Alteration of Carvedilol Pharmacokinetics as a Result of Concomitant Administration of Fluoxetine in Human

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ABSTRACT

Objective: The objective of this study is to assess the pharmacokinetics changes of carvedilol when given with a known CYP2D6 inhibitor like fluoxetine. Background: Carvedilol is β-blockers with vasodilating activity, and it is first β-blocker approved by the Food and Drug Administration (FDA) as adjunctive therapy in the treatment of chronic heart failure (CHF). Carvedilol is extensively metabolized in the liver by cytochrome P-450 enzymes (CYP2D6 and CYP2C9). Fluoxetine is a selective serotonin reuptake inhibitors, it has an antidepressant effect. When fluoxetine co administered with carvedilol, it may precipitate drug-drug interaction at the site of carvedilol metabolism. Subjects and methods: In a randomized, crossover study in two groups, each contains 6 volunteers. The first group received carvedilol alone firstly, while the second group received carvedilol and fluoxetine firstly. On the day of the study each volunteer in the first group received a single dose of 50 mg carvedilol, the second group of the volunteers received a dose of 20 mg fluoxetine on the night before the study (8 hours before carvedilol administration). Plasma carvedilol was measured up to 8 hours using HPLC. Results: Carvedilol plasma concentration starts to increase rapidly after oral administration to reach maximum concentration (Cmax) 65.5 ± 5.2 ng/ml whereas, upon co-administration of fluoxetine with carvedilol, the Cmax of carvedilol was increased by 2.21 fold. (145.3 ± 8.5 ng/ml). The calculated mean AUC0-∞ after the co-administration of carvedilol with fluoxetine was increased by 2.54 fold, (184.88±15.71 ng. hr/ mL). Also co-administration of carvedilol with fluoxetine results in a significant decrease (P<0.05) in the calculated mean Cl/F (total body clearance of carvedilol dividing by its bioavailability) (0.11±0.01 L/hr) compared to administration of carvedilol only. A significant decrease (P≤0.05) in the mean calculated volume of distribution of carvedilol divided by its bioavailability (Vd/F) for carvedilol upon co-administration with fluoxetine by 42.2% compared to carvedilol alone. Conclusion: The simultaneous administration of carvedilol with fluoxetine can lead to clinical significant drug-drug interactions, as consequences of changes in pharmacokinetic parameters of carvedilol.

Key words: Carvedilol, fluoxetine, cytochrome P-450 CYP2D6, drug interactions, pharmacokinetics.

Introduction

β -adrenergic antagonists are usually used in treatment of conditions including hypertension, cardiac arrhythmia, and angina pectoris, in addition to topical administration for open angle glaucoma. The β -blockers are normally classified based on their selectivity for β -receptors. The non-selective β -blockers, including propranolol, oxprenolol, pindolol, nadolol, timolol and labetalol, antagonize both the β1 - and β2 -adrenergic receptors. The selective antagonists, including metoprolol, atenolol, esmolol, acebutolol, and bisoprolol have much greater binding affinity for the β1 adrenergic receptor. The selective beta-blocker are normally indicated for patients in whom β2 -receptor antagonism might be associated with an increased risk of adverse effects (Yancy, et al., 2001; Stoschitzky, et al., 1999).

Carvedilol is β-blockers with vasodilating activity, and it is first β-blocker approved by the Food and Drug Administration (FDA) as adjunctive therapy in the treatment of chronic heart failure. Carvedilol is extensively metabolized in the liver by CYP2D6 and CYP2C9 (Neugebauer et al., 2007; Giessmann et al., 2004; Zhou and Wood, 2005; Jeppesen et al., 2013).

There is some incidence of depression in patients with cardiovascular disease, so it is likely that an antidepressant agent will be co-administered with carvedilol, in addition, the lower cardiovascular side effects of the selective serotonin reuptake inhibitors (SSRIs) in comparison to the tri-cyclic antidepressants (TCAs), make them usually prescribed to patients with cardiovascular diseases. In this study we use fluoxetine which is SSRIs and has a potent CYP2D6 inhibition (Stoschitzky et al., 1999).

The results proved that upon concomitant administration of carvedilol with fluoxetine, significant changes in the pharmacokinetic parameters of carvedilol (P<0.05), that may lead to clinically significant drug-drug interaction. One of the most important pharmacokinetic parameter is the AUC of carvedilol was highly

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increased to 2.46 fold as a result of co-administration of fluoxetine (highly increase in carvedilol bioavailability).

Subjects, Materials and Methods

Materials

Standard Carvedilol, white to off white powder 1:1 mixture of (R) and (S) carvedilol, from Yick-Vick Chemicals and Pharmaceuticals, Hong Kong.

Drug products used:
1) Carvedilol tablets; Dilatrend®, 25 mg from Hoffman-La Roche Ltd. Basel, Switzerland, Germany.
2) Fluoxetine tablets; Philozac®, 20 mg from Amoun Pharmaceutical Company Abool, Egypt.
   a) Methanol, HPLC grade; Merck. Darmstadt, Germany.
   b) Triethanolamine, analytical grade; Riedel-deHaen, Germany.
   c) Ortho-phosphoric acid, analytical grade; Darmstadt, Germany.
   d) Ethanol, HPLC grade; Merck. Darmstadt, Germany.
   e) Acetonitril, HPLC grade; Merck. Darmstadt, Germany.
   f) Diethyl ether, HPLC grade; Prolabo.
   g) Trichloroacetic acid, analytical grade; Merck Schuchardt, Germany.
   h) Sodium hydroxide, analytical grade; Merck Schuchardt, Germany.

Equipment:
1. A high-pressure liquid chromatograph (Waters 600 controller, Waters, USA) equipped with a variable wave length ultraviolet detector (Waters 486).
2. Reversed-phase column, Hypersil® ODS 3 µm 4.6 X 150 mm Analytical Column, Waters, USA.
3. Vortex mixer (Maxi Mix II, Thermolyne Corporation, USA).

The clinical study

Subjects

Twelve healthy volunteers were enrolled in this study. The volunteers were informed about the objectives of the study and all the procedures were explained to them. A written consent form was signed by each agreement to participate in this study.

Inclusion criteria

Twelve healthy male adult volunteers with age ranging from 18 up to 26 years, and their weight ranging from 64 to 87 kg were enrolled (non obese). Physical examination showed that all the volunteers had no clinical evidences of chronic diseases. For each volunteer the liver function was assessed by measuring ALT and AST (Table 1) by using Transaminases - Colorimetric End-Point Method (Reitman, and, Frankel, 1957). As the main route of carvedilol elimination is the liver. The volunteers were instructed not to take any drug for at least 72 hours prior to and throughout the study period.

Exclusion criteria

Volunteers with liver diseases, smokers, regular prescription medication, chronic diseases (hypertension, diabetes, ischemic heart diseases), over and underweight volunteers were excluded.

Study design

The volunteers were instructed to never receive any medication (over the counter) for the 72 hours before the study and to fast over night (at least 10 hours) before the day of the study. On the day before the study the volunteers were randomly divided to two groups, each 6 volunteers, and the first group received carvedilol alone firstly, while the second group received carvedilol and fluoxetine firstly. On the day of the study each volunteer the liver function was assessed by measuring ALT and AST (Table 1) by using Transaminases - Colorimetric End-Point Method (Reitman, and, Frankel, 1957). As the main route of carvedilol elimination is the liver. The volunteers were instructed not to take any drug for at least 72 hours prior to and throughout the study period.

Sample collection

Blood samples (5 mL) were obtained by using vein puncture cannula before carvedilol administration (blank), and at 15, 30, 45, 60, 75, 90, minutes, and at 2, 3, 4, 6, 8 hour after carvedilol administration. All
samples were collected in heparinized tubes. Plasma was separated by centrifugation for 15 minutes at 4000 rpm and then stored at -20°C until analysis.

**Analysis of carvedilol in plasma**

A high performance liquid chromatographic method was adopted and validated for analysis of carvedilol in plasma samples. (Bartsch et al., 1990; Fujimaki et al., 1994; Ruffolo et al., 2006).

**Sample preparation**

To 500 µL of each standard plasma samples, 400 µL of 10% trichloroacetic acid were added, for protein precipitation. The test tubes were shaken well for 2 minutes using vortex mixer, and then centrifuged for 15 minutes at 4000 rpm. The supernatant was transferred to clean dry test tube for extraction of carvedilol. To each tube 400 µL of 1 M sodium hydroxide were added then the test tubes were shaken well for 2 minutes using vortex mixer. The standard samples were extracted with 3ml of diethyl ether, and centrifuged for 15 minutes at 4000 rpm. Then 2.5ml of the ether extract was transferred to clean dry test tube, and the extraction process was repeated again with another 3ml of diethyl ether. Then the two diethyl ether extracts were combined and then evaporated at room temperature over night until dryness. The residue was reconstituted in 100 µL of methanol by shaking well for 10 seconds using vortex mixer, and then 10 µL were injected to the HPLC. Unknown samples were treated exactly as the standard samples.

**HPLC Mobile phase for carvedilol**

The mobile phase consisted of water – acetonitrile – methanol – ethanol-1M triethylamine (83:58:55:3:1), the pH was adjusted to 2.5 with ortho-phosphoric acid, and the mobile phase was kept at room temperature. Separation was achieved using a C18 reversed-phase column, (HypersilODS 3 µm 4.6 X 150 mm) at room temperature, and the flow rate was 0.8 ml/min. The column eluent was monitored by ultraviolet detector at 242 nm. The retention time for carvedilol was 6 minutes (Eisenberg et al., 1989).

**Pharmacokinetic analysis**

Non-compartmental pharmacokinetic analysis was utilized to analyze the obtained results. The maximum plasma concentration (C_max) and the time of its occurrence (t_max) were determined from the concentration-time data. The area under the plasma concentration-time curve from 0 time to last sampling time (AUC_0→t) was calculated using the linear trapezoidal rule and the area under the curve from the last sampling time to infinity (AUC_t→∞) was calculated by dividing the last measured carvedilol plasma concentration by the elimination rate constant (k), then the area under the plasma concentration-time curve from time zero to infinity (AUC_0→∞) was calculated from the summation of the (AUC_0→t) plus the (AUC_t→∞). The elimination rate constant (k) was estimated from the slope of the terminal phase of the carvedilol plasma concentration from the following equation:

\[
\text{Slope} = \frac{-k}{2.303}
\]

The half life is calculated from the elimination rate constant (k).

\[
t_{1/2} = \frac{0.693}{k}
\]

The other pharmacokinetic parameters such as Cl/F where Cl is the total body clearance, and F is the bioavailability was calculated for the estimated pharmacokinetic parameters.

\[
\text{Cl} = \frac{F \times D}{\text{AUC}}, \quad \text{Cl/F} = \frac{D}{\text{AUC}}, \quad \text{where D is the dose.}
\]

The area under the curve was calculated utilizing the liner trapezoidal rule. The plasma concentration time profile was divided to trapezoids and the area of each trapezoid was calculated as follow:

\[
\text{Area of a trapezoid} = \frac{C_n + C_{n+1}}{2} \times (t_{n+1} - t_n)
\]

The \(\text{AUC}_{0→t}\) was calculated by adding the area of all the trapezoids.

The \(\text{AUC}_{t→∞}\) = \(\frac{C_p \times \text{last}}{k}\)

Where \(C_p \times \text{last}\) is the last measured drug plasma concentration and k is the rate constant for the terminal decline in the drug plasma concentrations.
The AUC \( 0 \rightarrow \infty \) was calculated as follow

\[
\text{AUC} \ 0 \rightarrow \infty = \text{AUC} \ 0 \rightarrow t_1 + \text{AUC} \ t_1 \rightarrow \infty
\]

The area under the first moment-time curve (AUMC) was calculated utilizing the linear trapezoidal rule after dividing the curve to trapezoids. The area of each trapezoid was calculated as follow:

\[
\text{Area of a trapezoid} = \left( \frac{t_n \ C_n + t_{n+1} \ C_{n+1}}{2} \right) \times (t_{n+1} - t_n)
\]

\[
\text{AUMC} \ t_1 \rightarrow \infty = \frac{t_{\text{last}} \times C_{p \ \text{last}}}{k} + \frac{C_{\text{plast}}}{k^2}
\]

The total AUMC \( 0 \rightarrow \infty \) was calculated from the following:

\[
\text{AUMC} \ 0 \rightarrow \infty = \text{AUMC} \ 0 \rightarrow t_1 + \text{AUMC} \ t_1 \rightarrow \infty
\]

\[
\text{MRT} = \frac{\text{AUMC}}{\text{AUC}}
\]

\[
\text{Vd}_{ss} = \text{Cl} \times \text{MRT}
\]

\[
\frac{\text{Vd}_{ss}}{F} = \frac{\text{Cl}}{F} \times \text{MRT}
\]

Where, Vd \( ss \) is the volume of distribution at steady state.

Statistical analysis

The pharmacokinetic parameters used for comparison were \( C_{\text{max}} \), t\( \text{max} \), t\( \frac{1}{2} \), k, \( \text{AUC} \ 0 \rightarrow t_1 \), AUMC \( 0 \rightarrow \infty \), MRT, Cl/F, and, Vd/F. The pharmacokinetic parameters were calculated for each individual under each treatment and the results were presented as the mean ± standard deviation (±SD) and were analyzed by Statistical Package for Social Science (SPSS) version 20. The Paired t-test was used. The level of significance was set at P value of 0.05 or less. The mean is the arithmetic average and can be calculated by

\[
X = \frac{\sum X}{n} \quad \text{Where } \Sigma X \text{ is the sum of all observations and } n \text{ is the number of observations}
\]

Results

In this study, twelve healthy adult male volunteers were enrolled in this study. The volunteers received 50 mg carvedilol alone and 50mg carvedilol with 20 mg fluoxetine orally in two separate occasions with three weeks washout period between treatments, our results were as follows:

The mean plasma concentration-time curves of carvedilol and carvedilol with fluoxetine are shown in figure (1). After administration of 50mg carvedilol as single oral dose, the concentration of carvedilol in plasma starts to increase rapidly after oral administration to maximum concentration (65.5 ± 5.2 ng/ml) after 60 to 75 minutes from the time of administration as shown in table (2), and then plasma concentration starts to decline by first order elimination. Whereas, after administration of single oral 50 mg carvedilol with 20mg fluoxetine, our results showed that, the mean plasma concentrations of carvedilol starts to increase rapidly to mean maximum concentration of 145.3±8.5 ng/ml., (P≤0.05) , as shown in table (2) and figure (1).

In table (3), the calculated area under plasma concentration time curve (AUC\( 0 \rightarrow \infty \)) for carvedilol in volunteers after administration of 50mg carvedilol alone and after administration of 50mg carvedilol with 20mg fluoxetine. The calculated mean of (AUC\( 0 \rightarrow \infty \)) for volunteers who administered carvedilol only is 184.88±15.71 (ng.hr/ml). Whereas, the mean of AUC\( 0 \rightarrow \infty \) for volunteers administered 50mg carvedilol with 20mg fluoxetine was significantly increased by 250 % (P<0.05) compared to carvedilol only as shown in table (3) and figure (2).

The mean maximum plasma concentrations \( (C_{\text{max}}) \) of carvedilol in volunteers received 50mg carvedilol is 65.5±5.2 ng/ml. Whereas, the mean \( C_{\text{max}} \) of carvedilol in volunteers received 50mg carvedilol with 20mg fluoxetine was significantly increased by 2.2 (P≤0.05) folds as shown in table (3) and figure (3).

A significant decrease in the calculated mean total body clearance of carvedilol dividing by its bioavailability (Cl/F) (0.11±0.01 L/hr) in volunteers taken 50mg carvedilol with 20mg fluoxetine, compared to that received 50mg carvedilol only(0.27±0.02 L/hr). (P≤0.05), as shown in table (3).

Table (3) shows that the mean calculated volume of distribution of carvedilol divided by its bioavailability (Vd/F) for carvedilol in volunteers received 50mg carvedilol with 20mg fluoxetine is significantly decreased (P≤0.05) by 42.2% compared to carvedilol administrated alone.

No significant change in the mean calculated (MRT) for the two groups (P≥0.05), in addition there is no a statistically significant difference between the mean calculated elimination rate constant (K), moreover,
there is no statistical significant difference between the mean calculated \( t_{1/2} \) (hr) for carvedilol alone (4.22±1.25 hr.) and 50mg carvedilol with fluoxetine administration (3.52±1.32 hr.) as shown in table (3) \((P≥0.05)\).

![Fig. 1: Mean (±SD) plasma concentration-time curve (ng/ml) observed after administration of a single oral dose50mg of carvedilol only and carvedilol with 20 mg fluoxetine orally to 12 volunteers in cross over study.]

**Table 1:** Lists the demographic information of the enrolled volunteers participated in the study

<table>
<thead>
<tr>
<th>Volunteer no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>21</td>
<td>19</td>
<td>18</td>
<td>26</td>
<td>24</td>
<td>20</td>
<td>25</td>
<td>19</td>
<td>22</td>
<td>25</td>
<td>23</td>
<td>22</td>
<td>22 ± 2.67</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70</td>
<td>83</td>
<td>67</td>
<td>74</td>
<td>67</td>
<td>64</td>
<td>83</td>
<td>87</td>
<td>71</td>
<td>82</td>
<td>69</td>
<td>72</td>
<td>74.08 ± 8.7</td>
</tr>
<tr>
<td>Liver Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT* (IU/L)</td>
<td>23</td>
<td>17</td>
<td>26</td>
<td>19</td>
<td>31</td>
<td>12</td>
<td>19</td>
<td>24</td>
<td>28</td>
<td>33</td>
<td>29</td>
<td>38</td>
<td>24.9 ± 7.4</td>
</tr>
<tr>
<td>AST** (IU/L)</td>
<td>35</td>
<td>31</td>
<td>23</td>
<td>22</td>
<td>27</td>
<td>18</td>
<td>23</td>
<td>29</td>
<td>30</td>
<td>19</td>
<td>23</td>
<td>26.3 ± 5.6</td>
<td></td>
</tr>
</tbody>
</table>

* ALT is alanine aminotransferase (normal range 5-40 IU/L)
* AST is aspartate aminotransferase (normal range 7-56 IU/L)

**Table 2:** Mean plasma concentrations (ng/ml) of carvedilol at different time points to twelve volunteers after administration of single oral dosage of 50 mg of carvedilol only and 50 mg of carvedilol with 20mg of fluoxetine

<table>
<thead>
<tr>
<th>Time (hr.)</th>
<th>0</th>
<th>0.25</th>
<th>0.50</th>
<th>0.75</th>
<th>1</th>
<th>1.25</th>
<th>1.50</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol only (ng/ml)</td>
<td>13±1.4</td>
<td>17±2.5</td>
<td>26±1.2</td>
<td>65±5.2</td>
<td>53±4.5</td>
<td>38±3.9</td>
<td>27±5.5</td>
<td>18±3.9</td>
<td>14±2.3</td>
<td>9.6±1.4</td>
<td>7.3±0.8</td>
<td></td>
</tr>
<tr>
<td>Carvedilol with fluoxetine (ng/ml)</td>
<td>16.5±1.3</td>
<td>24.4±1.5</td>
<td>45.1±3.6</td>
<td>106.7±6.4</td>
<td>145.3±8.5</td>
<td>94.4±3.6</td>
<td>70.7±1.9</td>
<td>61.2±1.9</td>
<td>41.6±1.5</td>
<td>26.3±2.2</td>
<td>17.2±0.9</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD
SD = Standard Deviation

**Table 3:** Some pharmacokinetics parameters of carvedilol in the 12 volunteers after administration of single oral dose of 50 mg carvedilol alone and after pretreatment with 20mg fluoxetine orally.

<table>
<thead>
<tr>
<th>Pharmacokinetics parameters</th>
<th>AUC (ng. hr/ mL)</th>
<th>C max (ng/ml)</th>
<th>CL/F (L/hr)</th>
<th>Vd/F (L)</th>
<th>MRT (hr)</th>
<th>K (hr⁻¹)</th>
<th>t½ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol alone</td>
<td>184.88±15.7</td>
<td>66±4.2</td>
<td>0.27±0.02</td>
<td>1.06±0.01</td>
<td>3.59±0.617</td>
<td>0.18±0.04</td>
<td>4.22±1.25</td>
</tr>
<tr>
<td>Carvedilol with fluoxetine</td>
<td>453.97±4*</td>
<td>145±8.4*</td>
<td>0.11±0.01*</td>
<td>0.45±0.01*</td>
<td>4.68±0.409</td>
<td>0.21±0.04</td>
<td>3.52±1.32</td>
</tr>
</tbody>
</table>

Data are Mean ± SD
* Significantly different from carvedilol alone (Paired t-test, P<0.05)
Fig. 2: AUC (ng.hr/ml) calculated after administration of a single oral dose 50mg of carvedilol only and carvedilol with 20mg fluoxetine orally to 12 volunteers in cross over study.

Fig. 3: Plasma concentration (ng/ml) measured after administration of a single oral dose 50mg of carvedilol only and carvedilol with 20mg fluoxetine orally to 12 volunteers in cross over study.

Discussion

The elimination of most β-blockers occurs via hepatic metabolism and/or renal excretion of the unchanged drug. While the lipophilic β-blockers, such as propranolol and carvedilol, are eliminated mostly by metabolism in liver, the more hydrophilic beta-blockers, such as atenolol and nadolol, are almost exclusively excreted unchanged in urine.

In this study, carvedilol clearances in the absence of fluoxetine were similar to those seen in individuals expressing the CYP2D6 extensive metabolizer (EM) phenotype (Ruffolo et al., 2006). Fluoxetine co-administration resulted in clearances typical of the CYP2D6 poor metabolizer (PM) phenotype (Ruffolo et al., 2006; Graff et al., 2004) Increases in AUC upon coadministration of fluoxetine also mimicked a phenotypic shift from EM to a PM, with approximate 2.54 fold (Ruffolo et al., 2006; Oldham and Clarke, 1997).

Table (3) showed that there is a statistically significant (P≤0.05) difference between the mean maximum plasma concentration (C_{max}) of carvedilol in volunteers on 50mg carvedilol therapy as single oral dose, and the mean C_{max} of carvedilol in volunteers on carvedilol (50 mg) with 20mg fluoxetine orally. This increase may be attributed to the inhibition effect of fluoxetine on CYP2D6. At the same time, the
pharmacokinetic parameters of carvedilol with and without the addition 20mg fluoxetine were compared with the paired t-test; the statistical analysis revealed the differences between the most of pharmacokinetic parameters of the two groups were significant.

The area under the curve (AUC_0→∞) after co-administration of fluoxetine (20 mg) was increased to 453.97 ng.hr/ml, this increase was about 2.54 fold of that found in volunteers taken the same dose of carvedilol only (184.8 ng.hr/ml). This result indicates that the CYP2D6 inhibitor (fluoxetine) increase the bioavailability of carvedilol compared with that in volunteers taken carvedilol only, (P<0.05). (Table 3).

However, there was a statistical significant decrease in Cl/F for volunteers taken carvedilol with fluoxetine (P<0.05). The mean Cl/F for the group on carvedilol only was 0.27 ± 0.02 L/hr versus 0.11 ± 0.01 L/hr for volunteers on carvedilol with fluoxetine. This result reveal to a significant decrease (P<0.05) in Cl/F upon the use of carvedilol with fluoxetine. To achieve that F must be increased, this was proved by the increase in carvedilol AUC by 2.54 times upon co-administration with fluoxetine (Table 3), the increase in AUC of carvedilol can be explained by inhibition of first pass effect of carvedilol through an inhibition of CYP2C6 by fluoxetine when used concomitantly with carvedilol. Such combination leads to a significant increase P<0.05 in F as a result a significant decrease in Cl/F which can be observed in the volunteers on carvedilol with fluoxetine.

Increased carvedilol exposure as a result of concomitant administration of fluoxetine could enhance adrenergic antagonism, and a greater proportional rise in carvedilol concentration could cause a shift toward greater adrenergic blockade. However, the pharmacodynamic effects of this and similar interactions in clinical studies to date have been mild (Packer et al., 1996).

**Conclusion**

This study demonstrated a pharmacokinetic drug-drug interaction between carvedilol and fluoxetine. There was considerable increasing in carvedilol bioavailability as a result of concomitant administration of fluoxetine. This drug interaction could potentially increase adrenergic antagonism of carvedilol and may have significant clinical effects in patients; these effects were not seen in our study (healthy volunteer subjects) after single dose administration.

**Acknowledgments**

I take this opportunity to show my greatest appreciation and greatest admiration to Prof. Dr. Mokhtar Mabrouk, Professor of Analytical Chemistry, Faculty of pharmacy, Tanta University.

**References**


