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# Pharmacokinetic Drug Interaction Profiles of Proton Pump Inhibitors

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## Abstract

Proton pump inhibitors are used extensively for the treatment of gastric acid-related disorders because they produce a greater degree and longer duration of gastric acid suppression and, thus, better healing rates, than histamine $H_2$ receptor antagonists. The need for long-term treatment of these disorders raises the potential for clinically significant drug interactions in patients receiving proton pump inhibitors and other medications. Therefore, it is important to understand the mechanisms for drug interactions in this setting. Proton pump inhibitors can modify the intragastric release of other drugs from their dosage forms by elevating pH (e.g. reducing the antifungal activity of ketoconazole). Proton pump inhibitors also influence drug absorption and metabolism by interacting with adenosine triphosphate-dependent P-glycoprotein (e.g. inhibiting digoxin efflux) or with the cytochrome P450 (CYP) enzyme system (e.g. decreasing simvastatin metabolism), thereby affecting both intestinal first-pass metabolism and hepatic clearance.

Although interactions based on the change of gastric pH are a group-specific effect and thus may occur with all proton pump inhibitors, individual proton pump inhibitors differ in their propensities to interact with other drugs and the extent to which their interaction profiles have been defined. The interaction profiles of omeprazole and pantoprazole have been studied most extensively. A number of studies have shown that omeprazole carries a considerable potential for drug interactions, since it has a high affinity for CYP2C19 and a somewhat lower affinity for CYP3A4. In contrast, pantoprazole appears to have lower potential for interactions with other medications. Although the interaction profiles of esomeprazole, lansoprazole and rabeprazole have been less extensively investigated, evidence suggests that lansoprazole and rabeprazole seem to have a weaker potential for interactions than omeprazole.

Although only a few drug interactions involving proton pump inhibitors have been shown to be of clinical significance, the potential for drug interactions should be taken into account when choosing a therapy for gastric acid-related disorders, especially for elderly patients in whom polypharmacy is common, or in those receiving a concomitant medication with a narrow therapeutic index.

Proton pump inhibitors are the most effective antisecretory agents available for the treatment of gastric acid-related disorders. These drugs dose-dependently inhibit basal and stimulated gastric acid secretion by inhibiting the $H^+/K^+$-adenosine triphosphatase (ATPase), also known as the proton pump, that is located in the highly acidic luminal domain of the parietal cell.[1] Under acidic conditions, proton pump inhibitors are protonated and converted to cyclic sulphenimides. These active metabolites covalently bind to $H^+/K^+$-ATPase and consequently irreversibly inhibit the activity of the proton pump. In this way, proton pump inhibitors produce a profound suppression of gastric acid secretion that persists for longer than their presence in the plasma. Due to irreversible inhibition, resumption of $H^+/K^+$-ATPase action requires the *de novo* synthesis of the pump.[2] Rebound hypersecretion does not usually occur upon cessation of proton pump inhibitor therapy in *Helicobacter pylori* (*H. pylori*)-positive patients, although it has been noted after *H. pylori* eradication.[3]

Comparative studies have shown that proton pump inhibitors provide more effective gastric acid suppression, pain relief and healing of oesophageal lesions and gastric and duodenal ulcers than histamine $H_2$ receptor antagonists.[4-6] Consequently, proton pump inhibitors are currently the preferred treatments for gastro-oesophageal reflux disease, peptic ulcer disease (PUD) and Zollinger-Ellison syndrome and form a key component of triple therapy for the eradication of *H. pylori* in patients with PUD.[7] In addition, proton pump inhibitors have utility in the prophylaxis of stress- and NSAID-induced PUD.[8,9]

Gastric acid-related disorders are generally chronic, multi-factorial conditions that necessitate long-term treatment, increasing the likelihood of the use of concomitant therapies.[10] As the number of medications taken increases, the potential for interacting combinations also rises.[11] This is particularly relevant in elderly patients, in whom both gastric acid-related diseases[12] and polypharmacy[13] are common. Therefore, there is a real potential for clinically significant drug interactions in patients

receiving proton pump inhibitors and other medications,[14] especially those with narrow therapeutic indices.

Drug interactions are a common cause of treatment failure and adverse drug reactions.[15] Indeed, the incidence of adverse drug reactions is particularly high among hospitalised patients and community-dwelling older people taking multiple medications.[16,17] The occurrence of drug interactions varies among individuals and is influenced by patient age, the number of concomitant medications (which also increases with age),[18,19] the genetic make-up of the patient[20] and the therapeutic regimen and drug metabolic profiles.[20] However, although the potential for drug interactions with proton pump inhibitors is high, only few clinically significant interactions have been documented.[15] Although not a systematic analysis of the literature, the aim of this review is to highlight similarities and differences among the proton pump inhibitors in terms of the likelihood, relevance and mechanisms of drug-drug interactions. The review is based on a search of the literature using MEDLINE with Medical Subject Heading (MESH) terms such as "drug interactions AND PPIs", and additional articles were obtained from manual searches of the reference lists of relevant reviews and papers.

## 1. Mechanisms Involved in Proton Pump Inhibitor Drug Interactions

In general, drug interactions can be attributed to pharmacodynamic (i.e. due to synergistic or antagonistic effects) or pharmacokinetic (i.e. during drug absorption, distribution, metabolism or elimination) processes.[21] Moreover, interactions may also be based on biopharmaceutical modifications, e.g. altered solubility of the active drug ingredient or its release from the dosage form. Although certain interactions are predictable based on underlying pharmacological or biopharmaceutical mechanisms, other processes occur (or do not take place) unexpectedly considering the specific properties of the compounds.

Pharmacokinetic interactions can generally be considered in two ways: the influence of a drug on the pharmacokinetics of a co-administered medication or the influence of a concomitant medication on the pharmacokinetics of the drug. The former type of interaction is particularly relevant in patients receiving concomitant drugs with narrow therapeutic indices, such as phenytoin or warfarin. For these compounds, even small modifications in the pharmacokinetics can lead to significant changes in clinical efficacy and undesirable adverse effects.[22]

### 1.1 Modulation of Gastric pH

Increased gastric pH, induced by proton pump inhibitor administration, is one possible mechanism underlying interactions between proton pump inhibitors and other drugs. By decreasing gastric acidity, proton pump inhibitors have the potential to modify the solubility of other drug substances or alter drug release from products with pH-dependent dissolution properties. This kind of interaction is group-specific and, thus, not different between individual proton pump inhibitors.

Ketoconazole is an important example of a drug with pharmacokinetics that are affected by changes in gastric pH. Indeed, the bioavailability of orally administered ketoconazole was significantly reduced by a coadministered single dose of omeprazole 60mg, as indicated by an 80% decrease in the area under the plasma concentration-time curve (AUC).[23] This effect is thought to arise primarily as a result of an extremely poor solubility of ketoconazole at a pH >3. Moreover, pH-dependent dissolution properties have been observed with certain ketoconazole tablets.[24]

A second example is itraconazole which, because it is almost insoluble in dilute acidic solutions and water, is not recommended for patients who lack gastric acidity or who use gastric acid-lowering

medications such as proton pump inhibitors. This conclusion follows a study that found that concomitant omeprazole 40mg treatment reduced the mean $AUC_{24}$ and peak plasma concentration ($C_{max}$) of oral itraconazole 200mg capsules by 64% and 66%, respectively.[25] However, when itraconazole was administered as an oral solution, co-administration of omeprazole 40mg had no significant effects on the $C_{max}$, time to $C_{max}$ ($T_{max}$) or $AUC_8$.[26]

Similarly, the solubility of the HIV protease inhibitor indinavir decreases as the gastric pH rises with omeprazole treatment, which may reduce its absorption and, in turn, antiretroviral efficacy. For indinavir, induction of the cytochrome P450 enzyme (CYP) 3A isoenzyme by omeprazole may also undermine its efficacy. For example, in a small study of HIV-positive individuals, coadministration of omeprazole (20–40mg daily dose) and indinavir (800mg every 8 hours) resulted in a decrease in plasma indinavir concentrations in around half of the patients studied.[27] Conversely, the absorption of the antacid bismuth, taken as tripotassium dicitrato bismuthate, increased in patients who took omeprazole 40mg daily for 1 week and this was attributed to a rise in intragastric pH.[28]

Although such change in gastric pH may contribute to certain interactions, in recent years, most drug interactions have been interpreted to more likely be the result of effects on either P-glycoprotein or the CYP metabolic system.

### 1.2 Interactions with the Adenosine Triphosphate-Dependent Efflux Transporter P-Glycoprotein

Membrane-bound transporter systems, such as P-glycoprotein, present at the apical surface of the superficial columnar cells of the small intestines as well as in other tissues (e.g. blood-brain barrier, kidney or biliary system). The action of these transporter systems may also affect drug disposition.[29] The known range of substrates, inhibitors and inducers of this transporter system is wide and includes digoxin, cimetidine, tacrolimus, nifedipine, ketoconazole and amitriptyline.[20] The P-glycoprotein transporter system may also modulate access of orally administered compounds to the intestinal CYP3A4 enzyme, which is involved in the metabolism of a number of drugs, including ciclosporin and felodipine.[30]

*In vitro* findings in Caco-2 cell systems indicate that proton pump inhibitors may interact, to differing degrees, with the P-glycoprotein transporter system. As well as being substrates of this transporter system, omeprazole, lansoprazole and pantoprazole were all found to inhibit P-glycoprotein-mediated efflux of digoxin (the concentrations producing 50% inhibition were 17.7, 17.9 and 62.8 μmol/L for omeprazole, pantoprazole and lansoprazole, respectively).[29] There is, therefore, a certain potential for drug-drug interactions between proton pump inhibitors and compounds that act as substrates, inhibitors and inducers of P-glycoprotein.[20]

### 1.3 The Cytochrome P450 Enzyme (CYP) System

The major function of drug metabolism is to make drugs more hydrophilic and more easily excreted in the urine or bile. Many compounds undergo phase I metabolism, primarily catalysed by the CYP system, forming biotransformation products that are either directly eliminated via the kidneys or further metabolised in phase II reactions prior to elimination.[31]

The CYP system is a large family of isoenzymes that is found chiefly in the hepatocytes and small intestine enterocytes and, to a lesser extent, in the kidneys, lungs, brain and other tissues. The majority of human drug metabolism is mediated by six CYP isoenzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.[31] Recent studies suggest that these enzymes catalyse the biotrans-

formation pathways underlying most clinically important drug interactions.[20]

Analysis of these interactions is confounded by a number of other factors affecting the activity of the CYP enzyme system, including smoking, alcohol consumption, age, genetic enzyme polymorphisms, nutritional status and intercurrent illnesses. These factors account for the large inter-individual variability observed in both CYP system inhibition and induction and susceptibility to drug interactions.[21]

The majority of drug-drug interactions occur as a result of competitive inhibition, whereby two compounds compete with each other for the same binding site of a CYP isoenzyme. The extent and consequences of the resulting interaction depend on the relative affinities of both compounds for the CYP enzyme in question: the substance with the higher affinity for the enzyme will be bound and will consequently inhibit biotransformation of the lower-affinity substrate.[20] Most major drug-drug interactions mediated by competitive inhibition of the CYP system involve isoenzymes at two main sites: the intestine and liver.

#### 1.3.1 Interactions with Intestinal CYPs

Inhibition of the activity of intestinal CYPs may induce changes in first-pass metabolism. The predominant CYP isoenzyme in the human intestine is CYP3A4, and its activity is recognised as an important determinant of drug bioavailability.[30] A number of compounds undergo significant first-pass metabolism in the gut wall when administered orally, including ciclosporin,[32] midazolam[33] and nifedipine.[20] Thus, inhibition of intestinal CYP3A4 plays an essential role in drug interactions involving these agents.[34]

The precise clinical consequence of competitive inhibition of intestinal CYP3A4 is dependent on the relative affinities of both concurrently administered drugs for this enzyme. Indeed, metabolism is inhibited for drugs with low affinity for CYP3A4 in the gut wall (e.g. felodipine[35] or simvastatin[36]) and this can induce a several-fold increase in their oral bioavailability. On the other hand, compounds with a greater affinity for CYP3A4 than the proton pump inhibitors, such as ketoconazole and clarithromycin, can inhibit the metabolism of proton pump inhibitors and other drugs, thereby raising the plasma concentrations of the latter drugs.[15] Although not shown specifically in clinical studies, such changes in the bioavailability of coadministered compounds have the potential to impact their efficacy or the incidence of adverse effects.

#### 1.3.2 Interactions with Hepatic CYPs

Induction or inhibition of the activity of CYP isoenzymes in the liver can lead to changes in hepatic clearance. Proton pump inhibitors are predominantly metabolised in the liver by CYP2C19 and CYP3A4.[15] Li and colleagues[37] compared the potency and specificity of five currently used proton pump inhibitors with regards to inhibition of four CYP enzymes (CYP2C9, 2C19, 2D6 and 3A4), using human liver microsomal preparations and recombinant CYP2C19. Although the inhibitory profiles were similar, lansoprazole was the most potent *in vitro* inhibitor of CYP2C19 ($K_i$ = 0.4–1.5μM) and pantoprazole was the most potent inhibitor of CYP2C9 ($K_i$ = 6μM).

In another study,[38] omeprazole (R- or S-enantiomers) was metabolised at a higher rate than pantoprazole, using both human liver microsomes and recombinant CYP3A4 isoenzymes. However, when using recombinant CYP2C19, esomeprazole (*S*-omeprazole) and pantoprazole had similar metabolic rates and only *R*-omeprazole was metabolised faster.

Although these *in vitro* findings suggest the potential for drug-drug interactions and differences in potency among the proton pump inhibitors, similar effects are not necessarily found *in vivo*. For instance, the potent competitive inhibition of CYP2C9 (using diclofenac 4′ hydroxylation as a marker reaction for CYP2C9 activity) by pantoprazole is not

reflected clinically. *In vivo*, pantoprazole was found to have no effect on the pharmacokinetics of diclofenac, neither by competition with CYP2C9 nor by reducing gastric acid secretion. Similarly, diclofenac did not affect the pharmacokinetics of pantoprazole.[39] The more potent competitive inhibition of CYP2C19 by lansoprazole as compared with omeprazole or esomeprazole also has not been demonstrated to have clinical effects. Plasma levels of phenytoin, for example, which is a substrate for CYP2C19, were not significantly altered when the drug was co-administered with lansoprazole 60mg.[40]

In addition to interacting with specific CYP isoenzymes required for their own metabolism, proton pump inhibitors can also modify the activity of other CYP isoenzymes. Both omeprazole and lansoprazole, for example, can induce the activity of CYP1A2,[41] potentially affecting the biotransformation of drugs such as theophylline and warfarin.[20] However, there is a paucity of clinical evidence to support the existence of interactions of this type.

## 2. Interaction Profiles of Proton Pump Inhibitors

The interaction profiles of omeprazole and pantoprazole have been extensively studied, whereas those for esomeprazole, lansoprazole and rabeprazole are less well defined. The major findings of these studies are summarised in table I. Interactions that are relevant for the entire group, e.g. those based on the pharmacodynamic effect of proton pump inhibitors on gastric pH, will not be reiterated since they have been described above.

There have been reports of increased International Normalised Ratios (INR) and prothrombin times in patients receiving proton pump inhibitors and warfarin or phenprocoumon. Therefore, patients treated with proton pump inhibitors and warfarin or phenprocoumon should be monitored for increases in INR and prothrombin time.

### 2.1 Omeprazole

Omeprazole is almost completely metabolised; therefore, essentially no unchanged drug is excreted in urine or faeces.[99] The major phase I metabolic pathway is the formation of 5-hydroxyomeprazole catalysed by CYP2C19 and CYP3A4. Omeprazole is also metabolised by CYP2C19 to omeprazole hydroxysulphone and via CYP3A4 to omeprazole sulphone.[100] The parent compound has an almost 10-fold greater affinity for CYP2C19 than for CYP3A4.[99] Considering this rapid and extensive biotransformation mediated by the CYP isoenzymes 2C19 and 3A4, interactions with other substrates or inhibitors of both systems are likely.

A well characterised example of this type of drug interaction is the reduction in the clearance of diazepam induced by omeprazole. At a dose of 20mg once daily, competitive inhibition of CYP2C19 by omeprazole reduced the clearance of a single intravenous dose of diazepam by 20–26% in rapid metabolisers.[65,66,68] Omeprazole also reduced the clearance of demethyldiazepam, the major active metabolite of diazepam, in rapid metabolisers.[65,66,68] As expected, this interaction was not seen in slow metabolisers who exhibit significantly reduced CYP2C19 activity.[65,68]

*In vitro*, CYP2C19 inhibition by omeprazole (10 μmol/L) inhibited the biotransformation of proguanil 20 μmol/L to cycloguanil, and decreased proguanil oral clearance by about one third *in vivo*.[101] Omeprazole 40mg also inhibited the CYP2C19-dependent metabolism of the antidepressant moclobemide (300mg) in extensive metabolisers.[102]

Omeprazole-induced competitive inhibition of CYP2C19 also has the potential to alter the metabolism of phenytoin and warfarin. Pharmacokinetic studies in healthy volunteers, for example, indicated

**Table I.** Pharmacokinetic interaction profiles of proton pump inhibitors

| Concomitant drug | Effect of proton pump inhibitor on concomitant drug | | | | |
|---|---|---|---|---|---|
| | esomeprazole | lansoprazole | omeprazole | pantoprazole | rabeprazole |
| Antacid | Unknown | Conflicting results[42,43] | None[44] | None[45] | None[46] |
| Phenazone (antipyrine) | Unknown | ↑ Clearance [47] | ↓ Clearance [10] | None[48] | Unknown |
| Caffeine | Unknown | None[49] | Conflicting results[49,50] | None[49,51] | Unknown |
| Carbamazepine | Unknown | Unknown | ↓ Clearance[52] | None[53] | Unknown |
| Oral contraceptives | Unknown | Conflicting results[54] | Unknown[10] | None[55] | Unknown |
| Ciclosporin | Unknown | Unknown | Conflicting results[56-58] | None[59] | Unknown |
| Cinacalcet | Unknown | Unknown | Unknown | None[60] | Unknown |
| Diazepam | ↓ Clearance[61-63] | None[64] | ↓ Clearance[65,66] | None[67] | None[a][68] |
| Diclofenac | Unknown | Unknown | None[69] | None[39] | Unknown |
| Digoxin | Unknown | Unknown | ↑ Absorption[70] | None[b] | ↑ Absorption[72] |
| Ethanol | Unknown | None[73] | None[73] | None[74] | Unknown |
| Glibenclamide | Unknown | Unknown | Unknown | None[75] | Unknown |
| Levothyroxine | Unknown | Unknown | Unknown | None[76] | Unknown |
| Metoprolol | Unknown | Unknown | None[77] | None[78] | Unknown |
| Naproxen | Unknown | Unknown | None[69] | None[79] | Unknown |
| Nifedipine | Unknown | Unknown | ↑ Absorption<br>↓ Clearance[80] | None[c][81] | Unknown |
| Phenprocoumon | Unknown | Unknown | ↓ Clearance[82] | None[83] | Unknown |
| Phenytoin | ↓ Clearance[61,62] | None[40] | ↓ Clearance[66,84,85] | None[86] | None[87] |
| Piroxicam | Unknown | Unknown | None[69] | None[88] | Unknown |
| Tacrolimus | Unknown | ↓ Clearance[89] | Unknown | None[90] | None[89] |
| Theophylline | Unknown | Conflicting results[91,92] | None[91,93] | None[91,94] | None[95] |
| Warfarin | ↓ Clearance[d][61,62] | None[43] | ↓ Clearance[d][96,97] | None[98] | None[95] |

a Effects were seen with the desmethyl metabolite of diazepam but were significant only in CYP2C19-deficient individuals.

b β-Acetyldigoxin.[71]

c Only for nifedipine sustained-release.

d Only for *R*-warfarin.

↓ indicates decreases; ↑ indicates increases.

that omeprazole 40mg given once daily increased the AUC of orally administered phenytoin by 19%[84] and reduced plasma clearance of intravenous phenytoin to a similar extent.[66] However, there were no significant changes in phenytoin steady-state plasma concentrations after 3 weeks of concomitant treatment with omeprazole 20mg once daily in patients with epilepsy.[85] In other studies, omeprazole 20mg once daily exhibited a stereo selective effect on the hepatic metabolism of warfarin by inhibiting CYP2C19-mediated biotransformation of the *R*- but not the more potent *S*-enantiomer. As a result, a slight increase in mean plasma concentrations was observed for *R*-warfarin.[96,97] However, only one of these studies found a significant increase in coagulation time with administration of concomitant omeprazole.[96] There have been other case reports of an omeprazole-induced detrimental increase in the anticoagulant effect of warfarin,[103] and increased activity of the anticoagulant phenprocoumon after administration of concomitant omeprazole.[82]

The effects of omeprazole on the pharmacokinetics of antacids, metoprolol, NSAIDs, iron[104] and

theophylline have also been investigated and these studies have not noted any clinically significant findings.[44,69,77,80,93,104] There have been two case reports of an omeprazole-induced delay of methotrexate clearance, with the potential for toxic accumulation of methotrexate.[105,106]

Studies of coadministration of ciclosporin and omeprazole have yielded conflicting results. Although case reports have suggested an elevation of ciclosporin plasma concentrations associated with omeprazole,[56] results from systematic clinical trials have been less clear cut. Reichenspurner and colleagues,[57] for example, demonstrated that the ciclosporin dose versus concentration quotient was lowered in heart transplant patients during the administration of omeprazole (dose not stated) and consequently, a higher ciclosporin plasma concentration was achieved with the same dose. On the other hand, Blohme and colleagues[58] could not detect significant changes in ciclosporin plasma levels in renal transplant patients following administration of omeprazole 20mg.

#### 2.1.1 Effects of Other Drugs on Omeprazole Pharmacokinetics

Compounds exhibiting a high affinity for CYP3A4, such as ketoconazole,[107] clarithromycin,[108] and moclobemide,[109] may affect the bioavailability of omeprazole by increasing its serum concentrations. However, this is only thought to be of clinical relevance in patients with CYP2C19 deficiency (i.e. poor metabolisers) who rely on the CYP3A4 metabolic pathway for the metabolism of omeprazole. At a daily dose of 100–200mg for 4 days, ketoconazole inhibited the formation of omeprazole sulphone in all patients and induced a 2-fold increase in omeprazole serum concentrations in poor metabolisers.[107] Similarly, the administration of clarithromycin 400mg twice daily for 3 consecutive days significantly increased omeprazole plasma concentrations in healthy individuals whereas plasma levels of its sulphone metabolite were decreased.[108]

On the other hand, plasma concentrations of omeprazole and omeprazole sulfone were significantly decreased in patients who were treated twice daily for 12 days with the CYP2C19 inducer ginkgo biloba 140mg[110] or for 14 days with St John's wort 300mg.[111] Fluvoxamine (50mg daily for 6 days), an inhibitor of CYP2C19 and CYP1A2, reduced the metabolism of a single oral dose of omeprazole 40mg in extensive metabolisers, but not poor metabolisers, indicating its activity was via CYP2C19.[112]

A combined oral contraceptive containing ethinyloestradiol decreased CYP2C19 activity and increased the AUC of omeprazole accordingly in healthy women treated with a single 40mg dose of the proton pump inhibitor. No inhibitory effect of ethinyloestradiol on the formation of omeprazole sulphone by CYP3A4 was apparent.[113]

In summary, although there have been a number of omeprazole-related drug interactions reported, not all of them are considered clinically significant. There may also be a simple reason why there appear to be more drug interactions associated with omeprazole than with other proton pump inhibitors. Omeprazole, first introduced in 1989, is the proton pump inhibitor that has been available the longest, and the number of drug-interaction reports linked to a drug generally increases in proportion to the time the drug is on the market.

### 2.2 Esomeprazole

In general, racemic omeprazole and esomeprazole, the pure *S*-enantiomer of omeprazole, are subject to the same metabolic transformations. However, the *S*-enantiomer seems to follow a slightly different metabolic pathway than that of *R*-omeprazole. *In vitro* experiments in human liver microsomes indicate that CYP2C19 is responsible for ≈70% of the metabolism of *S*-omeprazole com-

pared with ≈90% of that of the *R*-enantiomer, with the bulk of the remaining 30% being metabolised by CYP3A4.[114]

These *in vitro* findings appear to be in line with the results from pharmacokinetic studies of omeprazole and esomeprazole in healthy volunteers.[61] Plasma concentrations of the hydroxy metabolite, which is primarily formed via CYP2C19, were higher following administration of racemic omeprazole than after the same dose of esomeprazole. In contrast, formation of the sulphone metabolite catalysed by CYP3A4 was higher after administration of esomeprazole than racemic omeprazole.[105] Furthermore, total metabolic clearance of esomeprazole was slightly lower than that of the racemate, resulting in higher plasma concentrations of the *S*-isomer compared with the racemate after administration of identical doses.[62]

Esomeprazole (and, to a lesser extent, racemic omeprazole) also appears to inhibit its own metabolism by CYP2C19,[115] a phenomenon that must be taken into account when assessing the extent of drug interactions with this proton pump inhibitor. This inhibition progresses over the first 5–7 days of treatment,[116,117] and then plateaus, explaining discrepancies that may result from single-dose and repeated-dose experimental designs.

Esomeprazole does not appear to have the potential to interact with drugs that are primarily metabolised by CYP1A2, CYP2A6, CYP2C9, CYP2D6 or CYP2E1.[62] On the other hand, drug interaction studies with phenytoin and *R*-warfarin indicate that esomeprazole has the potential to interact with compounds metabolised by CYP2C19; however, the magnitude of these interactions does not reach levels of clinical significance. Nevertheless, the CYP3A4 inhibitor clarithromycin was found to increase plasma concentrations of esomeprazole by a factor of almost two.[62]

Recently, multiple doses of esomeprazole (40mg) were shown to increase single-dose diazepam concentrations within 4 hours following a single 0.1 mg/kg dose.[63] These pharmacokinetic effects were manifested clinically as impaired angular velocity (as measured by saccadic eye movements), choice reaction time, and microsleep. Drewelow et al.[63] suggest that the effect of esomeprazole on diazepam has the potential to disrupt motor coordination and vigilance in patients receiving both drugs.

In conclusion, despite slight (quantitative but not qualitative) differences in the metabolic pathway of both omeprazole enantiomers, the interaction potentials of esomeprazole and racemic omeprazole seem not to differ significantly. In this context, it should be also taken into account that the recommended dosage of the racemate for treating gastric acid-related disorders is half that of the pure *S*-enantiomer.

### 2.3 Pantoprazole

Pantoprazole is metabolised by CYP2C19 and CYP3A4, but has a lower affinity for these enzymes relative to other proton pump inhibitors.[118] Unlike the majority of the phase I biotransformation products of other proton pump inhibitors, the initial metabolite of pantoprazole, 4-hydroxypantoprazole, which is formed by the CYP system, subsequently undergoes secondary (phase II) biotransformation via sulphate conjugation in the cytosol. This conjugation reaction, a relatively non-saturable route of drug metabolism, is often considered to explain the more limited potential of pantoprazole for drug interactions compared with other proton pump inhibitors.[6,119,120]

Studies in healthy volunteers and patients demonstrated no significant metabolic interactions when pantoprazole was used in combination with antacids,[45] phenazone (antipyrine),[48] caffeine,[51] carbamazepine,[53] cinacalcet,[60] clarithromycin,[121] ciclosporin,[59] diazepam,[67] diclofenac,[39] β-acetyldigoxin,[71] ethanol,[74] glibenclamide,[75]

levothyroxine sodium,[76] metoprolol,[78] naproxen,[79] sustained-release nifedipine,[81] oral contraceptives,[55] phenprocoumon,[83] phenytoin,[86] piroxicam,[88] tacrolimus,[90] theophylline[94] or warfarin.[98]

A study by Ferron and colleagues[122] showed a slight interaction between pantoprazole 40mg and cisapride 20mg, but this did have not clinically significant effects.

A single case of severe myalgia following methotrexate 15mg injections was reported in a patient with lymphoma taking pantoprazole 20 mg/day for Barrett's oesophagus. The authors found that the total exposure ($AUC_{144}$) for the methotrexate metabolite 7-hydroxymethotrexate was nearly 70% higher after drug administration with pantoprazole than without pantoprazole. The half-life was doubled for this metabolite (81.4 vs 36.4 hours), indicating an interaction affecting renal elimination rather than one affecting metabolism.[123] However, it remains unclear whether this effect is caused by the proton pump inhibitor or other factors and no further cases have been reported with pantoprazole. Pantoprazole had no effect on ciclosporin levels in renal transplant recipients.[59] Thus, pantoprazole may be given to transplant recipients without the risk of interference with ciclosporin immunosuppressive therapy.

A recent report compared the effects of multiple daily doses of pantoprazole 40mg and esomeprazole 40mg on the pharmacokinetics of single-dose diazepam 0.1 mg/kg. The diazepam $AUC_{120}$ was 28% greater with esomeprazole than pantoprazole. There was a late increase (>12h) in diazepam concentration, as seen in former studies, but differences in the $C_{max}$ also revealed an early increase of ≈34% in diazepam concentrations when receiving esomeprazole versus pantoprazole, an effect that resulted in clear pharmacodynamic effects. The clinical effects on choice reaction time and the occurrence of microsleep were significantly greater with esomeprazole ($p < 0.0028$ and $p < 0.0073$, respectively).[63]

In conclusion, extensive investigation shows that pantoprazole has a low potential to interact with other medications.

### 2.4 Lansoprazole

Lansoprazole is metabolised primarily by the CYP isoenzymes 2C19 and 3A4.[124] *In vitro* studies indicate that competitive inhibition of CYP2C19 occurs to a similar extent with lansoprazole as with omeprazole. However, *in vivo* data indicate that drug metabolism of CYP2C19 substrates (e.g. diazepam[64]) is not significantly affected by lansoprazole.

No clinically significant interactions have been observed between lansoprazole and phenazone,[47] diazepam,[64] magaldrate,[42] phenytoin,[40] prednisolone,[43] propranolol[43] or warfarin.[125] This also seems to be the case with oral contraceptives. After early results from an unpublished study generated controversy,[54] Fuchs and colleagues[126] subsequently could not confirm any impact of lansoprazole 60mg on the bioavailability of oral contraceptives.

Investigations assessing the effect of lansoprazole 30mg or 60mg on theophylline bioavailability have shown a 10%[91] to 13%[92,127] reduction in AUC; however, this effect is not thought to be of clinical significance.[91,92] Moreover, increased clearance of theophylline following treatment with lansoprazole 60mg[127] was not seen consistently.[91]

Lansoprazole (30 mg/day for 4 days) decreased oral tacrolimus clearance, resulting in a significant increase in blood tacrolimus concentration.[128] This effect was greater in individuals with CYP2C19 mutant alleles since both drugs are then metabolised by CYP3A4.[128,129]

The CYP2C19 inhibitor fluvoxamine has a significant effect on lansoprazole metabolism, depending on the CYP2C19 genotype. Plasma lansoprazole

concentrations were significantly increased by fluvoxamine 50mg in homozygous or heterozygous extensive metabolisers for CYP2C19 who received lansoprazole 60mg, but not in poor metabolisers.[130]

In conclusion, although the interaction profile of lansoprazole has not been as thoroughly investigated as that of omeprazole or pantoprazole, the compound does not seem to be associated with major clinically relevant drug interactions.

### 2.5 Rabeprazole

A number of interaction studies have been published on rabeprazole, with the majority reporting interactions attributed to the group effect of all proton pump inhibitors on gastric pH, e.g. interactions with digoxin[87] or ketoconazole.[131]

The major metabolic pathway for rabeprazole is non-enzymatic reduction to a thioether compound.[132] Thus, oxidative metabolism catalysed by CYP2C19 and CYP3A4 plays a minor role in its biotransformation. Moreover, *in vitro* studies have shown that rabeprazole has a reduced potential to inhibit CYP2C19.[68] However, the metabolism of rabeprazole at least partly depends on a CYP2C19-related genetic polymorphism. After single doses of rabeprazole 20mg, the mean $C_{max}$ and $AUC_{24}$ were significantly higher in individuals who were poor metabolisers of *S*-mephenytoin than those who were homozygous extensive metabolisers, with a relative ratio for the $AUC_{24}$ of 4.3 : 1 between the homozygous extensive metaboliser and poor metaboliser groups.[132] Rabeprazole has a low affinity for a range of CYP isoenzymes and, therefore, is expected to exhibit only a minor propensity for drug interactions mediated by this metabolic enzyme family.[15]

Rabeprazole was not found to be involved in metabolic drug interactions with theophylline,[95] warfarin,[95] phenytoin,[87] tacrolimus[89] or antacids.[46] Furthermore, at a dose of 20mg, its effect on the pharmacokinetics of the desmethyl metabolite of diazepam was significant only in poor metabolisers of S-mephenytoin 4′-hydroxylation (i.e. those deficient in CYP2C19). The authors speculated that this may reflect rabeprazole-mediated inhibition of CYP3A4, which is involved in the further metabolism of the desmethyl metabolite of diazepam.[68]

In conclusion, although based on a limited number of studies, significant pharmacokinetic drug interactions with rabeprazole are not likely. Further studies will prove useful to confirm this.

## 3. Conclusions

In recent years, our understanding of the mechanisms underlying the drug-drug interactions involving proton pump inhibitors has increased substantially. Although in the past the rise in gastric pH was considered a major determinant of interactions induced by these medications, more recently it has become apparent that biotransformative reactions in the liver, as well as in the intestinal cells, often play an important role.

Our deeper understanding of the mechanisms underlying drug interactions has also highlighted the fact that differences in metabolism among the proton pump inhibitors result in differential propensities to cause interactions. These predicted differences have largely been supported by findings from pharmacokinetic studies. However, it is worthwhile noting that proton pump inhibitors also vary in the extent to which their interaction profiles have been defined, with compounds that have been on the market the longest, such as omeprazole and pantoprazole, having undergone the most thorough investigations.

A number of drug-drug interactions have been detected involving omeprazole, the majority of which are the result of its high affinity for the CYP isoenzymes 2C19 and 3A4. Whilst it was initially believed that the effect of omeprazole on hepatic CYP2C19 was primarily relevant, a growing

body of evidence indicates that its competitive inhibition of intestinal CYP3A4 may affect the first-pass metabolism of a number of drugs, including ciclosporin, midazolam and nifedipine. Furthermore, CYP2C19 plays an even smaller role in the metabolism of esomeprazole; however, currently available data indicate that this compound seems to have a propensity for drug interactions comparable to that of the racemate.

In contrast, lansoprazole, pantoprazole and rabeprazole appear to be associated with lower incidences of drug interactions, resulting either from a lower affinity for specific CYP isoenzymes or the involvement of additional elimination processes. However, only the interaction profile of pantoprazole has been well characterised.

In practice, there appears to be little difference among the proton pump inhibitors in terms of clinical efficacy at equivalent doses and, therefore, their individual propensities for drug interactions become important factors to consider in prescribing decisions. The majority of drug interactions and adverse reactions associated with proton pump inhibitors are predictable and may be prevented by periodic review of treatment regimens and/or selecting drugs with low-interaction potentials. The clinical significance of drug interactions may be of particular importance in elderly patients who have a high risk of interactions because they are taking multiple medications at the same time, or those receiving drugs with a narrow therapeutic window. In such cases, a compound with a low-risk and a thoroughly characterised interaction potential would be the favourable choice.

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