

PHARMACOKINETIC INTERACTION STUDY BETWEEN LANSOPRAZOLE WITH PHENYTOIN OR CIPROFLOXACIN IN HEALTHY VOLUNTEERS

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Abstract

The pharmacokinetic interaction between lansoprazole with phenytoin and ciprofloxacin in healthy male volunteers was evaluated. In two separate experiments, a single dose of 30 mg lansoprazole was administered alone or in combination with phenytoin or ciprofloxacin to 11, respectively 18 healthy volunteers in two stages treatment of study design, separated by a period in which the phenytoin or ciprofloxacin alone were administered daily. The pharmacokinetic parameters of lansoprazole administered alone or in combination with phenytoin or ciprofloxacin were calculated using non-compartmental analysis. Non-statistically significant differences have been observed for the main pharmacokinetic parameters of lansoprazole when administered alone or with phenytoin or ciprofloxacin, demonstrating the lack of pharmacokinetic interaction between these drugs.

Rezumat

A fost evaluată interacțiunea medicamentoasă farmacocinetică dintre lansoprazol și fenitoină sau ciprofloxacină, la voluntari sănătoși. În două studii diferite, la 11 și respectiv 18 subiecți a fost administrată o doză unică de lansoprazol de 30 mg, singură sau în combinație cu fenitoina, respectiv cu ciprofloxacină, urmând un design cu două perioade între care s-a realizat tratament cu fenitoină sau ciprofloxacină. Parametrii farmacocinetici ai lansoprazolului administrat singur sau în combinație cu fenitoina sau ciprofloxacină au fost calculați utilizând analiza farmacocinetică non-compartimentală. Nu au fost găsite diferențe semnificative între parametrii farmacocinetici ai lansoprazolului administrat singur sau împreună cu fenitoina sau ciprofloxacină, demonstrând lipsa interacțiunii farmacocinetice dintre aceste substanțe medicamentoase.

Keywords: pharmacokinetic interaction, lansoprazole, phenytoin, ciprofloxacin.

Introduction

Proton-pump inhibitors have a strong inhibitory effect on gastric acid secretion [4]. Lansoprazole, (±)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl] benzimidazole, is a proton-pump inhibitor, that suppress gastric acid secretion by forming irreversible disulfide bounds with H^+/K^+ -ATPase. This pump releases hydrogen ions into the gastric lumen in exchange for potassium ions [2,19,22].

Lansoprazole, and the other PPIs (proton pumps inhibitors), play an important role in treatment of wide range of acid-related disorders: gastroesophageal reflux disease, peptic ulcer disease. PPIs are used as treatment or prophylaxis for gastrointestinal injury caused by nonsteroidal anti-inflammatory drugs. Together with antibiotic therapy, they are used to eradicate *Helicobacter pylori* infection [2, 3, 4,13,18].

Lansoprazole, after oral administration, is rapidly absorbed and his pharmacokinetic parameters are: bioavailability is 80-85%, time to peak plasma concentration approximately 1.7 hours and protein binding is 97%. It displays a linear increase in plasma concentrations over a dose range of 15–60 mg [10,15,18]. Pharmacokinetics of repeated doses is similar to that of a single dose [15]. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 µg/mL [10].

CYP 2C19 is the main enzyme involved in the metabolism of PPIs. In a lesser extent, CYP3A4 is also involved in the PPI metabolism [7]. By CYP 3A4 and CYP2C19 lansoprazole is extensively and rapidly ($t_{1/2}$:1-2 h) metabolized into sulfone and 5-hydroxylated metabolites [15,21]. 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 [10].

Phenytoin, 5,5-diphenylhydantoin, is among the most commonly prescribed antiepileptic drugs. This substance is used for the control of generalized tonic-clonic and psychomotor seizures, prevention and treatment of seizures occurring during or following neurosurgery [9]. The phenytoin is mainly metabolized by CYP 3A4 enzymatic system and can increase the activity of CYP3A4. Induction of the 3A4 system can increase the metabolism of other drugs [12]. After oral administration of phenytoin, the average plasma half-life is 22 hours, with a range of 7 to 42 hours [9].

Ciprofloxacin is a fluoroquinolonic antibiotic used in urinary tract infections, bacterial diarrhea, infections of soft tissues, bones, joints, intra-

abdominal and respiratory tract infections. After an oral dose of 500 mg, the half-life is 3-5 hours and the oral bioavailability is 70% [6]. Ciprofloxacin is a strong inhibitor for CYP 1A2 and weak for CYP 3A4 [5,20].

The aim of our study is to determine whether a potentially harmful pharmacokinetic interaction occurs between lansoprazole and phenitoin respectively lansoprazole and ciprofloxacin.

Materials and Methods

Subjects: In the first study, eleven non-smoking males, aged 21-29 years were enrolled and in the second study, eighteen non-smoking males, aged 18-26 years were enrolled (Table I). The study was conducted according to the principles of Declaration of Helsinki (1964) and its amendments (Tokyo 1975, Venice 1983, Hong Kong 1989) and Good Clinical Practice (GCP) rules. The clinical protocol was reviewed and approved by the Ethics Committee of the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania. All volunteers gave their written informed consent prior to study inclusion. 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.

Study design: Each study consisted of 2 periods: Period 1 (Reference), when each volunteer received a single dose of lansoprazole and Period 2 (Test), when each volunteer received a single dose of lansoprazole and either phenytoin or ciprofloxacin. Between the two periods, the subjects were treated with phenytoin or ciprofloxacin (Table I). All the drugs were administered in fasted state. The pharmaceutical products used were Levant[®] (30 mg tablets, producer Ranbaxy Laboratories Ltd. - India), Fenitoin[®] (100 mg tablets, producer Gedeon Richter Romania SA - Romania) and Ciprolen[®] (500 mg tablets, producer AC Helcor SRL - Romania). In first study, lansoprazole-phenytoin, venous blood (5 mL) was drawn into heparinized tubes, in the first and last day of the study, 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. In the second study, lansoprazole-ciprofloxacin, venous blood (5 mL) was drawn into heparinized tubes, in the first and last day of the study, before drug administration as well as at 0.5, 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.

Table I

The design of the pharmacokinetic interaction studies between
lansoprazole with phenytoin or ciprofloxacin

	Study 1	Study 2
Pharmacokinetic interaction	Lansoprazole - Phenytoin	Lansoprazole - Ciprofloxacin
Study type	Open label, two periods – Reference and Test	Open label, two periods – Reference and Test
Subjects	11 healthy volunteers	18 healthy volunteers
Drugs administered in Reference period:	Lansoprazole, 30mg	Lansoprazole, 30mg
CYP3A4 inhibitor drug	phenytoin	ciprofloxacin
Dose of inhibitor drug	300 mg p.o.	500 mg p.o.
Days of treatment with inhibitor	5	4
Drugs administered in Test period:	Lansoprazole, 30mg + Phenytoin, 300mg	Lansoprazole, 30mg + Ciprofloxacin, 500mg

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 a Brucker Ion Trap SL (Brucker Daltonics GmbH, Germany). A Zorbax SB-C18 chromatographic column (100 mm x 3.0 mm i.d., 3.5 μ m) (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 μ L 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 (20 ng/mL), accuracy and coefficient of variation were – 9.4% and 6.9% (intra-day) and 11.8% and 12.7% (inter-day), respectively.

Pharmacokinetic analysis: The noncompartmental pharmacokinetic analysis method was employed to determine the pharmacokinetic

parameters of lansoprazole given alone or in combination with phenytoin or ciprofloxacin. The maximal 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 (AUC_{0-t}) has been estimated by integration 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. The pharmacokinetic analysis was performed using Phoenix 6.0 (Pharsight, USA).

Statistical analysis: In order to evaluate a possible statistical or clinical significance of the pharmacokinetic interaction, an analysis of variance (ANOVA) was performed on the main pharmacokinetic parameters calculated, using general linear model procedures, in which sources of variation were subject and treatment. Then the 90% confidence intervals of the test/reference period ratios for $C_{\max}$ and $AUC_{0-\infty}$ (log transformed) were determined by the Schuirmann's two one-sided t test [1,8,11,14,16,17].

Results and Discussion

The mean plasma concentrations of lansoprazole when administered alone or in combination with either phenytoin (in Study 1) or ciprofloxacin (in Study 2) after pre-treatment with phenytoin or ciprofloxacin, are shown in Figure 1.

The mean pharmacokinetic parameters of lansoprazole administered alone or in combination with phenytoin (Study 1) or ciprofloxacin (Study 2) are given in Table II and Table III, respectively, as well as the statistical significance following their comparison.

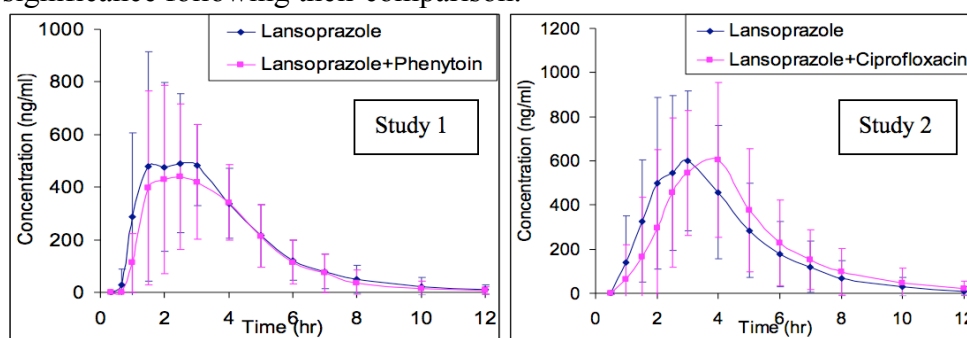


Figure 1

Mean ($\pm$ SD) plasma levels of lansoprazole given alone or in combination with phenytoin (Study 1) or ciprofloxacin (Study 2), after pre-treatment with phenytoin or ciprofloxacin

Table II
Pharmacokinetic parameters of lansoprazole administered alone
or after treatment with phenytoin (Study 1)

Pharmacokinetic parameter ($\pm$ SD)	Lansoprazole alone	Lansoprazole + phenytoin	p* value, ANOVA
$C_{\max}$ (ng/mL)	705.6 $\pm$ 262.8	596.9 $\pm$ 248.5	0.104
$t_{\max}$ (hr)	2.27 $\pm$ 0.88	2.59 $\pm$ 1.00	0.366
$AUC_{0-\infty}$ (ng.hr/mL)	2180.4 $\pm$ 938.6	1871.9 $\pm$ 1048.1	0.134
$t_{1/2}$ (hr)	1.66 $\pm$ 0.80	1.31 $\pm$ 0.65	0.142
MRT(hr)	3.89 $\pm$ 1.07	3.85 $\pm$ 0.55	0.865

* significance for $p < 0.05$

Peak plasma concentrations ($C_{\max}$) of lansoprazole before and after the treatment with multiple doses of phenytoin were not significantly different between the two treatments. The same was found when comparing $t_{\max}$, $AUC_{0-\infty}$, $t_{1/2}$ and mean residence time (MRT) parameters. The treatment with ciprofloxacin had no significant influence on the pharmacokinetic parameters of lansoprazole (Table III).

Table III
Pharmacokinetic parameters of lansoprazole administered alone
or after treatment with ciprofloxacin (Study 2)

Pharmacokinetic parameter ($\pm$ SD)	Lansoprazole alone	Lansoprazole + ciprofloxacin	p* value, ANOVA
$C_{\max}$ (ng/mL)	819.0 $\pm$ 282.7	792.9 $\pm$ 295.5	0.679
$t_{\max}$ (hr)	2.56 $\pm$ 0.87	3.11 $\pm$ 0.85	0.107
$AUC_{0-\infty}$ (ng.hr/mL)	2472.0 $\pm$ 1168.8	2604.2 $\pm$ 1311.8	0.343
$t_{1/2}$ (hr)	1.48 $\pm$ 0.37	1.56 $\pm$ 0.49	0.620
MRT(hr)	3.96 $\pm$ 0.80	4.51 $\pm$ 1.09	0.106

* significance for $p < 0.05$

The pharmacokinetic parameters $C_{\max}$, $t_{\max}$ and $AUC_{0-\infty}$, calculated for lansoprazole administered with phenytoin or ciprofloxacin were also used for bioequivalence evaluation of lansoprazole. The parametric 90% confidence interval for the ratio Test/Reference period of the mean pharmacokinetic parameters $C_{\max}$ and $AUC_{0-\infty}$ (log transformed) of lansoprazole and the significance of the difference of $t_{\max}$ are shown in Table IV.

Table IV
Bioequivalence evaluation of pharmacokinetic parameters of lansoprazole administered alone or after treatment with phenytoin or ciprofloxacin.

Pharmacokinetic parameter	90% Confidence intervals	
	Study 1 lansoprazole-phenytoin	Study 2 lansoprazole-ciprofloxacin
AUC _{0-∞} (ng.h/mL)	0.55-1.21	0.82-1.34
C _{max} (ng/mL)	0.62-1.12	0.80-1.16
t _{max} (hr)	$\chi^2=3.841$ (Friedman, NS)	$\chi^2=3.841$ (Friedman, NS)

The bioequivalence of lansoprazole was not demonstrated, perhaps because there is a minor pharmacokinetic interaction between substances involved, at which it contributes the high variability of lansoprazole.

Conclusions

The treatment with either phenytoin or ciprofloxacin until steady-state does not significantly influences the pharmacokinetics of lansoprazole. No systemic metabolic drug-drug interaction was observed between the studied drugs, as the half-life of lansoprazole is not significantly changing between treatments and the drug exposure (C_{max} and AUC_{0-∞}) is about the same. However, the drug exposure related pharmacokinetic parameters were not in the bioequivalence interval, possibly due to the high pharmacokinetic variability of lansoprazole.

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