Proton pump inhibitors and their drug interactions: an evidence-based approach
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The proton pump inhibitors (PPIs) are the most effective antisecretory agents used to treat acid-related disorders. As such, they are frequently prescribed for patients who are concurrently using other medications. PPIs may interact with other drugs through numerous mechanisms. The most important include competitive inhibition of hepatic cytochrome P (CYP) 450 enzymes involved in drug metabolism, and alteration of the absorption of other drugs via changes in gastric pH levels. Poor metabolizers, who lack CYP2C19, may be particularly predisposed to drug interactions. Although the potential for drug interactions is high, few clinically significant interactions have been reported for the PPIs. Nevertheless, caution is indicated when certain drugs are co-prescribed with these agents. The incidence of clinically significant drug interactions increases proportionately with the number of drugs taken and with the age of the patient. The drug interaction with the greatest clinical importance is the reduction in benzodiazepine clearance by omeprazole.


Keywords: CYP450, drug interactions, lansoprazole, omeprazole, pantoprazole, proton pump inhibitors, rabeprazole

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Introduction
Drug interactions are a common cause of treatment failure and adverse drug reactions. They are particularly likely to occur when multiple medications are being taken, as is often the case in elderly patients with acid-related disorders. The incidence of significant drug interactions ranges from 3% to 5% in patients taking few medications, but this may increase to 20% in patients taking 10–20 drugs [1]. If one or more of these medications has a narrow therapeutic range, then the clinical consequences can be particularly important [2].

Methodology
While previous reviews of proton pump inhibitors (PPIs) and their drug interactions have described potential and theoretical drug interactions, we aimed to make this review clinically relevant by focusing attention on the evidence supporting significant interactions derived from clinical trials. In order to achieve this focus, we used an evidence-based approach to the literature when assessing clinical trials. The scoring system used in this paper has been reported previously [3]. The nature of the evidence was placed in one of five categories, which are cited in the text alongside the references. The references were examined by two independent reviewers (Gerson and Triadalopoulos), who assigned a categorical rating to each statement where an evidence-based approach was appropriate. In cases where a difference of opinion existed, the literature was re-examined and a consensus was obtained.

Evidence classified as category ‘A’ refers to evidence from clinical trials that are randomized and well controlled. Category ‘B’ refers to evidence from cohort or case-controlled studies. Category ‘C’ refers to evidence from case reports or flawed clinical trials. Evidence categorized as ‘D’ is limited to the clinical experience of the authors. Category ‘E’ refers to situations where there is insufficient evidence available to form an opinion. In the review that follows, the level of evidence will be listed in parentheses following each statement, when appropriate.

Mechanisms involved in drug interactions
There are a variety of mechanisms by which drug interactions occur; most of them have relevance to the four PPIs now in clinical use. One particularly relevant mechanism involves altering drug absorption by changing the gastric pH. Drugs that raise gastric pH, such as the PPIs, will increase the absorption of weak acids (e.g. digoxin, furosemide, aspirin), and decrease the absorption and solubility of weak bases (e.g. ketoconazole) [4]. Drug interactions may also occur via displacement from protein binding sites, antagonistic or synergistic actions of the two drugs, and interference with renal tubule excretion through competition for the same transport system [5].

Probably the most important mechanism for drug interactions is modification of the activity and synthesis of hepatic enzyme systems responsible for drug metabo-
The cytochrome P (CYP) 450 enzyme system consists of at least 30 isoenzymes, organized into 12 gene families [6]. Three of these gene families (CYP 1, CYP 2, CYP 3) are considered to be important in drug metabolism in humans. Drugs that are metabolized by the same CYP isoforms compete with one another for the enzyme, and the drug with the least affinity will probably be inhibited [7,8]. In addition, some drugs stimulate or inhibit the expression of a particular CYP450 enzyme system, which can affect the extent of drug metabolism for substrates of that enzyme.

All of the PPIs are metabolized in the liver through the activity of multiple CYP450 enzymes (Fig. 1). The major metabolic enzymes involved are CYP2C19 and CYP3A4 [9]. CYP2C19 may be particularly important; for example, the anti-Helicobacter pylori effect resulting from the combination of a PPI with antibiotic treatment appears to be related to the CYP2C19 genotype, with CYP2C19 poor metabolizers demonstrating superior eradication of H. pylori [10,11] (evidence B). The CYP2C19 enzyme exists in two genetically determined forms, resulting in either a poor S-mephenytoin 4'-hydroxylase metabolizer phenotype or an extensive S-mephenytoin 4'-hydroxylase metabolizer phenotype [12]. The poor metabolizer phenotype is autosomal recessive, and has a variable frequency of expression that depends upon race: the phenotype is found in 1% of African Americans [13] (evidence C), 2–6% of Caucasians [14] (evidence B), 13% of Koreans [15] (evidence B), 15% of Chinese people and 19–23% of Japanese descent [16] (evidence B). The poor metabolizer phenotype results from a genetic mutation that causes a complete absence of active CYP2C19, inhibiting the clearance of drugs (including the PPIs) that depend upon it for their metabolism. As a result, other enzymes, such as CYP3A4, become the major metabolizers for these drugs. In poor metabolizers of CYP2C19, standard doses of PPIs may result in area-under-the-curve (AUC) measurements that are elevated up to 10-fold compared with extensive metabolisers [17,18]. Patients with gastro-oesophageal reflux (GORD) on once-daily PPI dosing who have inadequate symptom control are probably extensive metabolizers of CYP2C19. Slow metabolizers of CYP2C19 are also slow metabolisers of other drugs, such as diazepam [19] (evidence A) and phenytoin [17] (evidence B).

Fig. 1

Metabolic pathways of the proton pump inhibitors (PPIs) and the major cytochrome P (CYP) 450 enzymes involved. The thicker the arrow, the larger the contribution of the CYP isoform to the metabolic pathway. Reprinted with permission from [7].
Proton pump inhibitors and their drug interactions

Omeprazole

Omeprazole, the first PPI to be available for clinical use, is the PPI most associated with known drug interactions. Omeprazole is metabolized to hydroxylomeprazole and omeprazole sulphate primarily through the participation of the enzymes CYP2C19, CYP3A4 and CYP2D6 [20]. Omeprazole has a much greater affinity for interaction with CYP2C19 (responsible for its major metabolic pathway) than with CYP3A4, therefore it has a much greater potential for drug interactions compared with the other PPIs.

Clinically, the most important drug interaction induced by omeprazole is a 25–50% reduction in clearance of diazepam due to competitive inhibition of CYP2C19 [21,22] (evidence A); this effect is not seen in slow metabolizers, who lack CYP2C19 [19] (evidence A). Possible interactions of omeprazole with other benzodiazepines that are metabolized by the cytochrome P450 system should also be considered, such as alprazolam, chloridiazepoxide, clonazepam, midazolam [23], triazolam and flurazepam [24], although to date only one case report has described such an interaction (evidence C). Benzodiazepines that undergo glucuronidation and therefore would not interact with omeprazole include lorazepam, oxazepam and temazepam [25].

Omeprazole-induced competitive inhibition of CYP2C19 can affect the metabolism of drugs such as phenytoin and warfarin. While pharmacokinetic studies have demonstrated that omeprazole increases the AUC of phenytoin [26] and reduces its plasma clearance [27], a clinical study in epileptic patients taking phenytoin who received omeprazole for three weeks did not demonstrate any change in the plasma phenytoin levels [28] (evidence B). With regards to warfarin, there are few data to support a significant clinical interaction. Warfarin exists as two enantiomers: R-warfarin, which is metabolized primarily by CYP2C19, and S-warfarin, the more active isomer, which is metabolized mainly by CYP2C9. Although a case report described elevation of prothrombin time in an anticoagulated patient who received omeprazole [29] (evidence C), subsequent randomized trials have not shown a significant interaction. In healthy volunteers given omeprazole and warfarin, S-warfarin activity did not increase significantly during a two-week test period [30,31] (evidence A). The mean prothrombin time was not changed significantly in a cohort of chronically anticoagulated patients who received omeprazole versus placebo therapy [32] (evidence A). Therefore, the interactions of omeprazole with phenytoin and warfarin do not appear to be clinically significant.

Drugs that have a high affinity for CYP3A4, such as ketoconazole and clarithromycin, are capable of increasing omeprazole concentrations. Ketoconazole in doses of 100–200 mg has been shown to cause inhibition of the formation of omeprazole sulphate in both extensive and poor metabolizers, resulting in a twofold increase in omeprazole concentrations in poor metabolizers of CYP2C19 [33] (evidence B). Clarithromycin, which is used in combination with amoxycillin and omeprazole for H. pylori treatment, inhibits the metabolism of omeprazole in both extensive and poor metabolizers of CYP2C19, resulting in high eradication rates for H. pylori infection [34] (evidence A).

Omeprazole can also induce drug interactions via other mechanisms. For example, by causing elevation of gastric pH, omeprazole causes a 10% increase in AUC values for digoxin [35] (evidence A) and a 26% increase in AUC values for nifedipine [36] (evidence A) although neither of which are clinically significant. In addition, the absorption rate of salicylate from enteric-coated tablets is increased when administered with omeprazole, due to increases in gastric pH, leading to early disruption of the enteric coating and intragastric release of the drug [37] (evidence B). This effect is not noted, however, with uncoated salicylate tablets.

Other drugs that have been tested with omeprazole and have not been shown to have a significant interaction include propranolol [38] (evidence A), theophylline [39] (evidence A), quinidine [40] (evidence A) and ethanol [41,42] (evidence B). While case reports suggest an elevation of cyclosporin levels due to omeprazole administration [43] (evidence C), no evidence of such an interaction has been shown in randomised controlled trials [44] (evidence A).

Lansoprazole

Lansoprazole is metabolised primarily by CYP2C19 and CYP3A4 to 5-hydroxylansoprazole and lansoprazole sulphone [45]. In vitro studies using human hepatic microsomes have demonstrated that lansoprazole is at least as potent a competitive inhibitor of CYP2C19 as omeprazole, but it does not cause a significant inhibition of diazepam metabolism [46] (evidence A).

Lansoprazole, like omeprazole, induces the synthesis of CYP450 enzymes CYP1A1 and CYP1A2. This induction has been reported to increase the metabolism of theophylline, with a 13% decrease in AUC values [47] (evidence B). However, in randomized controlled trials where theophylline has been co-administered with lansoprazole, no significant alteration in theophylline levels has been demonstrated [39,48,49] (evidence A).

Administration of lansoprazole has not been shown to cause significant elevation in phenytoin levels [50] (evidence A) or prothrombin time in patients on
chronic warfarin therapy [51] (evidence A). Therefore, compared with omeprazole, lansoprazole does not appear to have any significant drug interactions.

Pantoprazole

Like the other PPIs, pantoprazole is metabolized initially by CYP2C19 and CYP3A4 to hydroxypantoprazole or pantoprazole sulphate. It is then converted rapidly to pantoprazole sulphate by a sulphotransferase, thereby minimizing the potential for significant drug interactions [52].

Pantoprazole does not appear to have any significant drug interactions. While pantoprazole has been reported to enhance the absorption of digoxin, presumably by raising gastric pH, significant elevations in digoxin levels have not been demonstrated [53] (evidence A). In addition, pantoprazole does not appear to interfere significantly with CYP450 enzyme-mediated metabolism. It therefore does not interact with nifedipine (CYP3A4) [54] (evidence A), diclofenac [55] (evidence A), phenytoin [56] (evidence A), warfarin (CYP2C9) [57] (evidence A), diazepam (CYP2C19) [58] (evidence A), metoprolol (CYP2D6) [59] (evidence A), theophylline (CYP1A2) [60] (evidence A) or carbamazepine [61] (evidence A). Pantoprazole also does not have any interactions with antipyrene in humans [62] (evidence A). Antipyrene is a substrate for a variety of cytochrome P450 enzymes, making it useful as a marker for mixed hepatic oxidase enzyme activity in general. The enzymes involved include CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18 and CYP3A4 [63]. All of these studies suggest that pantoprazole has virtually no CYP450 interactions. In vitro studies have demonstrated that pantoprazole has lower inhibitory activity on CYP450 enzymes than omeprazole or lansoprazole. Therefore no significant clinical interactions with pantoprazole have been reported [64].

Rabeprazole

Because of its metabolic pathways, rabeprazole has minimal drug interactions. As with the other PPIs, CYP2C19 and CYP3A4 play a role in metabolizing rabeprazole. However, that role is much less important compared with omeprazole. In vitro studies show that rabeprazole has approximately half the potential of omeprazole to inhibit CYP2C19 [65]. The major metabolic pathway for rabeprazole involves its non-enzymatic reduction to a thioether compound. Rabeprazole demonstrates no interactions with theophylline (CYP1A2), warfarin (CYP2C9) [66] (evidence A) or phenytoin (CYP2C9) [67]. While omeprazole has been shown to decrease the clearance of diazepam (CYP2C19), particularly in extensive metabolizers of S-mephenytoin, this effect is not seen with rabeprazole [65]. The very minor role that CYP2C19 plays in metabolizing rabeprazole accounts for the observation that rabeprazole is the least affected of all the PPIs by the lack of this enzyme in poor metabolizers.

Rabeprazole does have some drug interactions that appear to be related to its highly potent antisecretory activity. It increases the absorption of digoxin, elevating its AUC, resulting in modest increases in digoxin levels [67]. It also decreases the absorption of ketoconazole, resulting in lower serum concentrations [68]. Unfortunately, no data from clinical trials are available to assess whether these effects have any clinical significance. Nonetheless, it would be prudent to monitor patients taking ketoconazole or digoxin with rabeprazole or any of the other PPIs, all of which raise gastric pH. No clinically relevant changes in plasma rabeprazole concentrations are seen when rabeprazole is co-administered with antacids [69] (evidence A).

Discussion

In this age of frequent polypharmacy, it is important to consider potential drug interactions when prescribing antisecretory therapy. In theory, antisecretory agents may interact with drugs on multiple levels, beginning with changes in gastric absorption and culminating with competitive inhibition of metabolic enzymes. Some antisecretory agents, such as the histamine-2 receptor antagonist cimetidine, have numerous clinically significant drug interactions [70]. These interactions are associated primarily with effects of cimetidine on the activity of CYP450 enzymes.

Our conclusions from this evidence-based approach are that the PPIs appear to be relatively free of clinically significant drug interactions. The major interaction of concern is the resulting decrease in clearance of many benzodiazepines as a result of omeprazole administration. This effect is seen primarily in patients who are CYP2C19 metabolizers; it is not seen with administration of the other PPIs. Therefore, for patients on chronic benzodiazepine therapy, a PPI other than omeprazole should be administered. While rabeprazole has been associated with modest increases in digoxin levels and lowered serum concentrations of ketoconazole, these effects have not been studied extensively in clinical trials. Data are needed to assess whether these effects are of clinical importance. Lansoprazole and pantoprazole do not appear to have any drug interactions of clinical significance.

While drug interactions do not appear to play an important role in the use of PPIs, identification of PPI CYP2C19 metabolic activity is particularly important when assessing H. pylori eradication therapy. Evidence of this phenomenon has emerged from experience with the use of omeprazole in anti-H. pylori regimens. Case series of patients with active H. pylori infection and peptic ulcer have shown that patients who are exten-
sive metabolizers of CYP2C19 do not achieve the eradication rates of poor metabolisers [71,72] (evidence B), and therefore require higher doses of omeprazole in order to eradicate the infection [11] (evidence C). Several reasons have been proposed for the higher eradication rates witnessed in poor metabolizers of CYP2C19. The increased availability of omeprazole in poor metabolizers results in prolonged elevation of gastric pH levels, leading to superior eradication of the *H. pylori* organism. Omeprazole alone is thought to have an anti-*H. pylori* effect that is enhanced in poor metabolizers [73]. In addition, omeprazole is thought to increase intragastric concentrations of amoxicillin partly by reducing gastric juice volume [74]. Therefore, in situations where repeated treatment for *H. pylori* has been attempted without successful eradication of the organism, assessment of CYP2C19 genotype would be useful, with alteration of therapy for patients who are extensive metabolizers. In addition, since rabeprazole is metabolized less extensively by the CYP2C19 pathway, one would expect that extensive CYP2C19 metabolizers would have improved *H. pylori* eradication rates if administered rabeprazole. This assumption has not yet been tested in clinical trials.

In summary, significant drug interactions with PPIs have not been observed. The exception is for patients taking benzodiazepines metabolized by the cytochrome P450 system, who should not receive omeprazole therapy because of the significant potential for interaction. In addition, genotype status for CYP2C19, the principal isoenzyme involved in hepatic metabolism of the PPIs, plays an important role in the cure rate of *H. pylori* infection, and should be considered whenever a PPI is administered for eradication of this chronic infection.

References


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