Pharmacokinetic Interaction Between Fluoxetine and Omeprazole in Healthy Male Volunteers: A Prospective Pilot Study

Laurian Vlase, PhD¹; Maria Neag, MD²; Adina Popa, PhD²; Dana Muntean, PhD¹; and Sorin E. Leucuta, PhD¹

¹Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, University of Medicine and Pharmacy “Iuliu Hatieganu,” Cluj-Napoca, Romania; and ²Department of Clinical Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy “Iuliu Hatieganu,” Cluj-Napoca, Romania

ABSTRACT

BACKGROUND: Fluoxetine is an inhibitor of the main metabolizing enzymes (cytochrome P450 [CYP] 2C19 and CYP3A4) of omeprazole and thus might influence that drug’s pharmacokinetics. The changes in omeprazole’s pharmacokinetics may have clinical significance concerning efficacy and tolerability of the treatment.

OBJECTIVE: The aim of this study was to assess the pharmacokinetic interaction of fluoxetine with omeprazole in healthy volunteers.

METHODS: The study enrolled healthy adult men and consisted of 2 periods. In the first period, all subjects received a single 40-mg dose of omeprazole. This was followed by an 8-day period during which fluoxetine monotherapy (60 mg/d) was administered as a single oral daily dose. At the end of those 8 days, the subjects were administered a 40-mg dose of omeprazole with a 60-mg dose of fluoxetine. Plasma concentrations of omeprazole were determined at 0.5, 1, 1.33, 1.66, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 hour(s) after study drug administration. Omeprazole plasma concentrations were determined by a validated HPLC method. Pharmacokinetic parameters of omeprazole were calculated using noncompartmental analysis. Adverse events were assessed throughout the study duration.

RESULTS: Eighteen healthy male volunteers (mean [SD] age, 22.11 [2.52] years [range, 18–26 years]; body mass index, 23.34 [2.31] kg/m² [range, 19.1–27.1 kg/m²]) were enrolled and completed the study. In the 2 periods of treatment, the mean $C_{\text{max}}$ of omeprazole was 730.8 ng/mL (omeprazole monotherapy) and 1725.5 ng/mL (combination treatment with fluoxetine). The observed $AUC_{0-\infty}$ was 1453.3 and 5072.5 ng/mL/h and $AUC_{0-\infty}$ was 1465.0 and 5185.3 ng/mL/h, respectively. The $T_{\text{max}}$ was 1.30 and 1.63 hours and the elimination rate constant was 0.753 and 0.482 hr⁻¹. The $t_{1/2}$ was 0.96 and 1.47 hours, whereas the mean residence time was 2.33 and 3.35 hours, respectively. Statistically significant differences were observed for all parameters between periods 1 and 2 (all, $P < 0.001$).
**Conclusion:** The data found in this prospective pilot study suggest a pharmacokinetic interaction between fluoxetine and omeprazole in these healthy volunteers, but its relevance has to be confirmed. *(Curr Ther Res Clin Exp. 2010;71:360–368) © 2010 Elsevier HS Journals, Inc.*

**Key words:** omeprazole, fluoxetine, pharmacokinetics, drug interaction.

**INTRODUCTION**

Omeprazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl] sulfoxide]-1H-benzimidazole, is a gastric parietal cell proton-pump inhibitor. The drug has greater antisecretory activity than histamine hydrogen–receptor antagonists and has been used in the treatment of peptic ulcer, efflux esophagitis, and Zollinger–Ellison syndrome.*1,2* The bioavailability of omeprazole is 20% to 30% after the first dose, and it increases to ~60% with repeated doses. One potential reason for these characteristics is that the metabolism of omeprazole can be saturated over time, which is indicative of nonlinear pharmacokinetics.*3,4* Omeprazole is metabolized in the liver to the primary metabolites 5-hydroxyomeprazole and omeprazole sulfone. The formation of 5-hydroxyomeprazole is mainly mediated by the isoenzyme cytochrome P450 (CYP) 2C19, whereas the formation of omeprazole sulfone is via CYP3A4.*3–7* Omeprazole is generally well tolerated.2

Fluoxetine is an antidepressant for oral administration that is efficacious through selective inhibition of serotonin reuptake.*8* Fluoxetine is metabolized by N-demethylation to its active metabolite, norfluoxetine.*8* The elimination $t_{1/2}$ of fluoxetine has been reported to be between 1 and 4 days, while that of norfluoxetine is longer, ranging from 7 to 15 days.*8* The mean elimination $t_{1/2}$ of fluoxetine increases (from 1.9–5.7 days) with multiple doses, due to inhibition of its own metabolism.*8* Fluoxetine and its metabolite have been shown to be inhibitors of CYP2D6, CYP2C19, and CYP3A4.*9,10*

Being an inhibitor of the primary metabolizing enzymes of omeprazole, fluoxetine might influence its pharmacokinetics and it is important to determine whether a pharmacokinetic interaction occurs between these drugs. To date, this pharmacokinetic interaction has not been reported.

**SUBJECTS AND METHODS**

**Subjects**

Healthy, nonsmoking males, aged ≥18 years, were enrolled in the study. We utilized our subject recruitment database. Potential subjects submitted a prestudy interview and complete medical history; physical examination was conducted by a clinical investigator. The study was conducted according to the principles of the Declaration of Helsinki (1964) and its amendments (Tokyo 1975, Venice 1983, Hong Kong 1989). The clinical protocol was reviewed and approved by the Ethics Committee of the University of Medicine and Pharmacy “Iuliu Hatieganu,” Cluj-Napoca, Romania.
As provided in the study protocol, written informed consent was obtained from each subject prior to enrollment. All subjects were informed of their rights and obligations, potential adverse effects, and other study details. The volunteers were to be healthy according to medical history, physical examination, and laboratory tests, have no history of alcohol or drug abuse, and not be taking any medication. For the conclusion of the study, each subject underwent a final medical examination. All subjects were financially compensated for their participation in the study.

Study Design

The study consisted of 2 periods: period 1 (reference), when each volunteer received a single 40-mg dose of omeprazole* (2 enteric-coated capsules containing omeprazole 20 mg); and period 2 (test), when each volunteer received a single 40-mg dose of omeprazole and a 60-mg dose of fluoxetine† (three 20-mg capsules). Between the 2 periods, the subjects were treated for 8 days with a single daily 60-mg dose of fluoxetine. It was assumed that this dose of fluoxetine would result in plasma concentrations similar to those obtained after 6 weeks’ administration of a 20-mg daily dose. All study drugs were administered in the morning, following an overnight fast. A standardized meal was provided 3 hours after drug administration.

During each study period, venous blood (5 mL) was drawn into heparinized tubes before study drug administration (time 0) as well as at 0.5, 1, 1.33, 1.66, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 hour(s) after drug administration; the separated plasma was stored at –20°C until analysis.

Although the therapeutically recommended daily dose of fluoxetine is 20 mg, a previous study found that treatment with 60 mg/d for ~1 week results in plasma concentrations similar to those obtained after 6 weeks’ administration of a 20-mg daily dose. It was for this reason that the 60-mg dose of fluoxetine was chosen.

Analysis of Plasma Samples

Omeprazole plasma concentrations were determined by a validated HPLC method with ultraviolet (UV) detection. The HPLC system (binary pump, autosampler, thermostat, UV detector; Agilent 1100 series, Agilent Technologies, Darmstadt, Germany) was used together with a C18 column (75 mm × 4.6 mm; inner diameter, 3.5 μm; Zorbax SB-C18, Agilent Technologies). The mobile phase consisted of 33:67 (V/V) acetonitrile:monopotassium phosphate solution 30 mM (pH, 6.5) in water. The flow rate was 1.5 mL/min and the thermostat temperature was set at 35°C. UV detection was made at 303 nm. In a centrifuge tube, 100 μL disodium hydrogen phosphate 0.1 M and 6 mL 1/1 diethyl ether/dichloromethane (v/v) were added to 0.5 mL of plasma. The tube was capped and shaken for 5 minutes on a vortex mixer. After centrifugation (2000g) and separation, the organic layer was evaporated under a stream of nitrogen at 35°C. The residue was dissolved in 200 μL of mobile phase and a 50-μL sample was injected into the chromatographic system. The calibration curve was lin-

*Trademark: Omeran™ (Europharm SA, Brasov, Romania).
†Trademark: Fluoxin™ (Vim Spectrum SRL, Corunca, Romania).
ear over a concentration range of 8 to 4000 ng/mL plasma, with a correlation coefficient \( r > 0.995 \). At the lower limit of quantification (8 ng/mL), accuracy and precision were 8.8% and 7.2% (intraday) and 11.7% and 10.2% (interday), respectively.

**Pharmacokinetic Analysis**

Noncompartmental pharmacokinetic analysis was performed to determine the pharmacokinetic parameters of omeprazole monotherapy or in combination with fluoxetine. The \( C_{\text{max}} \) and \( T_{\text{max}} \) were obtained directly by the visual inspection of each subject’s plasma concentration–time profile. The \( \text{AUC}_{0-t} \) was calculated using the trapezoidal rule. \( \text{AUC}_{0-\infty} \) was determined by the following formula:

\[
\text{AUC}_{0-\infty} = \frac{C_t}{k_{\text{el}}} + \text{AUC}_{0-t},
\]

where \( C_t \) was the last quantifiable drug concentration and \( k_{\text{el}} \) was the elimination rate constant. The \( k_{\text{el}} \) was estimated by the least squares regression of plasma concentration–time data points lying in the terminal log-linear region of the curves. The \( t_{1/2} \) was calculated as \( 0.693/k_{\text{el}} \). The mean residence time (MRT) was calculated as follows:

\[
\text{MRT} = \frac{\text{AUMC}_{0-\infty}}{\text{AUC}_{0-\infty}},
\]

where the area under the first moment curve (\( \text{AUMC}_{0-\infty} \)) was calculated from the plasma concentration–time curve as the product of time and the plasma drug concentration versus time from time 0 to \( \infty \). All pharmacokinetic analyses were performed using Kinetica version 4.2 (Thermo Labsystems, Waltham, Massachusetts).

**Tolerability Analysis**

Tolerability assessment included adverse events (AEs) and vital signs, which were recorded throughout the study. Chemistry and hematology analysis were also recorded on inclusion and after completing the study.

**Statistical Analysis**

ANOVA was used to compare the calculated pharmacokinetic parameters of omeprazole (log-transformed) for the 2 periods, using general linear model procedures, in which sources of variation were subject and treatment. In order to evaluate a possible clinical significance of the pharmacokinetic interaction, the bioequivalence methodology was applied.\(^{12-15}\) The 90% CIs of the log-transformed test/reference period ratios for \( C_{\text{max}}, \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \) (each log transformed) were determined by the Schuirmann two 1-sided \( t \) test.\(^{16}\) The bioequivalence between omeprazole in the test and reference periods could be concluded if the 90% CIs for these pharmacokinetic parameters of the 2 periods were found to be within an accepted range of 0.8 to 1.25.\(^{12-14}\) Regarding the analysis of \( T_{\text{max}} \), the limit for bioequivalence range was expressed as untransformed data, the significance of the difference of \( T_{\text{max}} \) (test/reference) being established by a nonparametric test (Friedman test). All statistical analyses were performed using Kinetica version 4.2 software (Thermo Labsystems).
RESULTS
Eighteen healthy male volunteers (mean [SD] age, 22.11 [2.52] years [range, 18–26 years]; body mass index, 23.34 [2.31] kg/m² [range, 19.1–27.1 kg/m²]) were enrolled and completed the study.

The mean plasma concentrations of omeprazole monotherapy or in combination with fluoxetine, after 8 days treatment with fluoxetine, are shown in the figure.

The mean pharmacokinetic parameters of omeprazole monotherapy or in combination with fluoxetine, as well as the statistical significance following their comparison are shown in Table I.

The mean (SD) C_{max} of omeprazole, before and after the fluoxetine multiple-dose administration (730.8 [430.0] vs 1725.5 [493.1] ng/mL; P < 0.001), was significantly different between the 2 periods, as was also found to be the case when compar-

Figure. Mean (SD) plasma levels of omeprazole (40 mg PO) administered alone (dotted line) or in combination with oral fluoxetine 60 mg after treatment with fluoxetine 60 mg PO for 8 days (continuous line) in healthy male volunteers (N = 18).
Table I. Pharmacokinetic parameters of omeprazole (40 mg PO) administered alone or after treatment with fluoxetine 60 mg PO for 8 days in healthy male volunteers (N = 18). Data are mean (SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Omeprazole Monotherapy</th>
<th>Omeprazole + Fluoxetine</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max}, ng/mL</td>
<td>730.8 (430.0)</td>
<td>1725.5 (493.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T_{max}, h</td>
<td>1.30 (0.54)</td>
<td>1.63 (0.39)</td>
<td>–</td>
</tr>
<tr>
<td>AUC_{0–t}, ng/mL/h</td>
<td>1453.3 (1151.5)</td>
<td>5072.5 (1715.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUC_{0–∞}, ng/mL/h</td>
<td>1465.0 (1158.5)</td>
<td>5185.3 (1795.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>k_{el}, h^{-1}</td>
<td>0.753 (0.217)</td>
<td>0.482 (0.171)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t_{1/2}, h</td>
<td>0.96 (0.30)</td>
<td>1.47 (0.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRT, h</td>
<td>2.33 (0.57)</td>
<td>3.35 (0.41)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

k_{el} = elimination rate constant; MRT = mean residence time.

*ANOVA.

ing AUC_{0–t} (1453.3 [1151.5] vs 5072.5 [1715.5] ng/mL/h; P < 0.001), AUC_{0–∞} (1465.0 [1158.5] vs 5185.3 [1795.0] ng/mL/h; P < 0.001), k_{el} (0.753 [0.217] vs 0.482 [0.171] h^{-1}; P < 0.001), MRT (2.33 [0.57] vs 3.35 [0.41] h; P < 0.001), and t_{1/2} (0.96 [0.30] vs 1.47 [0.25] h; P < 0.001). However, T_{max} was not significantly different between periods (1.30 [0.54] vs 1.63 [0.39] h).

The parametric 90% CIs for the log-transformed test/reference ratio of the mean pharmacokinetic parameters C_{max}, AUC_{0–t}, and AUC_{0–∞} of omeprazole and the significance of the difference of T_{max} (test/reference, mean values) are shown in Table II.

Omeprazole and fluoxetine administered alone or in combination were well tolerated by all subjects participating in the study. Mild gastrointestinal (nausea, xerostomia, heartburn, diarrhea, anorexia) and central nervous system (fatigue, sedation, insomnia, dizziness) AEs were reported during the repeated administration of fluoxetine and after administration of fluoxetine and omeprazole in combination. Two subjects re-

Table II. Bioequivalence evaluation of pharmacokinetic parameters of omeprazole (40 mg PO) administered alone or after treatment with fluoxetine 60 mg PO for 8 days in healthy male volunteers (N = 18).

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>90% CIs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0–∞}</td>
<td>2.06–3.41</td>
<td>0.001*</td>
</tr>
<tr>
<td>AUC_{0–t}</td>
<td>1.99–3.38</td>
<td>0.001*</td>
</tr>
<tr>
<td>C_{max}</td>
<td>1.30–1.70</td>
<td>0.001*</td>
</tr>
<tr>
<td>T_{max}†</td>
<td>–</td>
<td>0.761†</td>
</tr>
</tbody>
</table>

*ANOVA.
†χ^2 = 3.841.
ported mild heartburn and dizziness, respectively, when omeprazole alone was administered. No clinically relevant changes were observed in laboratory parameters, blood pressure, or heart rate before and after omeprazole and fluoxetine treatment.

**DISCUSSION**

The 90% CIs for the geometric mean of omeprazole in individual test/reference ratios for $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were outside the acceptable limits to assume bioequivalence (0.8–1.25). The lack of bioequivalence between omeprazole administered alone or in combination with fluoxetine raises the possibility that the pharmacokinetic interaction between these drugs may be of clinical significance.

The difference between mean $T_{\text{max}}$ values of omeprazole in the test and reference periods was not statistically significant, indicating that the rate of absorption is not significantly changed. Omeprazole metabolism in humans is mediated through the CYP2C19 and CYP3A4 enzymes\(^5\)\(^7\) and fluoxetine has an inhibitory effect on them.\(^9\)\(^10\) Therefore, the observed pharmacokinetic interaction might be due to a reduced metabolic clearance of omeprazole which may affect both the presystemic and systemic elimination of the drug. Any reduction in the presystemic metabolism is likely to result in a reduced first-pass effect, increased bioavailability, and, consequently, increased $C_{\text{max}}$ and $AUC_{0-\infty}$. At the same time, a decrease in systemic metabolism will also contribute to an increase of $C_{\text{max}}$, $AUC_{0-\infty}$, and the $t_{1/2}$ of omeprazole.

Omeprazole is an integral part of the eradication drug regimens used for all *Helicobacter pylori*–positive individuals with gastric and duodenal ulcers. These regimens combine omeprazole with antimicrobials such as amoxicillin, clarithromycin, and metronidazole. It was suggested that the higher plasma concentration of omeprazole might be associated with higher effectiveness in anti-*H pylori* treatment,\(^17\)\(^19\) and possibly with higher stability of antimicrobials in the higher intragastric pH.\(^20\) This might result in a higher rate of ulcer eradication. Further study is necessary to determine whether or not concomitant administration of fluoxetine is clinically relevant as adjunctive treatment for eradication of *H pylori* because of AEs associated with fluoxetine.

Although no AEs were associated with the increased omeprazole exposure during the fluoxetine administration in this study, repeated administration of both omeprazole and fluoxetine might lead to omeprazole-related AEs. Polymyositis and other myopathies occurring in patients treated with omeprazole have been identified as possible adverse drug reactions. Reported muscle problems might be a result of an interaction leading to increased plasma concentrations of omeprazole.\(^21\)

Omeprazole, as with other proton-pump inhibitors, is associated with dose-dependent increases in serum gastrin concentrations that may lead to enterochromaffin-like hyperplasia as a result of the hypergastrinemia;\(^22\) however, there has been no evidence that these changes result in dysplasia, carcinoid tumors, or gastric adenocarcinoma. Long-term omeprazole treatment in *H pylori*–positive patients is associated with progressive atrophic gastritis of the gastric body. The risk of AEs might be higher in elderly patients because of factors such as age-related physiological changes, diseases, genetic constitution, and diet that may alter drug response.\(^23\)
The present study has several limitations that should be noted. The use of a 60-mg dose of fluoxetine for 8 days may approximate long-term plasma levels (as in the case of long-term 20-mg administration) but it may not reflect the same rate of metabolism (priming of cytochrome systems). Some patients require long-term maintenance treatment with both fluoxetine and omeprazole. Because a single-dose administration of omeprazole does not fully simulate clinical practice, further studies are required by using multiple dosing design (steady state) for both omeprazole and fluoxetine. Also, the interaction with fluoxetine, which also inhibits CYP2C19, was not studied. This was a small study in healthy volunteers; further clinical trials are required to confirm the results.

**CONCLUSION**

The present study found that the pretreatment of healthy volunteers with a single daily dose of fluoxetine 60 mg for 8 days prior to the administration of omeprazole 40 mg significantly changed the pharmacokinetics of omeprazole; however, the relevance of this finding needs to be confirmed.

**ACKNOWLEDGMENTS**

The authors have indicated that they have no conflicts of interest regarding the content of this article.

All authors participated in the writing of the manuscript. Dr. Vlase conducted pharmacokinetic analysis and HPLC determinations. Dr. Neag acted as the study medic, performed study drug administration, and participated in writing the clinical report. Dr. Popa was the clinical monitor and participated in writing the clinical report. Dr. Muntean prepared samples for analytic determination and performed the analytic validation and reporting. Dr. Leucuta conducted pharmacokinetic analysis and reporting.

**REFERENCES**


**Address correspondence to:** Laurian Vlase, PhD, Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, University of Medicine and Pharmacy “Iuliu Hatieganu,” Emil Isac 13, Cluj-Napoca, Cluj, 400023, Romania. E-mail: laurian.vlase@yahoo.com or laurian.vlase@umfcluj.ro