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REVIEW ARTICLE

Pharmacokinetic Drug Interaction Profiles of Proton Pump Inhibitors: An Update

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Abstract Proton pump inhibitors (PPIs) are used extensively for the treatment of gastric acid-related disorders, often over the long term, which raises the potential for clinically significant drug interactions in patients receiving concomitant medications. These drug–drug interactions have been previously reviewed. However, the current knowledge is likely to have advanced, so a thorough review of the literature published since 2006 was conducted. This identified new studies of drug interactions that are modulated by gastric pH. These studies showed the effect of a PPI-induced increase in intragastric pH on mycophenolate mofetil pharmacokinetics, which were characterised by a decrease in the maximum exposure and availability of mycophenolic acid, at least at early time points. Post-2006 data were also available outlining the altered pharmacokinetics of protease inhibitors with concomitant PPI exposure. New data for the more recently marketed dexlansoprazole suggest it has no impact on the pharmacokinetics of diazepam, phenytoin, theophylline and warfarin. The CYP2C19-mediated interaction that seems to exist between clopidogrel and omeprazole or esomeprazole has been shown to be clinically important in research published since the 2006 review; this effect is not seen as a class effect of PPIs. Finally, data suggest that coadministration of PPIs with methotrexate may affect methotrexate pharmacokinetics, although the mechanism of interaction is not well understood. As was shown in the previous review, individual PPIs 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 sodium (pantoprazole-Na) have been studied most extensively. Several studies have shown that omeprazole carries a considerable potential for drug interactions because of its high affinity for CYP2C19 and moderate affinity for CYP3A4. In contrast, pantoprazole-Na appears to have lower potential for interactions with other medications. Lansoprazole and rabeprazole also seem to have a weaker potential for interactions than omeprazole, although their interaction profiles, along with those of esomeprazole and dexlansoprazole, have been less extensively investigated. Only a few drug interactions involving PPIs are of clinical significance. Nonetheless, the potential for drug interactions should be considered when choosing a PPI to manage gastric acid-related disorders. This is particularly relevant for elderly patients taking multiple medications, or for those receiving a concomitant medication with a narrow therapeutic index.

1 Introduction

Proton pump inhibitors (PPIs) achieve a greater degree and longer duration of gastric acid suppression, and better healing rates in various gastric acid-related disorders, than histamine H_2 receptor antagonists [1–3]. They are thus considered essential in the management of gastro-oesophageal reflux disease, peptic ulcer disease (PUD) and Zollinger–Ellison syndrome. PPIs are also a key part of triple therapy (with two antibiotics, such as clarithromycin, amoxicillin or metronidazole) for the eradication of *H. pylori* in PUD [4], and may be used in the prophylaxis of stress- and NSAID-induced PUD [5, 6]. Many of these disorders generally require long-term treatment, which increases the potential for clinically significant drug interactions in patients (such as hospitalised patients and

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community-dwelling older people [7, 8]) receiving PPIs and other medications [9].

A previous review published in 2006 highlighted the similarities and differences among the PPIs in terms of the likelihood, relevance and mechanisms of drug–drug interactions [10]. In the review, the authors discussed how, by elevating pH, PPIs can modify the intragastric release of other drugs from their dosage forms, and also how PPIs influence drug absorption and metabolism by interacting with adenosine triphosphate-dependent P-glycoprotein or with the cytochrome P450 (CYP) enzyme system [10]. At the time of the review, the interaction profiles of omeprazole and pantoprazole sodium (pantoprazole-Na) had been studied most extensively. The authors concluded that omeprazole carried a considerable potential for drug interactions because of its high affinity for CYP2C19 and moderate affinity for CYP3A4, whereas pantoprazole-Na appeared to have a lower potential for interactions than omeprazole based on extensive evidence. Lansoprazole and rabeprazole also seemed to have a weaker potential for interactions than omeprazole, but this was based on limited evidence only. Much of the review remains relevant today; however, several PPI drug interaction papers have been published since 2006. Thus, here we present an update of the 2006 review, which, when read in conjunction with the original article, provides a comprehensive overview of drug interactions associated with the use of PPIs [10].

This review is based on literature published from 1 January 2007 to 31 December 2012 identified by searching (i) MEDLINE using Medical Subject Heading (MESH) terms for 'drug-interactions' and 'proton pump inhibitors'; and (ii) EMBASE using (Omeprazole/drug interaction) OR (Esomeprazole/drug interaction) OR (Lansoprazole/drug interaction) OR (Pantoprazole/drug interaction) OR (Rabeprazole/drug interaction) OR (Proton-Pump-Inhibitor/drug interaction). Searches were limited to English language and excluded comments, editorials, letters, notes or conference papers or reviews. PUBMED and EMBASE results were combined and duplicates removed; the remaining results were divided into articles investigating PPI interactions with clopidogrel (where this term was used in the title, abstract or as CAS number for MEDLNE or as descriptor for EMBASE) and other drug interaction articles. Additional articles were also obtained from manual searches of the reference lists of relevant reviews and papers. In total, 132 articles for interactions with clopidogrel and 174 articles for interactions with other drugs were obtained. The two authors independently selected additional articles for inclusion based on appropriate study design for drug-interaction studies, and any discrepancies were discussed and agreed. Forty new references were identified and used in this updated review.

2 Mechanisms Involved in Proton Pump Inhibitor Drug Interactions

2.1 Modulation of Gastric pH

Group-specific interactions between PPIs and other drugs may result from a PPI-induced increase in gastric pH, which can decrease the soluble amount of other drug substances, alter drug release from products with pH-dependent dissolution properties, or indirectly impact bioavailability by changing the kinetics of pro-drugs. Examples of drug pharmacokinetics that are affected by gastric pH have been discussed extensively in the 2006 review [10]. These include the reduced bioavailability of oral ketoconazole when co-administered with omeprazole 60 mg [11], and the reduced mean area under the concentration-time curve at 24 hours (AUC_{24}) and peak plasma concentration (C_{max}) of oral itraconazole 200-mg capsules administered with concomitant omeprazole 40 mg [12].

Of importance since the publication of the 2006 review, new data are available for the interaction of PPIs and mycophenolate mofetil. Administration of PPIs increases intragastric pH, which slows down the hydrolysis of mycophenolate mofetil resulting in decreased maximum exposure and availability of mycophenolic acid, at least at early time points. Compared with mycophenolate mofetil alone, coadministration of mycophenolate mofetil with pantoprazole-Na resulted in persistently lower plasma concentrations of mycophenolic acid in heart transplant recipients [13] and a significant decrease in total and maximum exposure in patients with autoimmune disease. This correlated with a 42 % increase ($p < 0.01$) in the area of inosine monophosphate dehydrogenase activity [14]. However, coadministration of pantoprazole-Na and enteric-coated mycophenolate sodium did not result in any significant changes in pharmacokinetic parameters in heart or lung transplant recipients [15]. These findings from steady-state studies confirmed results from an earlier study in healthy individuals [16]. Being in steady state for pantoprazole-Na (40 mg/day) significantly lowered total and maximum exposure of mycophenolic acid after administration of mycophenolate mofetil, but had no relevant effect after administration of enteric-coated mycophenolate sodium. Other pharmacokinetic parameters were not affected [16], suggesting that interaction on the enzymatic level is unlikely.

Other interactions not discussed in the previous review include changes in the contact of the PPIs themselves to the gastric environment, which will change the exposure to the PPI. This predominantly results from the instability of PPIs at low pH and makes administration of PPIs by means of gastro-resistant formulations a necessity. Consistent with

this, concomitant intake of the prokinetic mosapride led to increases of about 50 % in total and maximum exposure after administration of rabeprazole, which was explained by the increased transport time to the intestine [17]. These results substantiated earlier results for the combination of omeprazole and mosapride [18] and suggested that such an interaction would also benefit all other PPIs. However, this explanation does not address the fact that administration as a gastro-resistant formulation means no contact of PPI and gastric acid, suggesting that an undiscovered pharmacokinetic interaction with mosapride is also possible.

A group effect with clear clinical implications is assumed for several protease inhibitors that can have significantly altered bioavailability if coadministered with PPIs. For example, total and maximum exposure to single-dose atazanavir 400 mg was reduced by more than 90 % when administered with lansoprazole 60 mg [19]. The loss in solubility for atazanavir at increased pH values is considered responsible for this effect, as a CYP-mediated interaction is unlikely for this drug combination. For other combinations, the situation may be more complex. Exposure to nelfinavir, which is comparably pH-dependently soluble, was reduced at steady state after nelfinavir 1,250 mg twice daily for 4 days by about 35 % if coadministered with omeprazole 40 mg once daily for 4 days, but terminal elimination and clearance remained unaltered [20]. Nevertheless, nelfinavir is metabolised by CYP 2C19, whose inhibition by omeprazole probably counteracts the loss in exposure caused by solubility effects. This would also explain the decrease in the metabolic ratio of the main metabolite and nelfinavir.

In contrast, total and maximum exposure to single-dose raltegravir 400 mg are increased by a factor of 3 and 4, respectively, if administered with omeprazole 20 mg once daily for 4 days [21]. Enzyme-based interactions are unlikely given the metabolic pathway of raltegravir; however, raltegravir has greatly increased solubility at increased pH and is a substrate to P-glycoprotein, which is at least modestly inhibited by omeprazole, both effects probably being synergistic. As shown here, in addition to possible group effects of PPIs, individual interactions of each compound remain possible and should be considered.

The situation for protease inhibitors becomes even more complex with the common concomitant use of the booster ritonavir. Ritonavir itself has better solubility at a lower pH, boosts other protease inhibitors by inhibiting CYP3A4, is metabolised by CYP3A4 (similar to PPIs) and is a substrate and inhibitor of P-glycoprotein [22–24].

Total and maximum exposure of the non-ionizable lopinavir and ritonavir at steady state were both increased by about 25 % when administered with omeprazole, without obvious changes in the elimination [22]. These findings were explained by an increase in exposure to ritonavir resulting from inhibition of P-glycoprotein by omeprazole and a subsequent stronger inhibitory effect on CYP3A4 by ritonavir. Separation of protease inhibitor and omeprazole administration by 2 hours in another study largely prevented this effect; the increase in total and maximum exposure to ritonavir after dose separation was lowered from 14 to 3 % and from 16 to 8 %, respectively [23]. In contrast, exposure to concomitantly administered saquinavir remained increased by 50–70 % and, thus, was obviously not triggered by the change for ritonavir (i.e., another more systemic effect should account for this effect). Consistent with this, in another study, the increase in exposure to ritonavir was negligible, but exposure to saquinavir was increased by about 80 %, with a concomitant increase of omeprazole dose [24].

The combined effect of several factors was demonstrated in a study with a single dose of indinavir 800 mg, in which exposure to indinavir was decreased by 35 and 45 % with constant treatment with omeprazole 20 and 40 mg but was increased by 55 % when a single dose of ritonavir 200 mg was added to high-dose omeprazole [25].

2.2 Interactions with the Adenosine Triphosphate-Dependent Efflux Transporter P-Glycoprotein

Since the publication of the previous review [10], there have been no new studies involving PPIs and the P-glycoprotein transporter system. In the previous review, omeprazole, lansoprazole and pantoprazole-Na, which are substrates for the P-glycoprotein transporter system, were all reported to inhibit P-glycoprotein-mediated efflux of digoxin in an in vitro Caco-2 cell model [26]. Data were not available in this study for esomeprazole and rabeprazole.

2.3 The Cytochrome P450 Enzyme System

Discussion of interactions with intestinal and liver CYPs was extensive in the 2006 review [10] and is not reiterated here, except to remind readers that PPIs are predominantly metabolised in the liver by CYP2C19 and CYP3A4 [27].

Of significance since the previous review, there have been extensive discussions in recent reviews and meta-analyses on the drug interactions between certain PPIs and clopidogrel [28–34]. These interactions appear to be mediated by CYP2C19 and are of utmost clinical relevance. Although recent retrospective studies have suggested an attenuation of the beneficial effects of clopidogrel when administered concomitantly with PPIs in general, stratification of the analysis has indicated that such effects are not present in patients receiving pantoprazole-Na compared with those receiving omeprazole [35, 36]. Several studies demonstrated that being in steady state for

omeprazole significantly increased total exposure to clopidogrel and decreased exposure to the active metabolite [37]. These effects continued to persist even after separating administrations of the drugs by 12 hours, or after administration of doubled doses of clopidogrel. However, differences became clearly smaller after substitution of omeprazole by pantoprazole-Na [37].

This is consistent with the finding that clopidogrel must be activated by CYP2C19, an enzyme inhibited by omeprazole but not pantoprazole-Na [38]. It is further confirmed by data showing that exposure to the active metabolite after administration of clopidogrel was significantly decreased, and inhibition of platelet function diminished, under coadministration of omeprazole or esomeprazole [39]. The relevance of CYP2C19 is further stressed by a study showing that only a small effect was observed from coadministration of lansoprazole with prasugrel, the latter being activated more dominantly by CYP isoenzymes other than CYP2C19 [40].

The situation for lansoprazole seems more complex; however, unlike for rabeprazole, at least some information, including pharmacokinetic data, is available. Coadministration of lansoprazole with clopidogrel had no effect on the formation of clopidogrel's inactive carboxylic acid metabolite. Nonetheless, the pharmacodynamic effect was significantly lowered in good responders to clopidogrel, probably as a result of inhibition of clopidogrel activation via CYP2C19, which is without relevance for the formation of the carboxylic acid derivative via esterases [40]. However, evaluation of the total population in this study did not show more than a trend to a lowered efficacy of clopidogrel. This is consistent with findings reported from another study which found lansoprazole or dexlansoprazole exhibited no significant effect on the exposure to clopidogrel's active metabolite or its pharmacodynamics [39].

In summary an interaction between clopidogrel and PPIs seems to exist for omeprazole and esomeprazole, whereas there are only limited data for rabeprazole. Dexlansoprazole, lansoprazole and pantoprazole-Na had less effect on the antiplatelet activity of clopidogrel than did omeprazole or esomeprazole, which is supported by the Plavix label [41].

3 Interaction Profiles of Proton Pump Inhibitors

The interaction profiles of omeprazole and pantoprazole-Na 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 1, which includes new data on drug interaction studies with bortezomib [42], ciprofloxacin extended release [43], citalopram [44], clarithromycin [45], clopidogrel [37, 39], etravirine [46], gemifloxacin [47] and ivabradine [48].

Since 2006, a retrospective case-control study in patients with coronary artery disease indicated increased residual platelet aggregation and platelet activation during concomitant treatment with 75 mg/day non-enteric-coated acetylsalicylic acid and PPIs [49]. Coadministration of enteric-coated acetylsalicylic acid with pantoprazole-Na showed a decrease in platelet aggregation [50] and coadministration with lansoprazole showed no significant effect on platelet activity or in the levels of salicylates in the blood [51]. Thus, these prospective studies, which investigated the effects of the PPIs constituting concomitant treatment in about 70 % of patients in the case-control study, do not support the observed impairment of acetylsalicylic acid. Effects on platelet function with omeprazole and esomeprazole cannot be ruled out and monitoring of treatment efficacy might be recommended in cases of omeprazole or esomeprazole coadministration.

Case reports (from both the literature and the US Food and Drug Administration Adverse Events Reporting System) along with population pharmacokinetic studies suggest that coadministration of PPIs and methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, although the mechanism for this interaction is not clearly understood (see Bezabeh et al. [52] for a comprehensive review).

3.1 Omeprazole

In the previous review [10], omeprazole was reported to interact with diazepam [53–55], proguanil [56] and the antidepressant moclobemide (in extensive metabolisers) [57] via competitive inhibition of CYP2C19. Omeprazole-induced competitive inhibition of CYP2C19 also has the potential to alter the metabolism of phenytoin [54, 58] and warfarin [59–63] (see the previous review for an extensive discussion) [10]. More recently, CYP2C19 inhibition by omeprazole was identified as the reason for a 50 % reduction in the oral clearance of (+)-(*S*) citalopram, with a corresponding increase of approximately 120 % in plasma concentrations in healthy volunteers [44]. Similarly, such inhibition was found most likely to increase the total exposure of etravirine by 41 % after a single dose of etravirine 100 mg and multiple-dose omeprazole, an effect that was not observed with multiple-dose ranitidine [46].

The effects of omeprazole on the pharmacokinetics of antacids, bortezomib, ciprofloxacin extended release, gemifloxacin, nifedipine, metoprolol, NSAIDs, iron and theophylline have also been investigated, with no clinically significant findings [42, 43, 47, 64–69]. Systematic clinical trials have shown conflicting results for interactions between omeprazole and ciclosporin, with elevated

Table 1 Pharmacokinetic interaction profiles of proton pump inhibitors (PPIs)

Concomitant drug	Effect of PPI on concomitant drug				
	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole-Na	Rabeprazole
Antacid	Unknown	Conflicting results [108, 111]	None [64]	None [83]	None [123]
Phenazone (antipyrine)	Unknown	↑ Clearance [106]	↓ Clearance [125]	None [84]	Unknown
Bortezomib	Unknown	Unknown	None [42]	Unknown	Unknown
Caffeine	Unknown	None [126]	Conflicting results [126, 127]	None [85, 126]	Unknown
Carbamazepine	Unknown	Unknown	↓ Clearance [128]	None [86]	Unknown
Oral contraceptives	Unknown	Conflicting results [129]	Unknown [125]	None [98]	Unknown
Ciclosporin	Unknown	Unknown	Conflicting results [70, 71, 130]	None [88]	Unknown
Cinacalcet	Unknown	Unknown	Unknown	None [87]	Unknown
Ciprofloxacin ER	Unknown	Unknown	None [43]	Unknown	Unknown
Citalopram	Unknown	Unknown	↓ Clearance[a] [44]	Unknown	Unknown
Clarithromycin	Unknown	Unknown	None [45]	None [45]	Unknown
Clopidogrel	↓ Absorption [39]	None [39]	↓ Absorption [37]	None [37]	Unknown
Diazepam	↓ Clearance [80–82, 131]	None [107]	↓ Clearance [53, 54]	None [82, 89]	None[b] [55]
Diclofenac	Unknown	Unknown	None [65]	None [90]	Unknown
Digoxin	Unknown	Unknown	↑ Absorption [132]	None[c] [91]	↑ Absorption [133]
Ethanol	Unknown	None [134]	None [134]	None [92]	Unknown
Etravirine	Unknown	Unknown	↓ Clearance [46]	Unknown	Unknown
Gemifloxacin	Unknown	Unknown	None [47]	Unknown	Unknown
Glibenclamide	Unknown	Unknown	Unknown	None [93]	Unknown
Ivabradine	Unknown	None [48]	None [48]	Unknown	Unknown
Levothyroxine	Unknown	Unknown	Unknown	None [94]	Unknown
Metoprolol	Unknown	Unknown	None [66]	None [95]	Unknown
Naproxen	Unknown	Unknown	None [65]	None [96]	Unknown
Nifedipine	Unknown	Unknown	↑ Absorption ↓ Clearance [67]	None[d] [97]	Unknown
Phenprocoumon	Unknown	Unknown	↓ Clearance [63]	None [99]	Unknown
Phenytoin	↓ Clearance [80, 131]	None [110]	↓ Clearance [54, 58, 135]	None [100]	None [120]
Piroxicam	Unknown	Unknown	None [65]	None [101]	Unknown
Tacrolimus	Unknown	↓ Clearance [117]	Unknown	None [102]	None [117, 122, 136]
Theophylline	Unknown	Conflicting results [113, 114]	None [68, 113]	None [103, 113]	None [121]
Warfarin	↓ Clearance[e] [80, 131]	None [111]	↓ Clearance[e] [59–61]	None [104]	None [121]

Table modified from Blume et al. [10]. Reprinted with permission (with additions for bortezomib [42], ciprofloxacin ER [43], citalopram [44], clarithromycin [45], clopidogrel [37, 39], etravirine [46], gemifloxacin [47] and ivabradine [48])

↓ decreases, ↑ increases, *ER* extended release

[a] (+)-(*S*) enantiomer only

[b] Effects were seen with the desmethyl metabolite of diazepam but were significant only in CYP2C19-deficient individuals

[c] β-Acetyldigoxin

[d] Only for nifedipine sustained-release

[e] Only for *R*-warfarin; present in homozygous extensive metabolisers

ciclosporin concentrations occurring in heart transplant patients [70] but not in renal transplant patients [71] following coadministration of these agents.

Compounds with a high affinity for CYP3A4 (e.g., ketoconazole or fluconazole [72, 73], clarithromycin [74] and moclobemide [75]) may affect the bioavailability of omeprazole by increasing its serum concentrations, but this is only likely to be clinically relevant in those with CYP2C19 deficiency who metabolise omeprazole via the CYP3A4 metabolic pathway.

Omeprazole kinetics are also affected via the CYP2C19 pathway. Decreased plasma concentrations of omeprazole and omeprazole sulphone occurred after administration of ginkgo biloba [76] or St. John's wort [77]. Metabolism of omeprazole was reduced following administration of fluvoxamine (extensive metabolisers only) [78], and the omeprazole AUC was increased following use of a combined oral contraceptive containing ethinyloestradiol [79] (see previous review for details [10]).

In summary, several omeprazole-related drug interactions have been reported, although not all these interactions are considered significant. The number of reported interactions might be explained by the fact that omeprazole has been available longer than other PPIs (since 1989).

3.2 Esomeprazole

There are no additional new data for CYP-mediated interactions with esomeprazole. The 2006 review concluded that the interaction potentials of esomeprazole and racemic omeprazole seem not to differ significantly [10]. The authors reported that there were no apparent interactions between esomeprazole and drugs that are primarily metabolised by CYP1A2, CYP2A6, CYP2C9, CYP2D6 or CYP2E1 [80]. Esomeprazole, however, does interact with compounds metabolised by CYP2C19 as shown in studies using phenytoin and *R*-warfarin, although interactions did not reach clinical significance [80]. In addition, multiple doses of esomeprazole increased diazepam concentrations and reduced diazepam elimination, but no similar changes were reported with pantoprazole-Na [81, 82]. These effects with esomeprazole were manifested clinically as disrupted motor coordination and vigilance [81, 82].

3.3 Pantoprazole

Since the last review, pantoprazole-Na has been shown to have no significant interactions with clopidogrel [37]. The authors of the previous review concluded that extensive studies in healthy volunteers and patients have shown that pantoprazole-Na has a low potential to interact with other medications [10]. There were no significant metabolic interactions when combining pantoprazole-Na with antacids [83], phenazone (antipyrine) [84], caffeine [85], carbamazepine [86], cinacalcet [87], clarithromycin [45], ciclosporin [88], clopidogrel [37], diazepam [89], diclofenac [90], β-acetyldigoxin [91], ethanol [92], glibenclamide [93], levothyroxine sodium [94], metoprolol [95], naproxen [96], sustained-release nifedipine [97], oral contraceptives [98], phenprocoumon [99], phenytoin [100], piroxicam [101], tacrolimus [102], theophylline [103] or warfarin [104]. There was a slight, but clinically insignificant, interaction between pantoprazole-Na 40 mg and cisapride 20 mg [105].

Pantoprazole-magnesium (pantoprazole-Mg) is an improved formulation of pantoprazole that has been developed since the 2006 review. Pantoprazole-Mg was achieved by synthesizing a magnesium salt of the active ingredient, rather than a sodium salt as in pantoprazole-Na. Since pantoprazole-Na and pantoprazole-Mg are different salts of the same molecule, their drug interaction profiles are expected to be similar.

3.4 Lansoprazole

There have been no new CYP-mediated drug interaction studies with lansoprazole since the 2006 review [10]. As outlined previously, there are no clinically significant interactions reported between lansoprazole and phenazone [106], diazepam [107], ivabradine [48], magaldrate [108], oral contraceptives [109], phenytoin [110], prednisolone [111], propranolol [111] or warfarin [112]. Increases in theophylline bioavailability following lansoprazole administration are not considered to be clinically significant [113, 114], and increased clearance of theophylline following lansoprazole use [115] was not seen consistently [113]. Lansoprazole decreased oral tacrolimus clearance, significantly increasing blood tacrolimus concentration [116], particularly in those with CYP2C19 mutant alleles [116, 117]. Finally, the CYP2C19 inhibitor fluvoxamine had a significant effect on lansoprazole metabolism (increased plasma concentrations) in extensive metabolisers for CYP2C19 but not in poor metabolisers [118].

More recently, dexlansoprazole, the active enantiomer of lansoprazole, has been introduced into therapy. This compound is marketed with an innovative Dual Delayed Release™ technology, which is designed to release the entire dose in two separate portions to allow prolongation of plasma concentration-time profiles after once-daily administration. Considering the mechanism of action of PPI with irreversible inhibition of the proton pump, clinical advantages of such a biopharmaceutical profile should be carefully evaluated in therapeutic practice. Interactions of dexlansoprazole dual delayed release product have been investigated with diazepam, phenytoin, theophylline and warfarin as probe drugs (for interactions, e.g. with

CYP2C19, 2C9, 1A2 and 3A) and no impact on pharmacokinetics of the compounds has been found [119].

The interaction profiles of lansoprazole and dexlansoprazole have not been as thoroughly investigated as those of omeprazole or pantoprazole-Na. Nonetheless, neither compound appears to be associated with major clinically relevant drug interactions.

3.5 Rabeprazole

Information on drug interactions with rabeprazole has not changed since the 2006 review [10]. Drug interactions with rabeprazole are less well studied than those with omeprazole or pantoprazole-Na, as evidenced by the large number of unknown results in Table 1. Most studies report interactions attributed to the group effect of all PPIs on gastric pH (e.g. interactions with digoxin [120] or ketoconazole [121]). Significant CYP-mediated drug interactions with rabeprazole are generally not likely because rabeprazole has a low affinity for a range of CYP isoenzymes [27]. Further studies will prove useful to confirm this. In the 2006 review, rabeprazole was not found to be involved in metabolic drug interactions with theophylline [121], warfarin [121], phenytoin [120], tacrolimus [122] or antacids [123]. 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) [55].

The CYP2C19 inhibitor fluvoxamine had a significant effect on rabeprazole metabolism in extensive metabolisers of CYP2C19, with increased $AUC_{(0,\infty)}$ and elimination half-life of rabeprazole and rabeprazole thioether in homozygous and heterozygous extensive metabolisers [124]. In contrast, there were no differences in any pharmacokinetic parameters in poor metabolisers (*2/*2).

4 Conclusions

A thorough review of the literature since 2006 has yielded additional PPI drug interactions modulated by gastric pH, such as those reported with mycophenolate mofetil [13, 14, 16], the instability of PPIs themselves at low pH [17], and the altered pharmacokinetics of several protease inhibitors (including atazanavir [19], nelfinavir [20], raltegravir [21], ritonavir [22–24], and indinavir [25]). There are, however, a few new CYP-mediated drug interaction studies, with the most notable being the new data on dexlansoprazole and data for interactions between some PPIs and clopidogrel. Of clinical importance in recent years, CYP2C19-mediated interaction seems to exist between clopidogrel and omeprazole or esomeprazole, an effect not seen in PPIs as a class [35–37, 39]. In addition, the effects of omeprazole and esomeprazole on platelet aggregation when coadministered with acetylsalicylic acid cannot be ruled out without additional research. Finally, coadministration of PPIs with methotrexate may affect methotrexate pharmacokinetics, although the mechanism of interaction is not well understood [52].

Overall, the conclusions from the 2006 review still remain relevant. Lansoprazole, pantoprazole-Na and rabeprazole appear to be associated with lower incidences of drug interactions than omeprazole and esomeprazole, resulting either from their lower affinity for specific CYP isoenzymes or the involvement of additional elimination processes. However, only the interaction profile of pantoprazole-Na has been well characterised.

With little difference among the PPIs in terms of clinical efficacy at equivalent doses, differences in drug interaction propensities become important factors in prescribing decisions, particularly in patients who are taking multiple concomitant medications (such as the elderly) or those receiving drugs with a narrow therapeutic window. A PPI with a well proven low risk of drug interactions would be the favourable choice in these patients.

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