the second study (n=32), H. pylori-negative patients experienced an increase in maximal secretory capacity of 16 to 40% after PPI treatment cessation. In H. pylori-positive patients, basal and maximal secretory capacity were significantly higher at day 28 relative to baseline. In H. pylori-eradicated patients, secretory capacity was only increased at day 56; maximal secretory capacity was increased until day 28 after cessation. No comparisons were made between the three investigated groups.

Aspiration studies with determination of 24-hour intragastric acidity or integrated nocturnal acidity (2 studies).

In the first open study which included patients with duodenal ulcer (n=9), a lower 24-hour intragastric acidity was found at 7 days after PPI withdrawal, while similar levels were detected at 56 days. In the second study, 24 healthy men were randomised in a double-blind fashion to 300 mg ranitidine or 40 mg omeprazole for 25 days. A significant increase in integrated nocturnal activity was observed at 3 and 6 days after ranitidine withdrawal in the patients allocated to omeprazole withdrawal; integrated nocturnal activity returned to pre-treatment levels by day 6 after PPI withdrawal. The patients receiving omeprazole had higher gastrin levels on the last day of dosing compared with pre-treatment values.

Studies using intragastric pH monitoring.

In a randomised controlled double-blind trial which included 16 healthy patients, a similar intragastric pH was found at days 4, 7 and 14 after placebo or lansoprazole withdrawal. Serum gastrin levels increased significantly during therapy, returning to pre-treatment levels in all the study participants within 14 days after therapy discontinuation.

Authors' conclusions
There is no strong evidence to support a clinically relevant rebound acid hypersecretion after the discontinuation of PPIs.

CRD commentary
This review addressed a well-defined question in terms of the intervention and study outcomes. No inclusion criteria were specified for the participants or study design, which led to the inclusion of a diversity of studies. Two relevant databases and one register were searched, but it is unclear whether efforts were made to identify unpublished studies, therefore publication bias, which was not evaluated, cannot be excluded. It was not stated whether language restrictions were applied, and language bias cannot be ruled out. It was not reported whether two independent reviewers performed
the study selection, data extraction and study quality assessment; this might have introduced error and bias in the review process. The assessment of study quality was limited to study design, blinding and an overall grading, making it difficult to independently comment on the reliability of the evidence presented.

The results data were not consistently reported for the included studies and so the review findings could not be confirmed. The clinical heterogeneity of the included studies supports the authors' decision not to pool the data in a meta-analysis. The inclusion of relatively small, heterogeneous, poor-quality studies with few participants represents a major limitation of the review. The authors' cautious conclusions appear appropriate based on the limited evidence presented, but the lack of reporting of review methods and results data means it is difficult to assess the reliability of these conclusions.

Implications of the review for practice and research
Practice: The authors stated that a gradual tapering of PPI treatment should be considered in patients treated for longer periods or those who had experienced a rapid recurrence of symptoms after previous treatment discontinuation.

Research: The authors stated that further studies are needed to establish whether rebound acid secretion develops after PPI therapy and to clarify the role of H. pylori infection.

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Record Status
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.