

Pharmacokinetic interaction between fluvoxamine and lansoprazole in healthy volunteers

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Abstract. Background: Fluvoxamine is an inhibitor of the main metabolizing enzymes of lansoprazole and it could influence its pharmacokinetics. The changes in lansoprazole pharmacokinetics could have clinical significance concerning safety of the therapy. Objective: The main objective of this study was to evaluate the pharmacokinetic interaction of fluvoxamine with lansoprazole in healthy volunteers. Methods: A dose of 30 mg lansoprazole, alone or in combination with 100 mg fluvoxamine was administered to 11 healthy male volunteers in a two treatments study design, separated by 6 days period in which the fluvoxamine alone was administered as a single p.o. daily dose. Plasma concentrations of lansoprazole were determined during a 12 hour period following drug administration using a validated LC/MS analytical method. Pharmacokinetic parameters of lansoprazole were calculated using non-compartmental analysis. Results: In the two periods of treatments, the mean peak plasma concentrations (C_{max}) were 699.9 ng/ml (lansoprazole alone) and 1190 ng/ml (lansoprazole after pre-treatment with fluvoxamine). The observed areas under the curve (AUC_{0-t}) were 1955 ng.hr/ml and 6467 ng.hr/ml whereas the total areas under the curve ($AUC_{0-\infty}$) were 2048 ng.hr/ml and 7813 ng.hr/ml, respectively. The T_{max} (time to reach C_{max}) were 2.35 hr and 3.55 hr. The elimination rate constants (Kel) were 0.54 hr⁻¹ and 0.25 hr⁻¹ for lansoprazole administered alone or after pre-treatment with fluvoxamine. The half-life values ($t_{1/2}$) were 1.43 hr and 3.51 hr, whereas the mean residence time 3.8 hr and 7.5 hr, respectively. Statistically significant differences were observed for C_{max} ($p=0.0001$), AUC_{0-t} ($p<0.0001$), $AUC_{0-\infty}$ ($p<0.0001$), Kel ($p=0.0067$), $t_{1/2}$ ($p=0.002$) and mean residence time ($p=0.0002$) of lansoprazole when administered alone and lansoprazole and fluvoxamine, after 6 days treatment with fluvoxamine. Conclusion: The experimental data demonstrate the pharmacokinetic interaction between fluvoxamine and lansoprazole and suggest that the observed interaction may be significant, but its relevance has to be confirmed.

Key Words: lansoprazole, fluvoxamine, pharmacokinetics, drug interaction

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Introduction

Lansoprazole, a substitute of benzimidazole, is a proton-pump inhibitor (PPI) that suppresses gastric acid secretion by inhibiting H⁺/K⁺ ATPase by binding covalently (Gremse 2001, Yanagida et al 2009). The gastric H, K-adenosine triphosphatase (ATPase) is the primary target for treatment of acid related diseases. (Sachs et al 2010). Lansoprazole is used in Acid-Peptic Disease (Vanderhof & Tahboub 2002): on short-term treatment of the erosive reflux oesophagitis, active gastric ulcer, active duodenal ulcer and the treatment of non-steroidal anti-inflammatory drug-induced gastric and duodenal ulcers, and on long-term treatment of healing the reflux oesophagitis, duodenal ulcer and Zollinger-Ellison syndrome. It is also used for the eradication of *Helicobacter pylori* as a component of therapy with lansoprazole and antibiotics (Gremse 2001).

Lansoprazole is rapidly absorbed with mean peak plasma levels occurring at approximately 1.7 hours and displays a linear increase in plasma concentrations over a dose range of 15–60 mg (Shi & Klotz 2008, <http://www.abbott.ca/static/content/>

[document/Prevacid_PM_-_25SEP08.pdf](http://www.abbott.ca/static/content/document/Prevacid_PM_-_25SEP08.pdf)). Pharmacokinetics of repeated doses is similar to that of a single dose (Shi & Klotz 2008). Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 µg/ml (http://www.abbott.ca/static/content/document/Prevacid_PM_-_25SEP08.pdf).

The main enzyme involved in the metabolism of PPIs is CYP2C19. CYP3A4 is also involved in the PPI metabolism, but in a lesser extent (Ozdil et al 2010). Lansoprazole is extensively and rapidly ($t_{1/2}$: 1–2 h) metabolized into sulfone and 5-hydroxylated metabolites by CYP3A4 and CYP2C19 (Shi & Klotz 2008, Yacyshyn & Thomson 2002). Following single dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. After a 30 mg single oral dose of lansoprazole, approximately one-third of the dose was excreted in the urine and approximately two-thirds were recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole (http://www.abbott.ca/static/content/document/Prevacid_PM_-_25SEP08.pdf).

Pharmacokinetic drug-drug interactions are common for medication whose clearance involves CYP-mediated oxidative metabolism in the liver. Given the hepatic metabolism of the proton-pump inhibitors (PPIs) and their effect on hepatic enzymes, one might anticipate a potential for clinically important drug interactions. The potential for omeprazole to interact with other medications has been extensively studied. Lansoprazole has fewer documented drug interactions than omeprazole (Robinson & Horn 2003).

Fluvoxamine is an antidepressant for oral administration that is effective through selective inhibition of serotonin reuptake, widely used for treatment of depression and other psychiatric disorders (Katoh et al 2010). After oral administration, fluvoxamine is almost completely absorbed from the gastrointestinal tract, and the extent of absorption is unaffected by the presence of food (Ordacgi et al 2009); oral bioavailability in humans is approximately 50% (Van Harten 1995); 80% is bound to plasma proteins (Klinger & Merlob 2008). Fluvoxamine is extensively metabolized in the liver (Orlando et al 2010) by oxidative demethylation and oxidative deamination (Hiemke & Hartter 2000). The half-life of fluvoxamine is approximately 1 day (Westenberg & Sandner 2006). Fluvoxamine is a potent CYP1A2 and CYP2C19 inhibitor, and a moderate CYP2C9, CYP2D6, and CYP3A4 inhibitor (Hemeryck & Belpaire 2002). Being inhibitor of the main metabolizing enzymes of lansoprazole, fluvoxamine may influence its pharmacokinetics and it is important to determine whether a pharmacokinetic interaction occurs between these drugs, this being the aim of our study. Although it could have clinical significance concerning efficacy and safety of the therapy, to the date this pharmacokinetic interaction was not reported.

Patients and methods

Subjects

Eleven, non-smoking males, aged 22-29 years old took part in the study. The study was conducted according to the principles of 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, a written informed consent in compliance with the current revision of the Declaration of Helsinki has been obtained from each subject prior to enrolment, during which they are informed of their rights and obligations, potential side effects and other study details. The volunteers were healthy according to history, physical examination and laboratory tests, had no history of alcohol or drug abuse and did not take any regular medication. For the conclusion of the study, each subject underwent a final medical examination. Each subject was financially compensated for the participation to the study.

Study design

The study consisted of 2 periods: Period 1 (Reference), when each volunteer received a single dose of 30 mg lansoprazole and Period 2 (Test), when each volunteer received a single dose of 30 mg lansoprazole and 100 mg fluvoxamine. Between the two periods, the subjects were treated for 6 days with a single daily dose of 100 mg fluvoxamine. In other studies, steady-state

plasma concentrations were achieved within a week, after 100 mg fluvoxamine/day (Ordacgi et al 2009). All the drugs were administered in the morning, following an overnight fast.

The pharmaceutical products used were LevantTM (enteric-coated capsules containing 30 mg lansoprazole, producer Ranbaxy Ltd - UK) and Fevarin (capsules containing 100 mg fluvoxamine, producer Solvay Pharmaceuticals, Netherlands).

During each study period venous blood (5 ml) was drawn into heparinized tubes before drug administration as well as at 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10 and 12 hours after drug administration and the separated plasma was stored frozen (-20°C) until analysis.

Analysis of plasma samples

Lansoprazole plasma concentrations were determined by a validated high throughput liquid chromatography-mass spectrometry method. The HPLC system was an Agilent 1100 series (binary pump, autosampler, thermostat) (Agilent Technologies, USA) and was coupled with an Bruker Ion Trap SL (Bruker Daltonics GmbH, Germany). A Zorbax SB-C18 chromatographic column (100 mm x 3.0 mm i.d., 3.5 µm) (Agilent Technologies) was used. The mobile phase consisted of 40:60 (V/V) 2 mM ammonium acetate in water : methanol. The flow rate was 1 ml/min and the thermostat temperature set at 45°C. The mass spectrometry detection was in multiple reactions monitoring mode (MRM), positive ions, using an electrospray ionization source. The ion transitions monitored were m/z 370 → m/z 252.

1 ml methanol was added to 0.2 ml plasma in an Eppendorf tube. The tube was vortex-mixed for 10 seconds, and then centrifuged for 5 min at 10000 rpm. The supernatant was transferred to an autosampler vial and 1 µl was injected into the LC/MS system. The calibration curve of lansoprazole was linear at a concentration range of 20-2000 ng/ml plasma, with a correlation coefficient $r = 0.994$. At quantification limit, accuracy and precision were -9.4% and 6.9% (intra-day) and 11.8% and 12.7% (inter-day), respectively.

Pharmacokinetic analysis

Noncompartmental pharmacokinetic analysis was performed to determine the pharmacokinetic parameters of lansoprazole given alone or in combination with fluvoxamine. The maximum plasma concentration (C_{max} , ng/ml) and the time to reach the peak concentration (t_{max} , hr) were obtained directly by the visual inspection of each subject's plasma concentration-time profile. The area under the concentration-time curve from time zero to the last measurable concentration at time t (AUC_{0-t}) was calculated using the trapezoidal rule. The area was extrapolated to infinity ($AUC_{0-\infty}$) by addition of C_t/K_{el} to AUC_{0-t} where C_t is the last quantifiable drug concentration and K_{el} is the elimination rate constant. K_{el} was estimated by the least-square regression of plasma concentration-time data points lying in the terminal log-linear region of the curves. The half-life ($t_{1/2}$) was calculated as $0.693/K_{el}$. The mean residence time (MRT), was calculated as $AUMC_{0-\infty}/AUC_{0-\infty}$, where the area under the first moment curve ($AUMC_{0-\infty}$) was calculated from the plasma concentration-time curve as the product of time and the plasma drug concentration vs. time from time zero to infinity. The pharmacokinetic analysis was performed using Kinetica 4.2. (Thermo LabSystems, USA).

Table 1. Pharmacokinetic parameters of lansoprazole administered alone or after treatment with fluvoxamine, 100 mg p.o. for 6 days

Pharmacokinetic parameter (\pm SD)	Lansoprazole alone	Lansoprazole + fluvoxamine	p
C_{max} (ng/ml)	699.9 \pm 276.3	1190 \pm 293.3	0.0001
Tmax (hr)	2.35 \pm 0.88	3.55 \pm 1.48	NS
AUC _{0-t} (ng.hr/ml)	1955 \pm 903.4	6466 \pm 2107	<0.0001
AUC _{0-∞} (ng.hr/ml)	2048 \pm 917.2	7813 \pm 2887	<0.0001
Kel (1/hr)	0.54 \pm 0.18	0.25 \pm 0.17	0.0067
$t_{1/2}$ (hr)	1.43 \pm 0.52	3.51 \pm 1.44	0.0021
MRT (hr)	3.83 \pm 1.09	7.46 \pm 1.44	0.0002

Statistical analysis

The analysis of variance (ANOVA) was used to compare the calculated pharmacokinetic parameters of lansoprazole (log-transformed) for the two 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 assessment methodology was applied (U. S. Department of Health and Human Services et al 1999, 2002, The European Agency for the Evaluation of Medicinal Products 2001). The 90% confidence intervals of the test/reference period ratios for C_{max} , AUC_{0-t} and AUC_{0- ∞} (each log transformed) were determined by the Schuirmann's two one-sided t test (Schuirmann 1987). The bioequivalence between lansoprazole in Test and Reference period can be concluded when the 90% confidence intervals for these pharmacokinetic parameters of two products are found within an acceptable range of 0.8-1.25 (U.S. Department of Health and Human Services et al 1999, 2002, The European Agency for the Evaluation of Medicinal Products 2001). Regarding analysis of t_{max} , the limit for bioequivalence range was expressed as untransformed data, the significance of the difference of t_{max} (Test-Reference) being established by a nonparametric test (Friedman test). All the statistical analysis was performed using Kinetica 4.2 software.

Results

The mean plasma concentrations of lansoprazole when administered alone or in combination with fluvoxamine, after 6 days treatment with fluvoxamine, are shown in Fig.1.

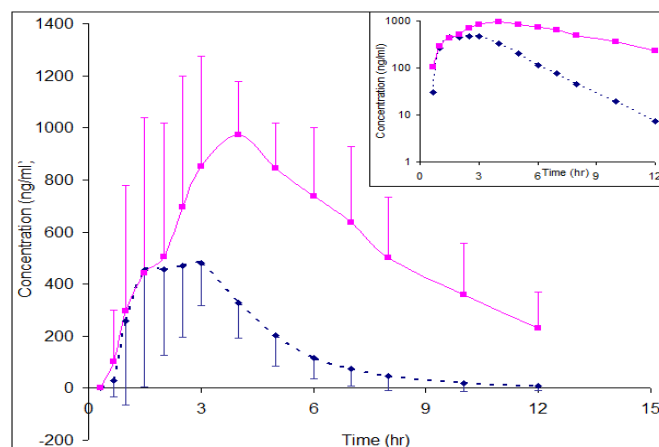


Fig.1 Mean \pm SD plasma levels of lansoprazole (30 mg p.o.) given alone (dotted line) or in combination with fluvoxamine

100 mg, p.o. after treatment with fluvoxamine for 6 days 100 mg p.o. (continuous line), n=18. In insert, log scale.

The mean pharmacokinetic parameters of lansoprazole administered alone or in combination with fluvoxamine, as well as the statistical significance following their comparison are given in Table 1.

Peak plasma concentrations (C_{max}) of lansoprazole, before and after the fluvoxamine multiple doses administration, were significantly different between the two treatments, as was also found to be the case when comparing AUC_{0-t}, AUC_{0- ∞} , Kel, MRT, t_{max} and $t_{1/2}$.

For the assessment of a possible clinical significance of the interaction between lansoprazole and fluvoxamine, the pharmacokinetic parameters C_{max} , t_{max} , AUC_{0-t} and AUC_{0- ∞} were also used to test the bioequivalence of lansoprazole administered in the Test and Reference periods. The parametric 90% confidence interval for the ratio Test/Reference of the mean pharmacokinetic parameters C_{max} , AUC_{0-t} and AUC_{0- ∞} (log transformed) of lansoprazole and the significance of the difference of t_{max} (Test-Reference, mean values) are shown in Table 2.

Table 2. Bioequivalence evaluation of pharmacokinetic parameters of lansoprazole administered alone or after treatment with fluvoxamine 100 mg p.o. for 6 days.

Pharmacokinetic parameter	90% CI	Bioequivalence conclusion
AUC _{0-∞}	3.10-4.83 (ANOVA, S)	Bio-inequivalent
AUC _{0-t}	2.81-4.25 (ANOVA, S)	Bio-inequivalent
C_{max}	1.50-2.09 (ANOVA, S)	Bio-inequivalent
t_{max}	Friedman, S	Bio-inequivalent

Discussion

The 90% confidence intervals for geometric mean of lansoprazole in Test/Reference individual ratios for C_{max} , AUC_{0-t} and AUC_{0- ∞} were outside of the acceptable limits of bioequivalence (0.8-1.25). The lack of bioequivalence between lansoprazole administered alone or in combination with fluvoxamine raises the possibility that the pharmacokinetic interaction between these drugs may be of clinical significance.

Since lansoprazole metabolism in man is mediated through CYP2C19 and CYP3A4 enzymes (Shi & Klotz 2008) and fluvoxamine has an inhibitory effect upon them (Hemeryck & Belpaire 2002, Baumann & Rochat 1995), the observed pharmacokinetic

interaction is probably due to a reduced metabolic clearance of lansoprazole which could therefore 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 C_{max} and $AUC_{0-\infty}$. At the same time, a decrease in systemic metabolism will also contribute to an increase of C_{max} , $AUC_{0-\infty}$ and the half-life of lansoprazole.

Many patients require long-term maintenance treatment with antidepressant, thus fluvoxamine is frequently co-prescribed with other medications. Such polypharmacy may lead to clinically important interactions with co-administered drugs. Because a single dose administration of lansoprazole does not fully simulate the clinical practice, further studies are required by using multiple dosing design (steady state) for both lansoprazole and fluvoxamine.

Although no side-effects due to the increased lansoprazole exposure during the fluvoxamine administration were observed under the conditions of this study, repeated administration of both lansoprazole and fluvoxamine might cause some adverse reaction to lansoprazole. The risk of minor adverse effects from PPIs is low, approximately 1%-3%, with no significant differences noted between the PPIs. The risk of symptomatic adverse effects with the PPIs is low as well (Thomson et al 2010, Martin et al 2000). Studies have indicated a correlation between higher doses of PPIs and increased incidence of adverse effects (Yang et al 2006). Concerning lansoprazole, in a prospective follow-up study of 5669 patients on lansoprazole, the most common reported adverse effects were diarrhea (4.1%), headache (2.9%), and nausea (2.6%) (Thomson et al 2010). In other studies, the most common lansoprazole-related adverse events, were mild or moderate in severity and included diarrhea, headache and abdominal pain (Kovacs et al 2009, Mukherjee 2003).

The data suggest a higher rate of diarrhea associated with lansoprazole than other PPIs, and also an increasing risk of diarrhea with increasing age (Martin et al 2000). This suggests the hypothesis that older age may be a risk factor for diarrhea in patients prescribed lansoprazole, particularly at higher doses. Long term use of PPIs has been associated with increased risk of hip fractures, Clostridium difficile infections and pneumonia (Fohl & Regal 2011, Vlase et al 2010).

Although nosocomial Clostridium difficile-associated diarrhea has been primarily linked with the use of antimicrobial agents, observational reports have suggested a link with the increased gastric pH caused by PPIs therapy. It is believed that the inhibition of gastric acidity limits the body's defense against ingested spores and bacteria (Aseeri et al 2008). A meta-analysis of 19 studies involving a total of 18468 patients receiving acid suppression therapy confirmed an association between H2RA or PPI therapy and Clostridium difficile infection (Dalton et al 2009). Others studies suggested that the administration of PPIs doubled the incidence of Clostridium difficile infections (Fohl & Regal 2011).

A meta-analysis conducted by Johnstone et al included six studies evaluating nearly 1 million patients. Despite the heterogeneity of the studies included in the meta-analysis, there was a significant increase in the incidence of pneumonia in patients taking PPIs. This increased incidence appeared to be limited to the short term exposure, specifically the first 30 days. There

was no difference in the risk of pneumonia in patients chronically exposed to PPIs. (Fohl & Regal 2011)

Polymyositis and other myopathies have been reported as a possible adverse drug reaction in patients treated with PPIs (Clark & Strandell 2006). In this analysis, in one-third of the 292 cases, the PPI was the single administered drug, and the PPI was the single suspected drug in 57% of reports where concomitant medication was used. These adverse events were noted with all available PPIs, suggesting a likely class effect. The reports indicate the adverse muscle reaction might be a result of an interaction leading to increased plasma concentrations of the PPI. Such interactions, involving clarithromycin a known inhibitor of CYP enzymes, including CYP3A4 and CYP2C19 have been reported in the literature (Furuta et al 2005). This interaction has been noted also between lansoprazole and clarithromycin, where clarithromycin significantly increases lansoprazole plasma concentrations (Saito et al 2005), increasing the likelihood of an adverse drug reaction, including myopathy. It could be possible also with other inhibitors of CYP enzymes, like fluvoxamine. Epidemiological studies have shown that patients taking proton-pump inhibitors, particularly at high doses, have an increased risk of hip fractures compared with non-users of acid suppression. The mechanisms underlying such an association are not clear. However, existing evidence seems to suggest that the proton-pump inhibitors may have a theoretical influence on bone metabolism (Wright et al 2008). The risk for osteoporotic fractures is increased by long-term therapy. These findings recommend for use of the lowest effective dose of proton-pump inhibitors, especially in older patients and those with risk factors for hip fracture (Yang et al 2006, Vlase et al 2010, Targownik et al 2008). Although the lansoprazole potential for drug interactions of clinical significance is low, it should be taken into account when choosing a therapy for gastric acid-related disorders, especially for elderly patients in whom polypharmacy is common. The risk of adverse reactions could be higher in elderly patients because of factors such as age-related physiological changes, diseases, genetic constitution and diet that may alter drug response (Spina & Scordo 2002).

Conclusions

The present study showed that the pretreatment of healthy volunteers with a single daily dose of 50 mg, respectively 100 mg fluvoxamine for 6 days prior to the administration of 30 mg lansoprazole significantly changes its pharmacokinetics. Because the differences in drug exposure to lansoprazole (C_{max} and $AUC_{0-\infty}$) were outside of bioequivalence interval, the observed pharmacokinetic interaction may have clinical significance, but its relevance has to be confirmed.

References

- Aseeri M, Schroeder T, Kramer J, Zackula R. Gastric acid suppression by proton pump inhibitors as a risk factor for Clostridium difficile-associated diarrhea in hospitalized patients. *Am J Gastroenterol*. 2008;103:2308-2313.
- Baumann P, Rochat B. Comparative pharmacokinetics of selective serotonin reuptake inhibitors: a look behind the mirror. *Int Clin Psychopharmacol* 1995;10(1):15-21.

- Clark DW, Strandell J. Myopathy including polymyositis: a likely class adverse effect of proton pump inhibitors? *Eur J Clin Pharmacol* 2006;62(6):473-479.
- Dalton BR, Lye-Maccannell T, Henderson EA, Maccannell DR, Louie TJ. Proton pump inhibitors increase significantly the risk of *Clostridium difficile* infection in a low endemicity, non-outbreak hospital setting. *Aliment Pharmacol Ther* 2009;29:626-634.
- Fohl A, Regal R. Proton pump inhibitor-associated pneumonia: Not a breath of fresh air after all? *World J Gastrointest Pharmacol Ther* 2011;2(3):17-26.
- Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokinet* 2005;20(3):153-167.
- Gremse DA. Lansoprazole: pharmacokinetics, pharmacodynamics and clinical uses. *Expert Opin Pharmacother* 2001;2(10):1663-1670.
- Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab* 2002;3(1):13-37.
- Hiemke C, Hartter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacology & Therapeutics* 2000;85:11-28.
- Katoh Y, Uchida S, Kawai M, Takei N, Mori N, Kawakami J, et al. Onset of Clinical Effects and Plasma Concentration of Fluvoxamine in Japanese Patients. *Biol Pharm Bull* 2010;33(12):1999-2002.
- Klinger G, Merlob M. Selective Serotonin Reuptake Inhibitor Induced Neonatal Abstinence Syndrome. *Isr J Psychiatry Relat Sci* 2008;45(2):107-113.
- Kovacs TO, Freston JW, Haber M, Hunt B, Atkinson S, Peura D. Long-Term Efficacy of Lansoprazole in Preventing Relapse of Erosive Reflux Esophagitis. *Dig Dis Sci* 2009;54:1693-1701.
- Martin RM, Dunn NR, Freemantle S, Shakir S. The rates of common adverse events reported during treatment with proton pump inhibitors used in general practice in England: cohort studies. *Br J Clin Pharmacol* 2000;50(4):366-72.
- Mukherjee S. Diarrhea associated with lansoprazole. *J Gastroenterol Hepatol* 2003;18(5):602-3.
- Ordacgi L, Mendlowicz M, Fontenelle L. Management of obsessive-compulsive disorder with fluvoxamine extended release. *Neuropsychiatric Disease and Treatment* 2009;5:301-308.
- Orlando R, De Martin S, Andrighetto L, Floreani M, Palatini P. Fluvoxamine pharmacokinetics in healthy elderly subjects and elderly patients with chronic heart failure. *British Journal of Clinical Pharmacology* 2010;69(3):279-286.
- Ozdil B, Akkiz H, Bayram S, Bekar A, Akgollu E, Sandikcy M. Influence of CYP2C19 functional polymorphism on *Helicobacter pylori* eradication. *Turk J Gastroenterol* 2010;21(1):23-28.
- Product Monograph. Prevacid®, lansoprazole Abbott Laboratories, Limited, Saint-Laurent, Canada (revised 9/2008, cited 7/2010). Available from: http://www.abbott.ca/static/content/document/Prevacid_PM_-_25SEP08.pdf
- Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors. What the practicing physician needs to know. *Drugs* 2003;63(24):2739-2754.
- Sachs G, Shin MJ, Hunt R. Novel Approaches to Inhibition of Gastric Acid Secretion. *Curr Gastroenterol Rep* 2010;12:437-447.
- Saito M, Yasui-Furublinkkori N, Uno T, Takahata T, Sugawara K, Munakata A, Tateishi T. Effects of clarithromycin on lansoprazole pharmacokinetics between CYP2C19 genotypes. *Br J Clin Pharmacol* 2005;59:302-309.
- Schuirmann DJ. A comparison of the two one-side test procedure and the power approach for assessment of the equivalence of average bioavailability. *J Pharmacokinet Biopharm* 1987;15(6):657-80.
- Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. *Eur J Clin Pharmacol* 2008;64:935-951.
- Spina E, Scordo MG. Clinically significant drug interactions with antidepressants in the elderly. *Drugs Aging*. 2002;19(4):299-320.
- Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *Can Med Assoc J* 2008;179:319-326.
- The European Agency for the Evaluation of Medicinal Products, Committee for proprietary medicinal products. Note for guidance on the investigation of bioavailability and bioequivalence. London, July 2001.
- Thomson ABR, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. *World J Gastroenterol* 2010;16(19):2323-2330.
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry. Bioavailability and Bioequivalence studies for orally administered drug products-general considerations. Rockville, July 2002.
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance: in vivo drug metabolism/drug interaction studies: study design, data analysis, and recommendations for dosing and labeling. Rockville, November 1999.
- Van Harten J. Overview of the pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 1995;29Suppl 1:1-9.
- Vanderhoff BT, Tahboub R. Proton Pump Inhibitors: An Updat. *American Family Physician* 2002;66(2):273-280.
- Vlase L, Popa A, Neag M, Muntean D, Leucuta SE. Effect of Fluoxetine on the Pharmacokinetics of Lansoprazole. *Clinical Drug Investigation* 2011;31(10):727-733.
- Westenberg HG, Sandner C. Tolerability and safety of fluvoxamine and other antidepressants. *Int J Clin Pract* 2006;60(4):482-491.
- Wright MJ, Proctor DD, Insogna KL, Kerstetter JE. Proton pump-inhibiting drugs, calcium homeostasis, and bone health. *Nutr Rev* 2008;66:103-108.
- Yacyshyn BR, Thomson AB. The Clinical Importance of Proton Pump Inhibitor Pharmacokinetics. *Digestion* 2002;66:67-78.
- Yanagida Y, Watanabe M, Takeba Y, Kumai T, Matsumoto N, Hayashi M, et al. Potential of Lansoprazole as a Novel Probe for Cytochrome P450 3A Activity by Measuring Lansoprazole Sulfone in Human Liver Microsomes. *Biol Pharm Bull* 2009;32(8):1422-1426.
- Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006;296:2947-2953.

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