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An evidence-based strategy for proton pump inhibitors and related medication interactions

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Abstract
The best antisecretory drugs for treating acid-related conditions are proton pump inhibitors (PPls). They are therefore often administered to patients who are taking other drugs at the same time. PPls may interact with other medications in a variety of ways. The two most significant ones are the competitive suppression of hepatic cytochrome P (CYP) 450 enzymes involved in drug metabolism and the modification of other medicines' absorption through pH changes in the stomach. Drug interactions may be more likely to occur in poor metabolizers who lack CYP2C19. Few clinically relevant interactions have been documented for the PPls, despite the substantial potential for pharmacological interactions. However, when certain medications are co-prescribed with these agents, care should be taken. The frequency of clinically relevant drug interactions rises in direct proportion to the patient's age and the number of medications they take.

Keywords: Proton pump inhibitors, lansoprazole, omeprazole, pantoprazole, CYP450, medication interactions, and rabeprazole

Introduction

Adverse medication responses and treatment failure are frequently caused by drug interactions. When taking several medications, as is frequently the case in older people with acid-related illnesses, they are especially likely to happen. In individuals taking few prescriptions, the incidence of serious drug interactions varies from 3% to 5%; however, in patients consuming 10–S0 drugs, this may rise to S0% [1]. The clinical implications may be especially significant if one or more of these drugs have a limited therapeutic range [S].

Methodology

We sought to make this review clinically relevant by concentrating on the data supporting substantial interactions acquired from clinical trials, whereas prior reviews of proton pump inhibitors (PPIs) and their medication interactions have highlighted hypothetical and theoretical drug interactions. We evaluated clinical trials using an evidence-based approach to the literature in order to accomplish this goal. This paper's grading mechanism was previously reported [3]. Five categories were identified based on the type of evidence, and these categories are listed in the text along with the references. Two independent reviewers, Gerson and Triadafilopoulos, looked over the references and gave each statement that called for an evidence-based strategy a categorical rating. When there was disagreement, the literature was reexamined and a consensus was reached.

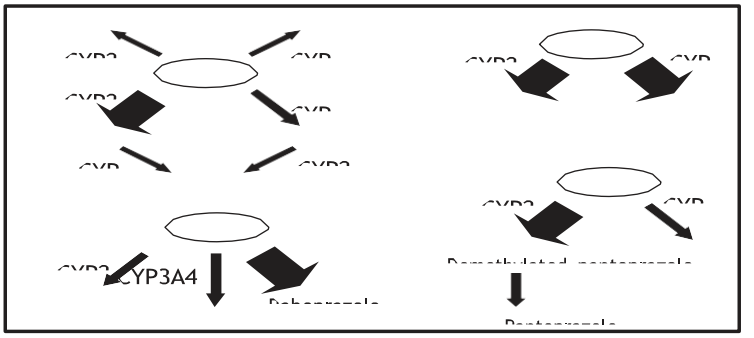
Evidence from well-controlled, randomized clinical studies is categorized as "A." Evidence from cohort or case-controlled studies is referred to as category "B." Evidence from case reports or faulty clinical studies is referred described as category "C." The authors' clinical experience is the only source of evidence classified as "D." Situations in which there is not enough information to develop an opinion are referred to as category "E." When relevant, the level of evidence will be indicated in parenthesis after each statement in the review that follows.

Drug interaction mechanisms Drug interactions can arise through a number of different routes, the most of which are relevant to the four PPIs now used in clinical settings. Changing the pH of the stomach to modify drug absorption is one particularly pertinent technique.

PPIs and other medications that elevate stomach pH will increase the absorption of weak acids (like digoxin, furosemide, and aspirin) and decrease the solubility and absorption of weak bases (like ketoconazole) [4]. Additionally, antagonistic or synergistic activities of the two medications, displacement from protein binding sites, and interference with renal tubule excretion through competing for the same transport route can all result in drug interactions [5].

Modification of the activity and synthesis of hepatic enzyme systems responsible for drug metabolism is likely the most significant mechanism for drug interactions. At least thirty isoenzymes, arranged into 1S gene families, make up the cytochrome P (CYP) 450 enzyme system [6]. Three of these gene families—CYP 1, CYP S, and CYP 3—are thought to be crucial for human drug metabolism. The medication with the lowest affinity will likely be blocked when drugs that are metabolized by the same CYP isoforms compete with one another for the enzyme [7, 8]. Furthermore, some medications may increase or decrease the expression of a specific CYP450 enzyme system, which may have an impact on the degree of drug metabolism for that enzyme's substrates.

Several CYP450 enzymes are involved in the liver's metabolism of all PPIs (Fig. 1). CYPSC19 and CYP3A4 are the two main metabolic enzymes involved [9]. CYPSC19 may be especially significant; for instance, the anti-Helicobacter pylori effect that arises from the combination of a PPI with antibiotic treatment seems to be related to the CYPSC19 genotype, with CYPSC19 poor metabolizers showing superior eradication of H. pylori [10,11] (evidence B). A poor S-mephenytoin 4'-hydroxylase metabolizer phenotype or an extensive S-mephenytoin 4'-hydroxylase metabolizer phenotype are the two genetically determined forms of the CYPSC19 enzyme [1S]. The autosomal recessive poor metabolizer phenotype is found in 1% of African Americans [13] (evidence C), S–6% of Caucasians [14] (evidence B), 13% of Koreans [15] (evidence B), 15% of Chinese people, and 19–S3% of Japanese descent [16] (evidence B). A genetic mutation that results in a total lack of active CYPSC19 creates the poor metabolizer phenotype, which prevents the clearance of medications (including PPIs) that rely on it for their metabolism. Other enzymes, like CYP3A4, consequently take over as these medications' primary metabolizers. Standard PPI dosages may cause area-under-the-curve (AUC) readings to be up to ten times higher in poor metabolizers of CYPSC19 than in extensive metabolizers [17,18]. Patients with gastro-oesophageal reflux disease (GORD) who take PPIs once a day and have poor symptom control are likely CYPSC19 extensive metabolizers. CYPSC19 slow metabolizers are likewise slow metabolizers of other medications, including phenytoin [17] (evidence B) and diazepam [19] (evidence A).



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

The PPI most frequently linked to known drug interactions is omeprazole, which was the first PPI to be made accessible for clinical use. The enzymes CYPSC19, CYP3A4, and CYPSD6 play a major role in the metabolism of omeprazole to hydroxyomeprazole and omeprazole sulfate [S0]. Compared to the other PPIs, omeprazole has a far higher potential for drug interactions since it has a significantly higher affinity for interaction with CYPSC19, which is responsible for its primary metabolic pathway, than with CYP3A4. The most significant clinical drug interaction caused by omeprazole is an S5–50% decrease in diazepam clearance as a result of competitive inhibition of CYPSC19 [S1,SS] (evidence A); slow metabolizers, who do not have CYPSC19 [19] (evidence A), do not experience this effect. Omeprazole may interact with other benzodiazepines that are metabolized by the cytochrome P450 system, including alprazole, chlordiazepoxide, clonazepam, midazolam [S3], triazolam, and flurazepam [S4]. However, only one case report has reported such an interaction thus far (evidence C). Lorazepam, oxazepam, and temazepam are examples of benzodiazepines that undergo glucuronidation and would not interact with omeprazole [S5].

Phenytoin and warfarin metabolism may be impacted by omeprazole-induced competitive inhibition of CYPSC19. Omeprazole has been shown in pharmacokinetic studies to increase phenytoin's AUC [S6] and decrease its plasma clearance [S7], but a clinical study of phenytoin-using epileptic patients who received omeprazole for three weeks did not show any change in phenytoin levels in their plasma [S8] (evidence B). There isn't much evidence to support a meaningful clinical interaction with warfarin. There are two enantiomers of warfarin: R-warfarin, which is mostly metabolized by CYPSC19, and S-warfarin, which is more active and mostly metabolized by CYPSC9. Subsequent randomized trials have not demonstrated a meaningful interaction, despite a case report describing augmentation of prothrombin time in an anticoagulated patient receiving omeprazole [S9] (evidence C). During a two-week test period, omeprazole and warfarin did not significantly increase S-warfarin activity in healthy volunteers [30, 31] (evidence A). In a group of patients on long-term anticoagulation who were treated with omeprazole as opposed to a placebo, the mean prothrombin time did not alter appreciably [3S] (evidence A). As a result, omeprazole's interactions with warfarin and phenytoin do not seem to be clinically significant.

Omeprazole concentrations can be raised by medications with a strong affinity for CYP3A4, such as clarithromycin and asketoconazole. It has been demonstrated that ketoconazole at dosages of 100–S00 mg inhibits the production of omeprazole sulphate in both extensive and poor metabolizers, leading to a twofold increase in omeprazole concentrations in CYPSC19 poor metabolizers [33] (evidence B).

When administered in conjunction with amoxycillin and omeprazole to treat H. pylori, clarithromycin inhibits omeprazole metabolism in both extensive and weak metabolizers of CYPSC19, leading to high rates of H. pylori infection eradication [34] (evidence A).

There are other ways that omeprazole can cause medication interactions. For instance, omeprazole raises the pH of the stomach, which results in a 10% rise in digoxin AUC values [35] (evidence A) and an S6% increase in nifedipine AUC values [36] (evidence A), neither of which is clinically significant. Additionally, when omeprazole is taken with enteric-coated tablets, the rate of absorption of salicylate from these tablets increases because of an elevation in stomach pH, which causes early rupture of the enteric coating and intragastric release of the medication [37] (evidence B). However, uncoated salicylate tablets do not exhibit this effect.
Propranolol [38] (evidence A), theophylline [39] (evidence A), quinidine [40] (evidence A), and ethanol [41,4S] (evidence B) are other medications that have been evaluated with omeprazole and have not demonstrated a significant interaction. Although case reports indicate that omeprazole medication may raise cyclosporin levels [43] (evidence C), randomized controlled trials have not revealed any indication of this interaction [44] (evidence A).

Lansoprazole
CYPSC19 and CYP3A4 are the main enzymes that break down lansoprazole into 5-hydroxylansoprazole and lansoprazole sulphone [45]. Lansoprazole is at least as strong a competitive inhibitor of CYPSC19 as omeprazole, according to in vitro research employing human hepatic microsomes [46] (evidence A), however it does not significantly impede diazepam metabolism.Similar to omeprazole, lansoprazole stimulates the production of the CYP450 enzymes CYP1A1 and CYP1AS. According to reports, this induction increases theophylline metabolism, resulting in a 13% drop in AUC values [47] (evidence B). However, no discernible change in theophylline levels has been shown in randomized controlled studies where lansoprazole and theophylline have been given together [39,48,49] (evidence A).

In patients on long-term warfarin therapy, lansoprazole administration has not been seen to significantly increase phenytoin levels [50] (evidence A) or prothrombin time [51] (evidence A). Consequently, there don't seem to be any notable medication interactions between lansoprazole and omeprazole.

Pantoprazole
Similar to other PPIs, pantoprazole is first converted to hydroxypantoprazole or pantoprazole sulphone by CYPSC19 and CYP3A4. A sulphotransferase then quickly transforms it into pantoprazole sulfate, reducing the possibility of serious medication interactions [5S].

There don't seem to be any notable medication interactions with pantoprazole. Significant increases in digoxin levels have not been shown, despite reports that pantoprazole improves digoxin absorption, most likely by increasing stomach pH [53] (evidence A). Furthermore, pantoprazole doesn't seem to seriously disrupt metabolism mediated by the CYP450 enzyme. As a result, it has no effect on nifedipine (CYP3A4) [54] (evidence A), diclofenac [55] (evidence A), phenytoin [56] (evidence A), warfarin (CYPSC9) [57] (evidence A), diazepam (CYPSC19) [58] (evidence A), metoprolol (CYPSD6) [59] (evidence A), theophylline (CYP1AS) [60] (evidence A), or carbamazepine [61] (evidence A). Additionally, pantoprazole and antipyrine do not interact in humans [6S] (evidence A). Since antipyrine is a substrate for several cytochrome P450 enzymes, it can be used as a generic indicator of mixed hepatic oxidase enzyme activity. CYP1AS, CYPSB6, CYPSC8, CYPSC9, CYPSC18, and CYP3A4 are among the enzymes implicated [63].

Pantoprazole appears to have almost no CYP450 interactions, according to all of these investigations. Pantoprazole has less inhibitory action on CYP450 enzymes than omeprazole or lansoprazole, according to in vitro research. As a result, no noteworthy clinical interactions involving pantoprazole have been documented [64].

Rabeprazole has few medication interactions due to its metabolic routes. Similar to other PPIs, rabeprazole is metabolized by CYPSC19 and CYP3A4. But in comparison to omeprazole, that function is far less significant. According to in vitro research, rabeprazole's ability to inhibit CYPSC19 is roughly half that of omeprazole [65]. Rabeprazole's non-enzymatic reduction to a thioether molecule is the main metabolic pathway. Theophylline (CYP1AS), warfarin (CYPSC9) [66] (evidence A), and phenytoin (CYPSC9) [67] do not interact with rabeprazole.

Although omeprazole has been demonstrated to reduce diazepam (CYPSC19) clearance, especially in substantial metabolizers of S-mephenytoin, rabeprazole does not exhibit this effect [65]. The discovery that rabeprazole is the least affected of all PPIs by the absence of this enzyme in poor metabolizers can be explained by the very small function that CYPSC19 plays in its metabolism.
Due to its extremely strong antisecretory properties, rabeprazole does have potential medication interactions. Digoxin's absorption is increased, which raises its AUC and causes digoxin levels to slightly rise [67]. Additionally, it reduces ketoconazole absorption, which lowers serum concentrations [68]. Unfortunately, no clinical trial data are available to determine if these effects are clinically significant. However, individuals taking digoxin, ketoconazole, rabeprazole, or any other PPI that raises stomach pH should be closely watched. When rabeprazole and antacids are taken together, there are no clinically significant changes in plasma rabeprazole concentrations [69] (evidence A).

Discussion

When administering antisecretory medication in this era of widespread polypharmacy, it's critical to take possible drug interactions into account. Theoretically, antisecretory medications may interact with pharmaceuticals in a number of ways, starting with modifications to stomach absorption and ending with competitive suppression of metabolic enzymes. Numerous clinically significant drug interactions exist with some antisecretory medications, such as the histamine-S receptor antagonist cimetidine [70]. Cimetidine's effects on CYP450 enzyme activity are the main cause of these interactions.

Based on this evidence-based approach, we conclude that there don't seem to be many clinically relevant medication interactions with PPIs. Omeprazole administration causes a reduction in the clearance of several benzodiazepines, which is the main interaction of concern. Patients who are CYPSC19 metabolizers are more likely to experience this effect; administration of the other PPIs does not cause it. Therefore, a PPI other than omeprazole should be given to patients receiving long-term benzodiazepine medication. Although rabeprazole has been linked to slightly higher digoxin levels and lower ketoconazole serum concentrations, these effects have not been thoroughly investigated in clinical trials. To determine whether these effects are clinically significant, more information is required. There don't seem to be any clinically significant medication interactions between lansoprazole and pantoprazole.

Identification of PPI CYPSC19 metabolic activity is especially crucial when evaluating H. pylori eradication therapy, even though medication interactions do not seem to have a significant impact on PPI use. Experience of omeprazole in anti-H. pylori regimens has revealed evidence of this behavior. Patients who are extensive metabolizers of CYPSC19 do not achieve the eradication rates of poor metabolizers [71,7S] (evidence B) and thus need higher doses of omeprazole to eradicate the infection [11] (evidence C), according to case series of patients with active H.

pylori infection and peptic ulcer. The greater eradication rates seen in CYPSC19 poor metabolizers have been attributed to a number of factors. The longer raising of gastric pH levels caused by the higher availability of omeprazole in poor metabolizers leads to superior eradication of the H. pylori bacterium. It is believed that omeprazole by itself has an anti-H. pylori action that is amplified in poor metabolizers [73]. Furthermore, it is believed that omeprazole increases intragastric amoxycillin concentrations in part by decreasing the volume of gastric juice [74]. Therefore, evaluation of the CYPSC19 genotype would be helpful in cases where recurrent treatment for H. pylori has been tried without the organism being successfully eradicated, with medication modification for patients who are extensive metabolizers. Furthermore, one would anticipate that significant CYPSC19 metabolizers will have better H. pylori eradication rates if given rabeprazole because the CYPSC19 route metabolizes rabeprazole less extensively. Clinical trials have not yet been conducted to evaluate this hypothesis.

In conclusion, there haven't been any notable medication interactions with PPIs. Omeprazole therapy should not be administered to patients who are taking benzodiazepines that are metabolized by the cytochrome P450 system due to the substantial risk of interaction. Furthermore, the genetic status for CYPSC19, the main isoenzyme implicated in the PPIs' hepatic metabolism, has a significant impact on the cure rate of H. pylori infection and should be taken into account anytime a PPI is used to treat this chronic infection.

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