https://doi.org/10.31925/farmacia.2019.4.9

ORIGINAL ARTICLE

INFLUENCE OF FLUVOXAMINE ON CARVEDILOL'S PHARMACOKINETICS IN RATS

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Manuscript received: February 2019

Abstract

Carvedilol is one of the most used cardiovascular drugs, highly metabolized by CYP450 2D6, 1A2, 2C9. Fluvoxamine, an antidepressant agent, is a moderate/potent inhibitor of these enzymes. There is the risk of drug-drug interaction when these two drugs are concomitantly administered. The aim of this study was to investigate the drug-drug interactions between carvedilol and fluvoxamine in rats. There were two periods: reference and test. In the first period each rat received an oral dose of 3.57 mg/kg body weight carvedilol. In the test period, carvedilol was administered after a pre-treatment with multiple oral doses of fluvoxamine (14.28 mg/kg b.w.). HPLC-MS was used to determine the plasma concentration of carvedilol. The PK parameters were calculated by non-compartmental analysis. Fluvoxamine co-administered with carvedilol can change the PK parameters (increase AUC, $t_{1/2}$, decrease the Cl). The present study demonstrated the pharmacokinetic drug-drug interaction between carvedilol and fluvoxamine *in vivo*.

Rezumat

Carvedilolul este unul dintre cele mai utilizate medicamente cardiovasculare, intens metabolizat prin intermediul CYP450 2D6, 1A2, 2C9. Fluvoxamina, agent antidepresiv, este un inhibitor moderat/puternic al acestor enzime. La co-administrarea acestor două medicamente, există riscul apariţiei unei interacţiuni. Scopul studiului este de a investiga interacţiunea dintre carvedilol şi fluvoxamină, la şobolani. Există două perioade: referinţă şi test. În prima perioadă, fiecare şobolan a primit o doză de 3,57 mg/kg carvedilol. În perioada test, carvedilolul a fost administrat după un pre-tratament cu doze orale multiple de fluvoxamină (14.28 mg/kg). Pentru determinarea concentraţiilor plasmatice de carvedilol, s-a folosit sistemul HPLC-MS. Parametrii farmacocinetici s-au calculat prin analiza non-compartimentală. Co-administrarea fluvoxaminei cu carvedilolul a dus la modificarea parametrilor farmacocinetici (creşterea AUC, a $t_{1/2}$, scăderea Cl). Studiul a demonstrat existenţa interacţiunii *in vivo* între carvedilol şi fluvoxamină.

Keywords: Carvedilol, cytochrome P450, inhibition

Introduction

Carvedilol is a non-selective beta-blocker drug with additional blockades of α_1 receptors [3, 29]. Nowadays, this drug is mostly used in cardiology having many beneficial effects: decreases the blood pressure, induces vasodilation, antioxidant and antiproliferative effects [21, 27, 31]. Due to these effects carvedilol is indicated in patients with hypertension, ischemic heart disease or chronic heart failure [15]. The clinically used carvedilol is a mixture between S and R-carvedilol. These two enantiomers act differently: R-carvedilol blocks α_1 adrenergic receptors while S-carvedilol blocks α_1, β_1 and β_2 receptors [23, 34].

Carvedilol is well absorbed from gastro-intestinal level, is bound in high proportion to plasma proteins (98%) and is metabolized in the liver [22] through both oxidation and glucuronidation reactions. The results of these processes are few metabolites: 4'-hydroxyphenyl carvedilol, 5'-hydroxyphenyl carvedilol, O-desmethyl carvedilol, hydroxy carbazolyl [28, 33]. CYP2D6 and CYP1A2 are the main enzymes which catalyse the oxidation of carvedilol in humans [35]. 4' and 5'-hydroxyphenyl carvedilol is formed by action of CYP2D6 enzyme, hydroxy carbazolyl by CYP1A2 and O-desmethyl carvedilol by CYP2C9 [25, 28]. It was demonstrated that the active metabolite 4'-hydroxy-phenyl carvedilol has higher beta-blocking effect than carvedilol [1, 7].

Fluvoxamine is an antidepressant agent which belongs to the selective serotonin reuptake inhibitors, SSRIs [11, 14] and is used in patients with depression or other psychiatric diseases [13, 20]. It has a good absorption (more than 90%) and a low plasma protein binding (77%), being metabolized in the liver and excreted in urine [9, 10, 16]. Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19 and moderate inhibitor of CYP2C9, CYP2D6 and CYP3A4 [4, 32]. Due to fluvoxamine inhibitory effect on the enzymes which metabolize carvedilol, fluvoxamine may influence carvedilol's pharmacokinetics. So, the aim of this study was to investigate the pharmacokinetic interactions between fluvoxamine and carvedilol when these two drugs are concomitantly administered. There are many patients suffering from cardiovascular and psychiatric diseases who use carvedilol and fluvoxamine as treatment at the same time. The results of this study could have an important role in the pharmacotherapy and safety profile of carvedilol, by choosing the right treatment plan when these drugs are used concomitantly.

Materials and Methods

Chemicals and reagents

Carvedilol and fluvoxamine were purchased from Moehs (Rubí, Spain). HPLC-grade acetonitrile, 98% formic acid and methanol of analytical-reagent grade were purchased from Merck KGaA (Darmstadt, Germany). Heparine sodique 25,000 UI/5 mL (5,000 UI/mL) was acquired from Panpharma Laboratoires (France).

In this study, there were used the following apparatus: BASi Culex ABC®–Automatic Blood Collector (BASi, Indiana, USA); two HPLC systems – Agilent 1100 series (binary pump, autosampler, thermostat; Agilent Technologies®, USA) – coupled with a Bruker Ion Trap VL (Bruker Daltonics GmbH®, Germany).

Animal treatment

Thirteen (n = 13) male Crl:WI rats with a median weight of 330 ± 20 g were used in the present study. The animals were housed in polysulfone type III-H open-top cages (Tecniplast, Buguggiate, Italy) and had access to filtered tap water in bottles and pelleted feed (Cantacuzino Institute, Bucharest, Romania) *ad libitum*. The bedding was a standard wood chip aseptic bedding (Lignocel®; J. Rettenmaier & Söhne GmBH+ Co. KG, Rosenberg, Germany). The rats were acquired from the Centre for Experimental Medicine of the "Iuliu Haţieganu" University of Medicine and Pharmacy and were kept at a standard temperature of 20 ± 2°C and a relative humidity of 55 ± 10%, in a 12:12-hour light:dark cycle (lights on, 7 am to 7 pm) with a light intensity of 285 lx at 1 m above the floor. All experimental protocols were approved by the Ethics Committee of "Iuliu Haţieganu" University of Medicine and Pharmacy and by the Romanian National Sanitary Veterinary and Food Safety Authority (authorization number 8/27.10.2016) and were conducted in accordance with "Guide for the care and use of Laboratory Animals" 8th Ed/2011, and the EU Directive 63/2010. Prior to the onset of the study, all animals were quarantined and left to acclimatize to the separation from the rat colony for 7 days. The "Guiding Principles in the Use of Animals in Toxicology" adopted by the Society of Toxicology (USA) and the Law 43/2014 regarding the protection of animals used for scientific research were the specific regulations and amendments from this study.

The connection of the animal to BASi Culex ABC® needs the cannulation on the left femoral vein of the rat. Before performing the cannulation procedure, each animal was anesthetized with a combination of anaesthetics: diazepam (Diazepam®, Terapia SA, Romania), ketamine (Vetased® 10%, Farmavet, Romania) and xylazine (XylazinBio® 2%, Bioveta, Czech Republic) (1:1:1).

High-performance liquid chromatography assay

A validated liquid chromatography-mass spectrometry method was used to determine the plasmatic concentration of carvedilol [6].

The HPLC system was an Agilent 1100 series (binary pump, autosampler, thermostat) (Agilent Technologies®, USA) and was coupled with a Bruker Ion Trap VL (Bruker Daltonics GmbH®, Germany). A Zorbax SB-C18 chromatographic column (50 x 2.1 mm, 3.5 µm) (Agilent Technologies®, USA) was used. The mobile phase consisted of a 34:66 (v/v) mixture of acetonitrile and 0.2% (v/v) formic acid in water. The flow rate was 0.5 mL/min, and the thermostat temperature was set at 42°C. The mass spectrometry detection was in multiple reaction monitoring mode, positive ions, using an electrospray ionization source. The ion transitions monitored were m/z 222, 224, 283 from m/z 407 for carvedilol. The calibration curve of carvedilol was linear at a concentration range of 6 - 577 ng/mL plasma.

Pharmacokinetic Analysis

The non-compartmental pharmacokinetic analysis using Phoenix WinNonlin software version 6.3 (Pharsight Co., Mountain View, CA, USA) was performed to determine the pharmacokinetic parameters of carvedilol 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 rat'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. The elimination rate constant (k_{el}) was calculated by log-linear regression of carvedilol

concentration data during the elimination phase, and the terminal half-life ($t_{1/2}$) was calculated as $0.693/k_{el}$.

Experimental design

Surgery

One silicon rubber cannula (BASi®, Indiana, USA) (length, 18.5 cm; internal diameter, 0.5 mm; and external diameter, 0.94 mm) was implanted in the left femoral vein. This procedural surgery was effectuated under the anesthesia with the same cocktail as above: diazepam, ketamine and xylazine (1:1:1). The distal end of the cannula was tunnelled subcutaneously and exited between the ears. The venous cannula was used for blood sampling. The cannulation procedure was realized before connecting the rat to BASi Culex ABC®.

In vivo experimental design

The study was open-label, sequential preclinical one and consisted of two periods: period 1 (reference), when each rat received carvedilol 3.57 mg/kg b.w. by oral route, and period 2 (test) when each rat received carvedilol 3.57 mg/kg b.w. and fluvoxamine 14.28 mg/kg b.w. by oral route. Between the two periods, the rats were treated for 3 days with a single daily dose of fluvoxamine.

200 µL venous blood samples were drawn into heparinized tubes during both periods of the study at 5, 10, 15, 20, 30, 45 min and 1, 2, 4, 8, 12, 18, 24, 30 h after carvedilol administration. The samples were stored frozen at –20°C until analysis.

Statistical Analysis

The statistical analysis was performed using Phoenix WinNonlin software version 6.3 (Pharsight Co.®, Mountain View, CA, USA) and were evaluated by one-way analysis of variance (ANOVA) for inter-group comparison. The level of significance was set at $p < 0.05$ for all analyses. All kinetic data were expressed as the mean ± standard deviation (SD).

Results and Discussion

The carvedilol's mean plasma concentration-time profiles in presence or absence of fluvoxamine are illustrated in Figure 1.

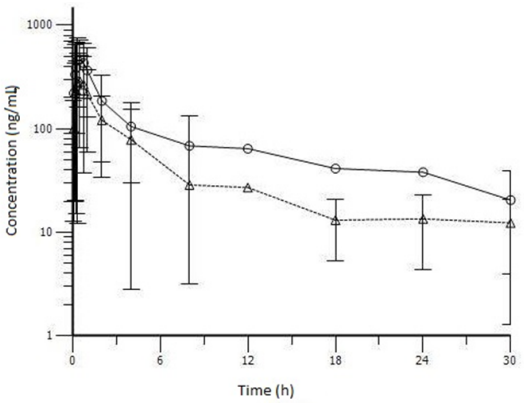

Figure 1.

Mean ± SD plasma concentrations of carvedilol after the oral administration of carvedilol (3.57 mg/kg b.w.) without (Δ) or with fluvoxamine (14.28 mg/kg b.w.) (○) in rats (n = 13).

The pharmacokinetic (PK) parameters and the statistical test results of carvedilol, when it was administered alone or with fluvoxamine, are summarized in Table I.

Table I

Main pharmacokinetic (PK) parameters of carvedilol in rats (n=13) after single oral dose of 3.57 mg/kg b.w. of carvedilol, before and after treatment with fluvoxamine (14.28 mg/kg b.w.) for 3 days and the results of statistical test used for comparison

PK parameter (mean ± SD)	Carvedilol	Carvedilol + Fluvoxamine	*p** value (ANOVA)
C_{max} (ng/mL)	361.10 ± 260.07	528.50 ± 288.20	0.0651, NS
t_{max} (hr)	2.12 ± 3.62	0.95 ± 1.31	0.2722, NS
$AUC_{0-\infty}$ (ng*hr/mL)	1113.42 ± 661.97	2299.96 ± 1465.32	0.0059, S
k_{el} (1/hr)	0.30 ± 0.42	0.09 ± 0.05	0.0188, S
$t_{1/2}$ (hr)	5.29 ± 3.22	12.42 ± 12.69	0.0188, S
Cl_F (L/hr/kg)	3677.29 ± 2133.11	2031.74 ± 1389.79	0.0174, S
Vz_F (L/kg)	25030.55 ± 21297.51	27486.02 ± 19941.52	0.5858, NS

*S - statistically significant when $p < 0.05$; NS – not significant

The $AUC_{0-\infty}$ of carvedilol was significantly increased by 206.55% ($p < 0.05$) in the presence of fluvoxamine after oral administration of carvedilol. Moreover, the body clearance and elimination half-life time were significantly affected by enzymatic inhibition of CYP2D6 and CYP1A2, the main enzymes responsible for the carvedilol's metabolism. The half-life time of carvedilol registered a 2.34 fold increase and the clearance (Cl) registered a 0.55 fold decrease when it was co-administered with fluvoxamine.

There were no significant changes neither for the C_{max} (361.10 ± 260.07 *vs* 528.50 ± 288.20) when co-administered with fluvoxamine nor T_{max} (2.12 ± 3.62 *vs* 0.95 ± 1.31). Although it was observed an increase with 46.35% for the value of C_{max} and a decrease with 55.18% for the value of T_{max}, they were proved not be statistically significant.

There was reported a high prevalence of depression among patients with cardiovascular diseases [5]. Carvedilol improves the ejection fraction, symptomatic

functional class, cardiac output and adrenergic activity. These advantages along with a potential increase in the risk for death with other β_1 selective blockers sustain the utilization of carvedilol in patients with cardiovascular diseases, especially for those with heart failure [8].

The most used drugs in the treatment of depression are selective serotonin reuptake inhibitors. Fluvoxamine is widely used for treatment of depression [26]. Because carvedilol is widely used to treat many cardiovascular diseases and is primarily metabolized by CYP2D6 and CYP1A2 [18] and fluvoxamine is a potent inhibitor of these metabolic pathway [17, 19], the clinical evaluation of this pharmacokinetic drug-drug interaction is important. The changes of CYP450 enzymes' function can generate drug-drug interactions. This interaction can have an impact on clinical practice for those patients who follow a concomitantly treatment with carvedilol and fluvoxamine. An elevated exposure over time to carvedilol was indicated by statistically significant alteration ($p < 0.05$) of pharmacokinetic parameters ($AUC_{0-\infty}$, k_{el}, $t_{1/2}$, Cl) after fluvoxamine pre-treatment. The alteration of the pre-systemic metabolism appeared as a result of this drug-drug interaction. Fluvoxamine inhibits the main isoenzymes (CYP2D6, CYP1A2) which are involved in the metabolization of carvedilol at pre-systemic level.

Many pre-clinical and clinical previous studies demonstrated the pharmacokinetic drug-drug interaction between carvedilol and other CYP450 inhibitors, including citalopram [1], bupropion [2, 12], fluoxetine [14, 24], paroxetine [30], ketoconazole and voriconazole [33]. The results were similar with that obtained by fluvoxamine inhibition in the present study.

In the last years, the safety profiles of many drugs, especially cardiovascular medication, have been evaluated. Carvedilol is one of the most used beta blockers but its safety profile still need to be studied, especially from the drug-drug interaction point of view.

Conclusions

In conclusion, the present study demonstrated the pharmacokinetic drug-drug interaction between carvedilol and fluvoxamine *in vivo*, in rats.

Fluvoxamine significantly influenced the pharmacokinetic of carvedilol, due to its capacity of CYP2D6 and CYP1A2 inhibition. As a result of this interaction the exposure to carvedilol was significantly increased. This is the reason why co-administration of carvedilol and fluvoxamine needs precaution.

Acknowledgement

This work was supported by CNCS Romania - project PNII-RU-TE-2014-4-0242, project manager CS III Dr. Muntean Dana Maria.

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