Systematic review: impaired drug absorption related to the co-administration of antisecretory therapy
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CRD summary
This review concluded that gastric pH appeared relevant for absorption of some cardiovascular or infectious disease agents. Antisecretory agents may significantly modify the absorption of co-administered drugs. This was a reasonably robust review; the authors' conclusions appeared to reflect the evidence and are likely to be reliable.

Authors' objectives
To investigate impaired drug absorption related to acid inhibition through the use of co-administered proton pump inhibitors and histamine H$_2$ receptor antagonists.

Searching
English language studies were identified through a search of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and SCOPUS databases from 1980 to September 2008. Search terms were reported. Reference lists of potentially relevant studies were also searched.

Study selection
Studies that reported drug malabsorption in adult patients related to acid inhibition from receiving proton pump inhibitors and/or histamine H$_2$ receptor antagonists for gastric conditions were eligible for inclusion. Randomised controlled trials, randomised cross-over trials, prospective/retrospective cohort and case-control studies, cross-sectional studies, and case series were eligible for inclusion. Case reports, meta-analyses and reviews were excluded. Studies that addressed impaired absorption of micronutrients (e.g. iron, zinc, cobalamin) and studies of patients with Helicobacter pylori-related gastritis and/or H. pylori-induced hypochlorhydria were excluded.

The primary outcome was the maximum plasma concentration of the investigated drug.

The interventions in included studies were: antifungal agents (ketoconazole and itraconazole); an antiviral agent (atazanavir); antibiotics (cefepodoxime and enoxacin); an antithrombotic agent (dipyridamole); a calcium channel blocker (nifedipine); a cardiac glycoside (digoxin); and a bisphosphonate (alendronate). The majority of included studies compared the investigated drug alone with the investigated drug plus proton pump inhibitors or histamine H$_2$ receptor antagonists. In half of the included studies, gastric acidity was assessed by nasogastric aspirate, or by a consumable radiotelemetric device (Heidelberg capsule); the other half did not assess gastric pH. All but one of the included studies was conducted in mainly healthy volunteers with a mean age of 26 years; 68% were male. Antisecretory agents were administered for a median of five days (range two to 11 days) in half of the included studies, or as a single or double dose in the remaining studies.

Two reviewers independently selected studies for inclusion and disagreements were resolved through consensus.

Assessment of study quality
Methodological quality was assessed by two independent reviewers using a modified Jadad scale, with scores ranging from 0 to 6 points, with higher scores indicating better quality. The scale evaluated: randomisation; blinding; inclusion and exclusion criteria; drop-outs and withdrawals; measures of adverse effects; and appropriateness of statistical analyses.

It was unclear how many reviewers performed the validity assessment.

Data extraction
The maximum plasma concentration or the area under the plasma concentration curve was considered as the common
outcome measure for drug absorption. This was expressed as a percentage of the variation of the maximum plasma concentration or the area under the plasma concentration curve of the investigated drug in the presence of antisecretory agents compared with basal conditions, where data were available.

It was unclear how many reviewers performed the data extraction.

**Methods of synthesis**
The studies were combined using a narrative synthesis supported by tables. Results were grouped by drug type and summarised by their function (e.g. drugs for infectious disease).

**Results of the review**
Sixteen randomised cross-over trials were included in the review (n=217 participants). The mean number of participants was 12 in each study (range 6 to 24). Overall study quality was high; the mean Jadad score was 4.25 (±0.1).

**Infectious disease drugs** (anti-fungal, anti-viral and antibiotics; eight studies): Acid suppression induced by antisecretory agents led to a reduced absorption of infectious disease drugs with a median maximum plasma concentration reduction of 66.5% compared with infectious disease drugs alone.

**Cardiovascular drugs** (antithrombotic, calcium channel blocker and cardiac glycoside; seven studies): Acid suppression induced by antisecretory agents led to reduced absorption (approximately 50%) for the antithrombotic agent dipyridamole in one study, but increased absorption of nifedipine and digoxin with a median AUC increase of 10% in five studies.

**Metabolic drugs** (bisphosphonate; one study): One study investigated alendronate in post-menopausal women and found that hypochlorhydria was associated with nearly two-fold increase in alendronate availability; taking the drug with orange juice reduced bioavailability by approximately 60%.

**Authors’ conclusions**
Gastric pH appeared relevant for absorption of some cardiovascular or infectious disease agents. Antisecretory agents may significantly modify the absorption of co-administered drugs.

**CRD commentary**
This review addressed a clear question, supported by appropriate inclusion criteria. Relevant databases were searched, although the restriction to English language studies may mean that some information could have been missed. Search terms were reported. It appeared that no attempts were made to identify unpublished studies; publication bias was not considered in the report. Suitable methods to minimise risk of reviewer error and bias were reported for study selection, but it was unclear whether steps were taken to reduce bias for data extraction or validity assessment.

The decision to present included studies narratively, and not to pool studies in a meta-analysis, was appropriate given the heterogeneity between studies. The authors recognised some of the methodological difficulties with the review, specifically the small number of participants in included studies, the inclusion of mainly healthy volunteers in the majority of studies, and the investigation of drug absorption over a very short-term use of acid suppression agents.

This is a reasonably robust review; the authors’ conclusions appeared to reflect the evidence and are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that clinicians should keep in mind the possible interaction between antisecretory agents and drugs, the absorption of which may be influenced by impaired gastric acid secretion.

**Research:** The authors stated that large clinical trials investigating the impaired absorption of drugs due to acid suppression using proton pump inhibitors or histamine H\textsubscript{2} receptor antagonists are lacking.
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