INFLUENCE OF FLUVOXAMINE ON CARVEDILOL’S PHARMACOKINETICS IN RATS

MARIA BIANCA ABRUDAN 1, DANA MARIA MUNTEAN1*, LAURIAN VLASE 1, ANA-MARIA GHELĐIU1, CRISTIAN BERCE 2, LAURENȚIU STOICESCU 3, MARIA ADRIANA NEAG 4

1Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, “Iuliu Hațieganu” University of Medicine and Pharmacy, 41 Victor Babeș, Cluj-Napoca 400012, Romania
2Centre for Experimental Medicine, “Iuliu Hațieganu” University of Medicine and Pharmacy, 6 Louis Pasteur, Cluj-Napoca 400349, Romania
3Department of Cardiology, Vth Medical Clinic, Clinical Municipal Hospital, “Iuliu Hațieganu” University of Medicine and Pharmacy, Faculty of Medicine, 11 Tâbăcării, Cluj-Napoca 400139, Romania
4Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, “Iuliu Hațieganu” University of Medicine and Pharmacy, 41 Victor Babeș, Cluj-Napoca 400012, Romania

*corresponding author: dana.muntean@umfcluj.ro

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, t1/2, decrease the Cl). The present study demonstrated the pharmacokinetic drug-drug interaction between carvedilol and fluvoxamine in vivo.

Keywords: Carvedilol, cytochrome P450, inhibition

Introduction

Carvedilol is a non-selective beta-blocker drug with additional blockades of α1 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 α1, β1 and β2 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 carbasolyl [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 carbasolyl by CYP1A2 and O-desmethyl carvedilol by CYP2C9 [25, 28]. It was demonstrated that the active metabolite 4'-hydroxyphenyl carvedilol has higher beta-blocking effect than carvedilol [1, 7].
Fluv oxamine 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]. Fluv oxamine is a potent inhibitor of CYP1A2 and CYP2C19 and moderate inhibitor of CYP2C9, CYP2D6 and CYP3A4 [4, 32]. Due to fluv oxamine inhibitory effect on the enzymes which metabolize carvedilol, fluv oxamine may influence carvedilol's pharmacokinetics. So, the aim of this study was to investigate the pharmacokinetic interactions between fluv oxamine and carvedilol when these two drugs are concomitantly administered. There are many patients suffering from cardiovascular and psychiatric diseases who use carvedilol and fluv oxamine 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 fluv oxamine 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). 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 fluv oxamine. The maximum plasma concentration (Cmax, ng/mL) and the time to reach the peak concentration (Tmax, hr) were obtained directly by the visual inspection of each rat’s plasma concentration-time profile. The area under the concentration-time curve from zero time to the last measurable concentration at time t (AUC0-t) was calculated using the trapezoidal rule. The area was extrapolated to infinity (AUC0-∞) by addition of C1/k1 to AUC0-t, where C1 is the last quantifiable drug concentration and k1 is the elimination rate constant. The elimination rate constant (k1) 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 intergroup 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.) (ε) in rats (n = 13).](image)

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

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

* indicates 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 β1 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 (AUC0-∞, \( \text{k}_{\text{el}}, t_{1/2}, \text{Cl} \)) 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 metabolism 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.

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References


