Digestive Diseases and Sciences, Vol. 36, No. 12 (December 1991), pp. 1665–1669

REVIEW ARTICLE

Clinical Implications of Drug Interactions with the Cytochrome P-450 Enzyme System Associated with Omeprazole

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Interactions with the hepatic cytochrome P-450 microsomal enzyme system, as evidenced by statistically significant changes in pharmacokinetic parameters, have been described with some H_2-receptor antagonists. Omeprazole is the first of a new class of antisecretory agents inhibiting gastric secretion by blocking hydrogen potassium ATPase. Omeprazole contains a benzimidazole moiety and thus has the potential to interact with the cytochrome P-450 enzyme group. In vitro, in vivo *and human clinical studies have assessed whether such an interaction occurs, and the potential clinical consequences, in patients receiving omeprazole therapy.* In vitro *studies have demonstrated that omeprazole influences* O-*deethylation and* N-*demethylation in liver microsomes and the clearance and elimination half-life of antipyrine in isolated perfused liver preparations. Overall, the studies reviewed suggest that omeprazole has a differential affinity toward specific cytochrome P-450 isozymes.* In vivo *animal studies have demonstrated that omeprazole prolongs pentobarbital sleep times and half-life and decreases [^{14}C]-aminopyrine elimination. Human clinical studies have not demonstrated the "all or none" effect of omeprazole on cytochrome P-450-mediated drug interactions, as is seen with cimetidine. These studies confirm* in vitro *findings that omeprazole is a differential inhibitor of drug metabolism: interactions have been demonstrated with the model drugs aminopyrine and antipyrine, and the therapeutic drugs diazepam, phenytoin, and warfarin but not with theophylline or propranolol. Although caution should be exercised when initiating omeprazole therapy in patients taking concomitant diazepam, warfarin, and phenytoin, clinically significant drug interactions appear unlikely.*

KEY WORDS: cytochrome P-450; drug metabolism; omeprazole; cimetidine; drug interactions.

The hepatic cytochrome P-450 or mixed function oxidase microsomal enzyme system is involved in the oxidative metabolism of many drugs. Cimetidine, the first H_2-receptor antagonist to be marketed, has been shown to reversibly inhibit the cytochrome P-450 system in either a competitive or noncompetitive manner, depending on the drug involved. The mechanism of this inhibition appears to involve the imidazole ring of cimetidine and to be a class characteristic of imidazole compounds. Although the list of interactions with cimetidine is long, and currently includes warfarin, theophylline, phenytoin, carbamazepine, beta-blockers, lidocaine, and tricyclic antidepressants, few interactions have proved to be of clinical significance after many years of widespread experience with this compound (1). Clinical caution is indicated when cimetidine is taken with concomitant drugs that have a narrow range of therapeutic concentration, such as warfarin, theophylline, and phenytoin.

Manuscript received October 26, 1989; revised manuscript received May 15, 1991; accepted May 16, 1991.

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0163-2116/91/1200-1665$06.50/0

Ranitidine, a thiazole ring–based H^2-receptor antagonist, has been demonstrated to have a low level of binding to hepatic microsomal cytochrome P-450. There have been a few reports suggesting interaction between ranitidine and theophylline and warfarin, but the clinical implications of a cytochrome P-450 interaction with ranitidine are felt to be minimal (2). Similarly, famotidine, a more recent development in the H_2-receptor antagonist class, has been shown to have negligible interaction with the cytochrome P-450 system. *In vitro* and clinical studies have shown no evidence of significant interactions between famotidine and drugs known to be metabolized through the cytochrome P-450 system (3).

Omeprazole is a substituted benzimidazole that inhibits gastric secretion by interfering with the proton pump or hydrogen potassium ATPase on the secretory membrane of the parietal cell, and represents the first of a new class of extremely effective antisecretory compounds. Omeprazole has been approved in several countries for the treatment of duodenal and gastric ulcers, reflux esophagitis, and Zollinger-Ellison syndrome (ZES). In view of this drug's marked efficacy in reflux esophagitis and ZES, and its superiority over H_2-receptor antagonists, particularly in esophagitis (4), significant usage is likely. Since omeprazole contains a benzimidazole moiety, a potential for cytochrome P-450 interactions exists. The purpose of this paper is to review the *in vitro, in vivo,* and clinical studies designed to assess the potential of omeprazole to interact with the cytochrome P-450 system and to present a perspective on potential drug interactions and their clinical implications.

IN VITRO STUDIES

Jensen and Gulger (5) conducted preliminary experiments that demonstrated omeprazole's capacity to interact with human liver microsomes *in vitro* by studying the effects of omeprazole on cytochrome P-450-mediated 7-ethoxycoumarin deethylation in human liver microsomes. In this study, human liver microsomes were prepared from histologically normal human liver tissue obtained from a patient undergoing partial hepatectomy. Deethylation of 7-ethoxycoumarin was chosen as a model substrate of monooxygenase activity because dealkylation represents a common pathway of drug metabolism in man and animals. Addition of omeprazole (0.2, 0.5, and 1.0 mM) to the microsomes resulted in a decrease in deethylase activity. Omeprazole inhibited both the high- and low-affinity components of deethylation with an estimated inhibition constant (K_i) of 0.03 mM for the high-affinity component and 0.67 mM for the low-affinity component (5).

Webster et al (6) investigated the influence of omeprazole as compared to cimetidine on antipyrine metabolism using an isolated, perfused rat liver model. At a steady-state perfusate concentration of 1 μg/ml, omeprazole reduced the clearance of antipyrine by 18% and increased the elimination half-life by 25%. A 10-mg bolus dose of omeprazole (29 μmol) reduced antipyrine clearance by 24% and prolonged its elimination half-life by 41%. None of these results reached statistical significance. Cimetidine in a 5-mg bolus dose (19.8 μmol) produced a statistically significant 450% increase in the elimination half-life of antipyrine. This finding suggests that, in the isolated perfused liver model, omeprazole is a less potent inhibitor of hepatic drug metabolism than is cimetidine (6).

Inhibition of microsomal deethylation reactions by omeprazole was also observed by Miwa (7). Comparative inhibition of benzphetamine *N*-demethylation by equimolar doses of omeprazole or cimetidine (0.25–2.0 mM) was investigated in human liver microsomes. Omeprazole 0.25 mM inhibited benzphetamine *N*-demethylation by 29%, while 2.0 mM cimetidine was required to cause an equivalent amount of inhibition. A similar pattern of inhibition of benzphetamine *N*-demethylation was observed in microsomes from untreated and phenobarbital-pretreated rats. Although omeprazole appears to be a more potent inhibitor of this demethylation reaction *in vitro,* this may not necessarily mean that omeprazole is a more clinically important inhibitor of drug metabolism than cimetidine because of the marked differences in therapeutic doses of these two drugs (7). Since the therapeutic dose of omeprazole of 20–40 mg a day is 30- to 60-fold less than a therapeutic dose of cimetidine, it appeared unlikely that omeprazole would produce clinically significant interactions with the cytochrome P-450 system as observed with cimetidine (7). In other studies, Miwa demonstrated that omeprazole's ability to inhibit the *O*-deethylation of 7-ethoxycoumarin in rat liver microsomes, as reported by Gugler and Jensen (5), was dependent upon the pretreatment of rats with various inducers of cytochrome P-450 metabolism. Inhibition of 7-ethoxycoumarin *O*-deethylation by omeprazole 2.0 mM was greatest in microsomes from rats

pretreated with 3-methylcholanthrene (91%), less marked with microsomes from phenobarbital-induced rats (73%), and lowest in microsomes from untreated rats (44%). This differential inhibition suggests that omeprazole has a greater affinity toward specific cytochrome P-450 isozymes.

IN VIVO ANIMAL STUDIES

Henry et al studied the effect of omeprazole on pentobarbital sleep times, pentobarbital half-life, and [^{14}C]aminopyrine elimination in rats (8). Single equimolar doses of omeprazole (40 mg/kg) and cimetidine (30 mg/kg) prolonged phenobarbital sleep times by 55% and 65%, respectively. A single dose of omeprazole at 40 mg/kg prolonged the pentobarbital half-life by 26% and inhibited the [^{14}C]aminopyrine elimination in the breath test by 30%. Continuing omeprazole treatment for five days produced no greater effect. Omeprazole doses of 20 mg/kg or less produced no significant changes on either phenobarbital or [^{14}C]aminopyrine elimination.

These studies suggest that omeprazole and cimetidine are equipotent inhibitors of phenobarbitone elimination in rats on a molar basis, but the dose of omeprazole producing these inhibitory effects was more than 50 times the antisecretory dose in this species.

HUMAN CLINICAL STUDIES—ANTIPYRINE AND AMINOPYRINE

Henry et al studied the ability of omeprazole, 30 and 60 mg, to interfere with the metabolism of the model drugs aminopyrine and antipyrine, assessed in healthy male volunteers before and after 14 days of treatment with omeprazole (9). Omeprazole given 60 mg daily for 14 days prolonged aminopyrine half-life by 21% ($P \leq 0.05$) and reduced the percent of the dose demethylated by 19% ($P \leq 0.05$). The same dose of omeprazole prolonged antipyrine half-life by 10% ($P \leq 0.025$) and antipyrine clearance was reduced by 14% ($P = 0.063$). Omeprazole 30 mg/day for 14 days prolonged aminopyrine half-life by 13% and reduced the percent of the dose demethylated by 11%—changes that were not statistically significant. At this dose, antipyrine metabolism was unaltered.

Thus, a dose-related effect of omeprazole on the metabolism of aminopyrine and antipyrine was demonstrated. However, the extent of inhibition with these model drugs was only moderate and would suggest that therapeutic doses of omeprazole ≤30 mg daily would not produce clinically significant inhibition.

HUMAN CLINICAL STUDIES—THERAPEUTIC DRUGS

Several clinical studies investigating the potential of omeprazole to interact with the metabolism of diazepam, phenytoin, warfarin, theophylline, and propranolol have been conducted and the effects of omeprazole on the pharmacokinetics of these drugs are shown in Table 1.

Diazepam. Statistically significant increases in the area under the plasma concentration time half-life curve (AUC) and half-life ($T½$) and decreases in clearance of diazepam given intravenously 0.1

TABLE 1. CLINICAL STUDIES OF DRUG INTERACTIONS WITH OMEPRAZOLE

Ref	*Test drug*	*Daily oral omeprazole dose (mg)*	*Pharmacokinetic interactions (%)*			*Clinical evidence of interaction*
			AUC	*T1/2*	*CL*	
11	Diazepam IV	40	↑ 142*	↑ 130*	↓ 54*	None
10	Diazepam IV	20	↑ 39*	↑ 36*	↓ 27†	None
11	Phenytoin IV	40	↑ 18†	↑ 27†	↓ 15†	None
12	Phenytoin PO	40	↑ 25†	↑ 45		None
13	Warfarin	20	‡	‡	‡	Thrombotest decreased from 21.1% to 18% (NS)
14	Theophylline IV	40	↓ 14†	↓ 14	↑ 21	None
15	Theophylline PO	40	↓ 5	↓ 1	↑ 9	None
16	Propranolol	20	↑ 2		↓ 14	No effect on propranolol pharmacodynamics

*$P \leq 0.001$.
†$P \leq 0.05$.
‡A small (11.8%) but significant ($P \leq 0.001$) increase in the mean plasma concentration of (*R*)-warfarin was seen. No effect on (*S*)-warfarin was noted.

mg/kg were shown after at least seven days of omeprazole 20 mg (10) or 40 mg (11) in normal volunteers. As with the aminopyrine–antipyrine study, dose-related effects were seen in all parameters. The changes induced in the AUC, $T½$ and clearance (CL) were statistically significant. Additionally, the plasma concentration of desmethyldiazepam, the demethylated metabolite of diazepam, was reduced following treatment with omeprazole 40 mg. However, no adverse clinical reactions occurred in the 20 subjects involved in these studies. Due to the long half-life of diazepam (~45 hr) and a wide interindividual variation in doses required to achieve desired therapeutic effects, the metabolic interaction between omeprazole and diazepam would not be expected to have significant clinical consequences.

Phenytoin. The effect of omeprazole on the plasma concentration profile produced by oral and intravenous doses of phenytoin was determined in two studies. The first study (11) was an open, two-way crossover trial in eight healthy male subjects who took omeprazole 40 mg daily for eight days. At baseline (pretreatment) and on day 7, phenytoin 250 mg was given intravenously and blood samples were drawn for drug analysis over the ensuing 72 hr. Ten male volunteers participated in the second study (12) that followed a similar design as the first, except that phenytoin 300 mg was given orally at baseline and after seven days of omeprazole 40 mg daily. In both studies, omeprazole was associated with statistically significant increases in the AUC for phenytoin. A significant decrease in phenytoin clearance was seen in the intravenous phenytoin study. The increase in $T½$ produced by omeprazole was similar for both oral and intravenous phenytoin, but reached statistical significance only with intravenous phenytoin. Again, no adverse clinical consequences occurred in any of the volunteers in these two studies.

Warfarin. Twenty-one healthy male volunteers completed a placebo-controlled crossover study investigating the possibility of an interaction of omeprazole with warfarin (13). Warfarin was administered for 3 weeks prior to the crossover portion of this study at a dose that was individually adjusted and maintained to allow vitamin K-dependent coagulation factors to fall within 10–20% of the normal range. The dose of warfarin required was then maintained throughout the crossover portion of the study that involved two randomized 14-day treatment periods with omeprazole 20 mg daily or placebo. Blood coagulation factors were monitored using thrombotest (TT), and the plasma concentrations of (*R*)- and (*S*)-warfarin were evaluated by stereospecific liquid chromatography. Table 2 shows the results of this study.

TABLE 2. COMPARISON OF MEAN STEADY-STATE PLASMA CONCENTRATIONS OF WARFARIN ENANTIOMERS AND THROMBOTEST VALUES*

	(R)-Warfarin (ng/ml)	*(S)-Warfarin (ng/ml)*	*TT (%)*
Omeprazole	548	379	18.7
Placebo	490	387	21.1
P	0.001	NS	0.04
95% CI† for the difference of means:	28 to 88	−30 to 14	−4.6 to −0.1

*$N = 21$.
†CI = confidence interval.

Concomitant administration of 20 mg of omeprazole did not have any significant effect on the plasma concentrations in (*S*)-warfarin but did cause a small but statistically significant increase in (*R*)-warfarin concentrations. A marginal decrease in thrombotest values was demonstrated in the omeprazole group, 18.7% from 21.1%. There was overlap in thrombotest values in all but two subjects. This study demonstrates that omeprazole interacts with the less potent *R* enantiomer of warfarin, as has been demonstrated with cimetidine (1).

Theophylline. The effect of omeprazole 40 mg, administered for at least 7 days, on theophylline plasma profiles produced by single doses of theophylline (161 mg orally and 193 mg intravenously) was investigated in healthy male subjects. As can be seen in Table 1, the coadministration of omeprazole did not statistically influence the overall disposition kinetics of omeprazole administered either intravenously (14) or orally (15), with the sole exception of a small change in the AUC after intravenous administration (14% decrease). That change was not considered clinically significant.

Propranolol. Omeprazole also did not alter the pharmacokinetics or pharmacodynamics of propranolol in a study of eight healthy male subjects (16). Concomitant administration of propranolol 80 mg twice daily and omeprazole at a dose of 20 mg for seven days did not significantly affect the AUC or clearance of propranolol, or the extent of periph-

eral β_1-blockade produced by propranolol as measured by exercise challenge.

DISCUSSION

These studies demonstrate a selectivity of omeprazole in its interaction with other drugs metabolized by the cytochrome P-450 system. Omeprazole appears to interfere with the elimination of antipyrine, aminopyrine, diazepam, warfarin, and phenytoin but has no apparent effect on the kinetics of theophylline and propranolol. The studies with phenytoin, warfarin, and theophylline are especially important since each has a relatively narrow range of therapeutic, yet nontoxic, plasma concentrations. Although these studies demonstrated statistically significant evidence of drug interactions with diazepam, phenytoin, and warfarin, no adverse clinical effects due to the interaction were seen in any of the volunteer subjects in these studies. The selectivity of omeprazole in its interaction with other drugs suggests that it inhibits only specific isozymes of cytochrome P-450 in the human liver. However, it is not possible to predict from the pattern of inhibition, as currently defined, which other drugs may also show a significant metabolic interaction with concomitant omeprazole therapy. Although appropriate caution should be exercised when initiating omeprazole therapy in patients taking concomitant diazepam, warfarin, phenytoin, and other drugs with narrow therapeutic ranges and metabolized by the cytochrome P-450 system, it would appear unlikely that clinically significant drug interactions would occur. This conclusion is supported by the clinical experience with cimetidine, a drug with a broad spectrum of cytochrome P-450 interactions yet with few clinically significant consequences of such interaction potential.

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