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Interaction of Proton Pump Inhibitors with Cytochromes P450: Consequences for Drug Interactions

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Omeprazole, lansoprazole and pantoprazole are metabolized by several human cytochromes P450, most prominently by CYP2C19 and CYP3A4. Only pantoprazole is also metabolized by a sulfotransferase. Differences in the quantitative contribution of these enzymes and in the relative affinities of the substrates explain some of the observed interactions with carbamazepin, diazepam, phenytoin and theophylline and of the impact of the CYP2C19 (mephenytoin) genetic polymorphism. Of these drugs, pantoprazole has the lowest potential for interactions, both *in vitro* and in human volunteer studies.

INTRODUCTION

The proton pump inhibitors (PPIs)[b] omeprazole, pantoprazole and lansoprazole are substituted benzimidazole sulfoxides with similar dose-efficacy profiles. Elimination of these drugs occurs almost entirely by rapid metabolism to inactive or less active metabolites, so that virtually no unchanged drug is excreted in urine and feces. The clearances of PPIs are between 0.1 and 0.5 l/h/kg-body-weight and the plasma half-lives range from 0.3 to 2.2 hr [1-4]. Drug metabolism is subject to genetic and environmental variation, which is a frequent cause of patient-to-patient differences in drug effects. The differences in the metabolism of these drugs, therefore, may favorably or unfavorably affect the potential for interactions, enzyme induction and genetically polymorphic metabolism. On the other hand, it is well known that the inhibitory effect of these drugs on acid secretion persists for a long time, in spite of their rapid elimination.

METABOLISM OF OMEPRAZOLE, LANSOPRAZOLE AND PANTOPRAZOLE

Omeprazole

Omeprazole remains the most extensively studied of the PPIs in regard to its metabolism (Figure 1) [5, 6]. Omeprazole is primarily metabolized by aliphatic hydroxylation of the pyridinyl methyl group to hydroxy-omeprazole and by oxidation of the sulfoxide group to form omeprazole sulfone. Both metabolites are further metabolized to the hydroxysulfone. *In vitro* studies in human liver mircrosomes have also revealed some participation of CYP2C19, CYP3A and CYP2D6 in the formation of secondary and minor metabolites [6]. Two well-known cytochromes P450, CYP2C19 (S-mephenytoin hydroxylase) and CYP3A4 (nifedipine oxidase), catalyze these reactions. CYP2C19 exhibits a significant genetic polymorphism, and poor metabolizers of S-mephenytoin are also poor metabolizers of omeprazole [7-10] (see below).

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[b]*Abbreviations:* PPI, proton pump inhibitor; PM, poor metabolizer; EM, extensive metabolizer.

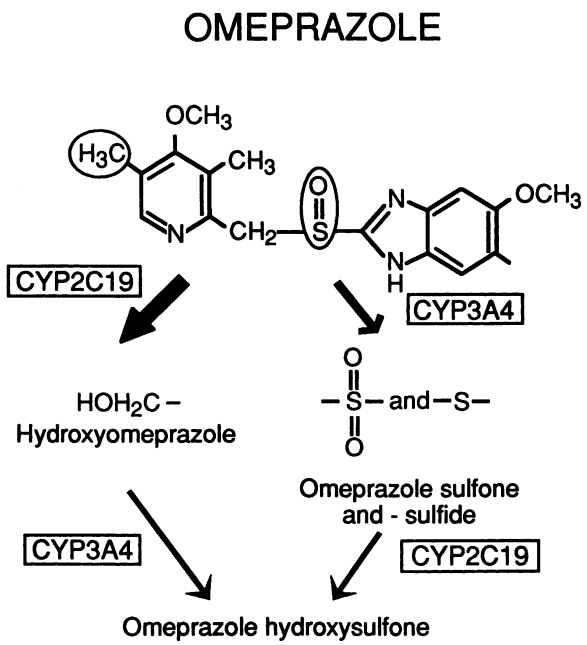

Figure 1. Major metabolic pathways of omeprazole and the enzymes involved. The size of the arrows approximates the overall importance of the pathway for elimination.

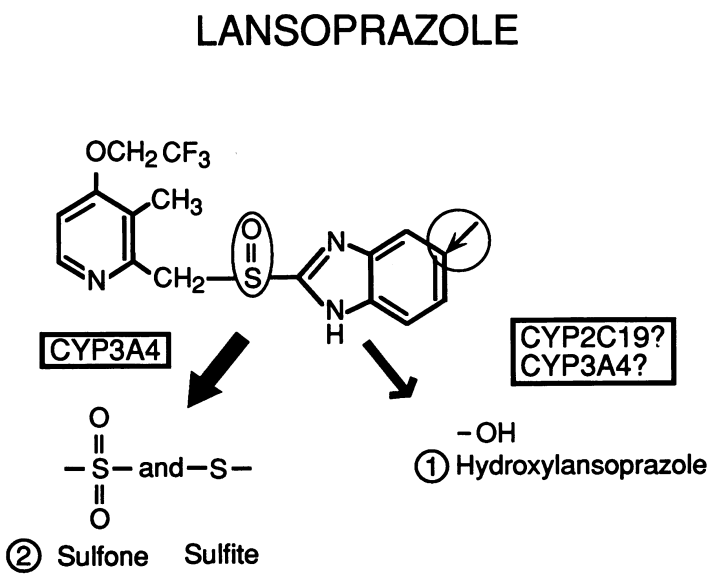

Figure 2. Major metabolic pathways of lansoprazole.

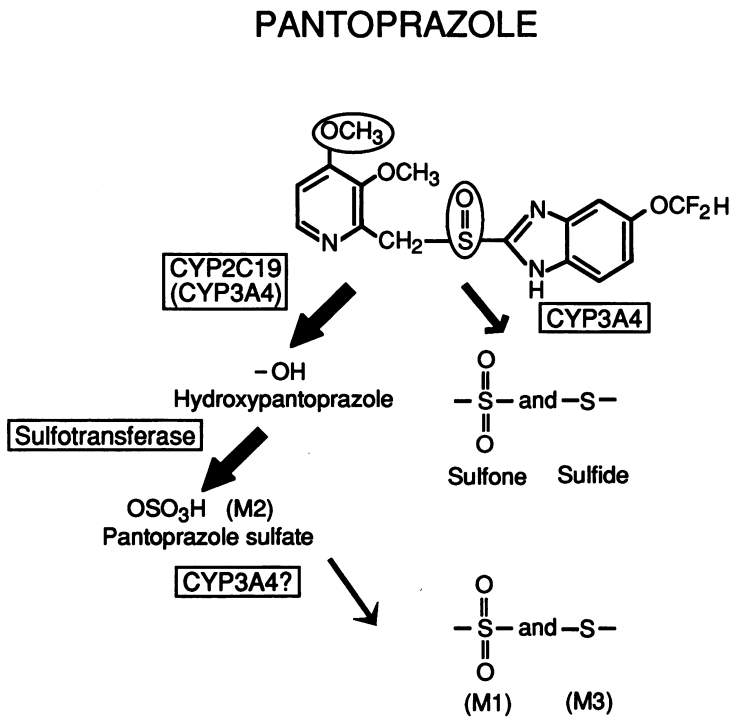

Figure 3. Major metabolic pathways of pantoprazole. M1, M2 and M3 are the major metabolites detected in serum.

Lansoprazole

The major metabolic pathway of lansoprazole involves the formation of lansoprazole sulfone from the sulfoxide group (Figure 2). Lansoprazole sulfone is also the main metabolite present in serum. Hydroxylansoprazole is also formed, but the hydroxylation occurs at a different position (carbon 5 of the benzimidazole moiety) than for omeprazol (5-methyl carbon of the pyridinyl group). Studies with human liver microsomes and human hepatocytes in culture [1] indicate that, as with omeprazole, CYP3A4 is the major enzyme involved in the sulfone formation. However, the enzymes catalyzing the hydroxylation are less clearly identified and contributions of the cytochromes CYP3A4, CYP2C18, CYP2C19 and others are suspected [11].

Pantoprazole

Pantoprazole (Figure 3) is also completely metabolized in the liver. It undergoes O-demethylation by CYP2C19, which is followed by sulfate conjugation and some sulfone or sulfide formation, either by oxidation or reduction of the sulfoxide group [3, 4]. Recent *in vivo* and *in vitro* studies in human liver microsomes suggest that in addition to a cytosolic sulfotransferase, CYP2C19 and CYP3A4 affect the clearance of pantoprazole, i.e., poor metabolizers of pantoprazole were also poor metabolizers of mephenytoin (Table 1, W.A. Simon, unpublished data). The same studies suggest that additional enzymes such

as CYP2C9 and CYP2D6 may contribute in a minor way to some of the reactions involved in the metabolism of pantoprazole.

In summary, CYP2C19 and CYP3A4 (and in the case of pantoprazole a sulfotransferase) are sequentially and alternatively involved in the metabolism of these drugs. However, the affinities of these enzymes for the different substrates and metabolites apparently vary remarkably. CYP2C19 and CYP3A4 are well-studied human drug-metabolizing enzymes and their substrates, inhibitors and inducers have been extensively reviewed [12, 13].

ROLE OF THE CYP2C19 POLYMORPHISM FOR THE KINETICS OF PPI'S

CYP2C19 or S-mephenytoin 4′-hydroxylase manifests a common genetic polymorphism [14]. Two mutations, m1 and m2, of the CYP2C19 gene have recently been demonstrated to cause loss of function alleles of this enzyme [15, 16]. Homozygous carriers of the mutation, thus, completely lack CYP2C19 enzyme and are so-called poor metabolizers (PMs) of mephenytoin. These PMs have an up to 10-fold higher value of the area under the plasma concentration-time curve of omeprazole [7, 8, 17-19] as compared to extensive metabolizers. 2.5 to 6 percent of Caucasians and up to 30 percent of Oriental individuals are PMs [20]. During treatment with 40 mg/d omeprazole, approximately 80 percent of omeprazole clearance can be attributed to CYP2C19. When the dose is increased, CYP2C19 becomes limiting, and non-linear saturation kinetics may occur. Thus, at high doses, the kinetic parameter in EMs is shifted toward values observed in PMs who do not have a CYP2C19 enzyme. For omeprazole, at least, CYP3A4 appears to function as a high-capacity enzyme and prevents accumulation of very high omeprazole concentrations. Under these condition, CYP3A4 may become the major target of drug interaction. Similar studies have not been done for lansoprazole and pantoprazole, but as already discussed, CYP2C19 also plays a role in the metabolism of these drugs. PMs of mephenytoin were also PMs of pantoprazole (Table 1), and lansoprazole was shown in *in vitro* studies to be in part metabolized by CYP2C19.

The relevance of the polymorphism for the efficacy and safety of acid inhibitory therapy by PPI's has not been evaluated. Chang et al. [18] reported higher gastrin levels in PMs after eight daily doses (20 mg) of omeprazole in PMs as compared to EMs, but no studies on acid secretion are yet available. This would be of particular importance in populations with a high percentage of PMs of mephenytoin. Moreover, gastrin levels were also higher in heterozygous carriers of a mutant alleles of CYP2C19. This finding suggests that approximately 60 percent of Orientals (including the homozygous and heterozygous carriers of CYP2C19 mutant alleles) may have a slower metabolism of CYP2C19 substrates than the majority of Caucasians.

INDUCTION OF DRUG-METABOLISM BY PPI'S

Omeprazole and lansoprazole induce the synthesis of CYP1A1 and CYP1A2 [21]. For omeprazole, induction of CYP1A enzymes has been demonstrated in biopsies of

Table 1. Plasma half lives (h ± S.D.) of omeprazole and pantoprazole in extensive metabolizers and poor metabolizers of mephenytoin. The phenotype for S-mephenytoin hydroxylation was determined by the urinary S/R enantiomeric ratio.

	Omeprazole*	Pantoprazole**
Extensive metabolizers	0.69 + 0.41 (6)†	1.3 + 0.9 (11)
Poor metabolizers	2.30 + 0.44 (6)	7.6 + 1.1 (4) (range 6.2-9)

*Data from [8]. **Data from Byk Gulden, Konstanz, Germany. †Number of volunteers.

human liver [21] and gut [22]. This effect has also been demonstrated *in vivo* in human volunteers by increased N3-demethylation of caffeine after omeprazole administration [24, 25] or increased clearance of theophylline after lansoprazole treatment [26]. In human hepatocyte cultures [27], CYP3A4 also was induced by omeprazole and its sulfone, and by lansoprazole. The induction effect is concentration-dependent and, thus, occurs at lower doses in poor metabolizers of mephenytoin. The molecular mechanism of the induction of CYP1A1/2 and CYP3A4 by these drugs is not exactly known [28, 29]. These observations have generated a debate on the risk of induced P450s for carcinogenesis, since both CYP1A1 and CYP3A4 can activate or inactivate procarcinogens. For some procarcinogens, induction can be an advantage, for others a disadvantage. Lack of induction of antipyrine, caffeine and theophylline clearance by pantoprazole suggests that this drug has little or no potential for induction [30, 31].

DRUG INTERACTIONS

PPIs interact with cytochromes P450 not only as substrates, but also as competitive inhibitors and inducers. Omeprazole inhibits the clearance of diazepam by 26 to 54 percent [32, 33], and this inhibition is more apparent in individuals of the mephenytoin extensive metabolizer phenotype (EMs), indicating that at therapeutic concentrations omeprazole and diazepam compete for the same site on CYP2C19. Neither lansoprazole [34] nor pantoprazole [35] seem to affect diazepam kinetics. A decrease in the clearance of phenytoin [36] and carbamazepin [37] points to interaction of omeprazole with other cytochromes P450, presumably of the CYP2C9 subfamily. Lansoprazole and pantoprazole

Table 2. Interactions of PPIs with other drugs.

Drug tested	Major P450	Omeprazole	Lansoperazole	Pantoprazole
Theophylline	CYP1A2	No IA	(↑Cl)	No IA
Caffeine	CYP1A2	IM	NT	No IA
Phenytoin	CYP2C9	↓Cl	No IA	No IA
Warfarin	CYP2C9	(↓Cl)	No IA	No IA
Carbamazepin	CYP2C8	↓Cl	DC NT	No IA
Diclofenac	CYP2C9	NT	NT	No IA
Phenprocoumon	?	NT	NT	No IA
Mephenytoin	CYP2C19	↓M	NT	No IA
Diazepam	CYP2C19	↓Cl	No IA	No IA
Debrisoquine	CYP2D6	No IA	NT	No IA
Propanalol	CYP2D6 + others	No IA	No IA	NT
Metoprolol	CYP2D6	No IA	NT	NT
Nifedipin	CYP3A4	(↓Cl?)	NT	No IA
Cyclosporine	CYP3A4	No IA	NT	NT
Lidocaine	CYP3A4	No IA	NT	NT
Quinidine	CYP3A4	No IA	NT	NT
Contraceptives	CYP3A4	NT	Eff. on ovul.?	No IA
Alcohol	CYP2E1	NT	NT	No IA
Antipyrine	CYP3A/2C/1A2	(↓Cl)	(↑Cl)	No IA
Methotrexate		↓renal excr.	NT	NT
Digoxin	Absorption	(↑ absorption)	NT	No IA
Bismuth	Absorption	↑ absorption	NT	NT

IA = interaction; Cl = clearance; M = metabolism; NT = not tested; ( ) = of questionable significance.

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