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PHARMACOKINETIC INTERACTION BETWEEN IVABRADINE AND CIPROFLOXACINE IN HEALTHY VOLUNTEERS

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ABSTRACT. The pharmacokinetic interaction of ivabradine with ciprofloxacin in healthy volunteers was evaluated. A dose of 5 mg ivabradine in combination with 500 mg ciprofloxacin was administered to 18 healthy male volunteers in a two treatment study design, separated by 6 days in which the ciprofloxacin alone was administrated as a single p.o. dose daily. Plasma concentrations of ivabradine were determined during a 12 hours period following drug administration. Ivabradine plasma concentrations were determined by a validated LC/MS method. Pharmacokinetic parameters of ivabradine were calculated using non-compartmental and compartmental analysis. In the two periods of treatments, the mean peak plasma concentrations (C_{max}) were 8.52 ng/ml (ivabradine alone) and 8.40 ng/ml (ivabradine after pre-treatment with ciprofloxacin). The times taken to reach C_{max}, t_{max}, were 0.86 hr and 1.52 hr respectively and the total areas under the curve ($AUC_{0-\infty}$) were 27.9 ng.hr/ml and 28.1 ng.hr/ml, respectively. The absorption rate constants (k_a) of ivabradine were 10.8 hr^{-1} and 5.27 hr^{-1}, respectively. Statistically significant differences have been observed for both t_{max} and k_a of ivabradine when administered alone or with ciprofloxacin, whereas for C_{max} and $AUC_{0-\infty}$ the differences were non-significant. The experimental data demonstrate the pharmacokinetic interaction between ciprofloxacin and ivabradine, however, the observed interaction may not be clinically significant.

Keywords: *ivabradine, ciprofloxacin, pharmacokinetics, drug interaction*

INTRODUCTION

Ivabradine (3-(3-{[((7S)-3,4-dimethoxi-bicyclo[4.2.0]octa-1,3,5-trien-7-yl) methyl]methylamino}propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride) (Figure 1a) is a novel heart rate–lowering agent that selectively and specifically inhibits the depolarizing cardiac pacemaker I*f* current in the sinus node. Its activity provides pure heart rate reduction at rest and

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during exercise, which improves myocardial oxygen balance and increases coronary perfusion, without any relevant influence on conduction, contractility, ventricular repolarization or blood pressure. The anti-ischemic efficacy and the safety of ivabradine have been demonstrated in patients with stable angina pectoris [1-5].

Despite its therapeutical benefit, ivabradine has some important side effects, including bradycardia, AV block, ventricular extrasystoles and luminous phenomena [1,3,5]. Due to high potential of ivabradine to give adverse reactions on overdosing, but also lack of therapeutic effect on under-dosing, is important to know the way in some other substances modify the ivabradine pharmacokinetics.

After oral administration, the metabolic clearance of ivabradine accounts for about 80% of its total clearance, with the other 20% corresponding to renal clearance. Only CYP3A4 is involved in invabradine's metabolism, so numerous potential interactions can therefore arise with CYP3A4 inhibitors and inducers [6-8].

Ciprofloxacin (1-cyclopropyl- 6-fluoro- 4-oxo- 7-piperazin- 1-yl- quinoline-3-carboxylic acid) (Figure 1b) is a fluoroquinolone used for treating severe bacterial infections. Ciprofloxacin is a potent inhibitor of CYP1A2 and medium inhibitor of CYP3A4 [9-11], thus it can interfere with metabolism of ivabradine.

The aim of our study is to determine if a potentially harmful pharmacokinetic interaction occurs between ivabradine and ciprofloxacin, when administered together.

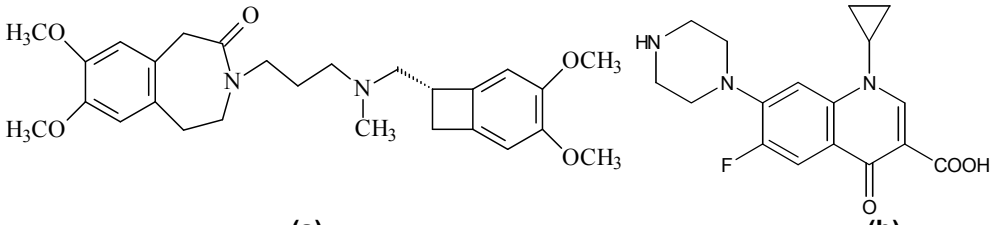

Figure 1. Molecular structure of ivabradine (a) and ciprofloxacin (b)

RESULTS AND DISCUSSION

The mean plasma concentrations of ivabradine when administered alone or in combination with ciprofloxacin after 5 days treatment with ciprofloxacin are shown in Figure 2. The bi-phasic plot describes absorption and elimination consecutive processes (see eq. in section Pharmacokinetic analysis).

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

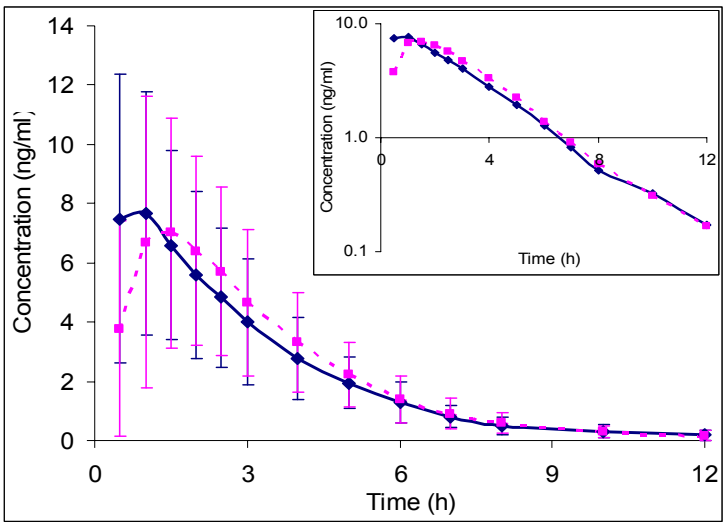

Figure 2. Mean (±SD) plasma levels of ivabradine (5 mg p.o.) given alone (continuous line) or in combination with ciprofloxacin (500 mg, p.o.) after treatment with ciprofloxacin for 6 days (500 mg p.o.) (dotted line), n=18; in insert: semilogaritmic presentation.

Table1. Pharmacokinetic parameters of ivabradine administered alone or after treatment with ciprofloxacin and the result of statistical t test used for comparison

Pharmacokinetic parameter (±SD)	**Ivabradine alone**	**Ivabradine + ciprofloxacin**	**p* value, t-test**
C_{max} (ng/ml)	8.52(4.37)	8.40(4.67)	0.78
t_{max} (hr)	0.86(0.41)	1.52(0.52)	* 0.0014
$AUC_{0-\infty}$ (ng.hr/ml)	27.92(13.59)	28.15(13.74)	0.85
k_{el} (1/hr)	0.35(0.10)	0.37(0.08)	0.36
k_a (1/hr)	10.8(6.8)	5.27(6.71)	* 0.025
$t_{½}$ (hr)	2.10(0.60)	1.93(0.44)	0.28

* significance for $p<0.05$

Peak plasma concentrations (C_{max}) of ivabradine before and after the ciprofloxacin multiple doses treatment (8.52 ng/ml vs. 8.40) were not significantly different between the two treatments. The same was found when comparing $AUC_{0-\infty}$, k_{el} and $t_{½}$ parameters. However, the time to reach the peak plasma concentration (t_{max}) and the absorption rate constant $\mathbf{k_a}$ were significantly different between treatments (p=0.0014 and 0.025 hr^{-1}, respectively).

The pharmacokinetic parameters C_{max}, t_{max} and $AUC_{0-\infty}$, were also used for bioequivalence evaluation of ivabradine administered in Test and Reference period respectively. 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 ivabradine and the significance of the difference of t_{max} are shown in Table 2.

Table 2. Bioequivalence evaluation of pharmacokinetic parameters of ivabradine administered alone or after treatment with ciprofloxacin.

Pharmacokinetic parameter	90% Confidence intervals
$AUC_{0-\infty}$ (ng.h/ml)	0.93-1.08 (ANOVA, NS)
C_{max} (ng/ml)	0.89-1.07 (ANOVA, NS)
t_{max} (hr)	χ^2=3.841 (Friedman, S)

The 90% confidence intervals for geometric mean of ivabradine in Test/Reference individual ratios for C_{max} and $AUC_{0-\infty}$ were in the acceptable limits of bioequivalence (0.8-1.25). However, the difference between mean t_{max} values of the test and reference formulations was statistically significant.

The present study shows that the treatment with ciprofloxacin influences the pharmacokinetics of ivabradine. No systemic metabolic drug-drug interaction was observed, as time the half-life is not changing between treatments and the drug exposure (C_{max} and $AUC_{0-\infty}$) is about the same. However, the ciprofloxacin has a negative effect of absorption rate of ivabradine, because the related pharmacokinetic parameters (t_{max} and k_a) are significantly changing between treatments. Despite those observed differences, since the drug exposure related pharmacokinetic parameters (C_{max} and $AUC_{0-\infty}$) were in bioequivalence interval, the observed pharmacokinetic interaction may not have clinical significance.

CONCLUSIONS

A pretreatment with ciprofloxacin until achieving the steady state plasma concentrations influences the pharmacokinetics of ivabradine co-administered as a single oral dose in healthy volunteers.

EXPERIMENTAL SECTION

Subjects

Eighteen, non-smoking males, aged 22-27 years 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) 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

The study consisted of 2 periods: Period 1 (Reference), when each volunteer received a single dose of 5 mg ivabradine and Period 2 (Test), when each volunteer received a single dose of 5 mg ivabradine and 500 mg ciprofloxacin. Between the two periods, the subjects were treated for 6 days with a single daily dose of 500 mg ciprofloxacin. All the drugs were administered in the morning, in fasted state. The pharmaceutical products used were Corlentor (5 mg tablets, producer Les Laboratoires Servier, France) and Ciprolen (500 mg tablets, producer AC Helcor, Romania). Venous blood (5 ml) was drawn into heparinized tubes, in the first and in the 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.

Analysis of plasma samples

Ivabradine plasma concentrations were determined by a validated LC/MS method. [12]

Pharmacokinetic analysis

The noncompartmental and compartmental pharmacokinetic analysis method was employed to determine the pharmacokinetic parameters of ivabradine given alone or in combination with 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 trapezoildal rule from time zero to the last measurable concentration at time t. The area was extrapolated to infinity ($AUC_{0-\infty}$) by addition of $C_t/ \mathbf{k_{el}}$ to AUC_{0-t} where C_t is the last quantifiable drug concentration and $\mathbf{k_{el}}$ is the elimination rate constant.

The elimination rate constant $\mathbf{k_{el}}$ was estimated by the least-square regression of plasma concentration-time data points lying in the terminal region by using semilogarithmic dependence that corresponds to a first-order kinetics. The half-life ($t_{½}$) was calculated as $0.693/k_{el}$. The absorption constant rate of ivabradine (k_a) was calculated using a mono-compartmental pharmacokinetic model by fitting the data using the equation:

$$Q = D\frac{k_a}{k_a - k_{el}}(e^{-kelt} - e^{-kat})$$

where Q is the quantity of ivabradine in the body at time "t" after oral administration, D is the doze and k_a and k_{el} are the absorption and elimination rate constants in hr^{-1}.

The pharmacokinetic analysis was performed using Kinetica 4.0.2 (Thermo Labsystems, U.S.A.) [13].

Statistical analysis

The *t*-test for paired values was used to compare the calculated pharmacokinetic parameters of ivabradine for the two periods. In order to evaluate a possible clinical significance of the pharmacokinetic interaction, an analysis of variance (ANOVA) was performed on the pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$ using general linear model procedures, in which sources of variation were subject and period. 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 [14]. The bioequivalence between ivabradine 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 [15-18]. 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 4.0.2 software [13].

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