Short Communication

The Angiotensin-Converting Enzyme Inhibitor, Captopril, Alters Some Biochemical Laboratory Measurements In Vitro

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Abstract

Captopril is an angiotensin-converting enzyme inhibitor used essentially for the treatment of hypertension. In the present study, we demonstrated that captopril, when directly added to pooled serum samples in vitro, caused some alterations in the biochemical measurements which may have been the result of enzymatic, chemical and/or physical interactions with the drug or its metabolites. When captopril was added to pooled normal human sera to concentrations equivalent to the C\(_{\text{max}}\) of the drug, the serum values obtained for glucose, total protein, urea, creatinine, total cholesterol, and triglyceride concentrations were generally reduced in a dose dependent manner. The enzymatic activities of hepatic enzymes were also increased by captopril at specific concentrations, while creatine kinase activity was reduced in the presence of the drug. 

Keywords: Captopril, biochemical laboratory tests, drug interactions

Introduction

Captopril, D-3-mercapto-2-methyl (propanoyl-L-proline, 1), is a potent and selective inhibitor of angiotensin I-converting enzyme (ACE) [1], the enzyme responsible for the conversion of angiotensin I to angiotension II [2]. The therapeutic uses of captopril are based on its vasodilatory effects and enhancement of renal excretion of sodium [3-8]. These benefits are most clearly seen in hypertension and in cardiac conditions, mainly post myocardial infarction or congestive heart failure. It is also used in the preservation of kidney function in diabetic nephropathy. It is a white to off-white crystalline powder, with a characteristic sulfur-like odour.

Captopril is freely soluble in water, methanol, ethanol and chloroform [9]. In the gastro-intestinal tract, at least 75% of the drug is rapidly absorbed. Captopril is partially metabolized, whereby approximately 50% of it is converted to inactive mixed disulfides with endogenous thiol compounds. Both metabolites and unchanged captopril appear in the urine. The elimination half-life of captopril is about 1.9 h in healthy volunteers [10]. Although ACE inhibitors have been reported to cause rare episodes of hepatotoxicity [11], captopril in particular, has been reported to be of very low risk in causing toxicity [12]. However, the direct effects of captopril on the clinical chemistry tests have not been disclosed.

With the wide use of captopril as a therapeutic agent, the drug has been selected in this study to demonstrate its effects on some common biochemical laboratory tests, especially those that could explain drug-laboratory test interactions.

Materials and Methods

A stock solution of captopril was prepared by dissolving 14 mg of captopril in 100 ml distilled water. When 5.5 \(\mu\)l of this solution were added to 1 ml of pooled normal human sera, a final concentration of 770 ng/ml was obtained. This represents the C\(_{\text{max}}\) of the drug in the serum following its oral administration of 100 mg [10]. Serial dilutions were carried out to obtain final concentrations of 385, 192.5, and 96.25 ng/ml, which represent the C\(_{\text{max}}\) of the drug in serum following administration of 50 mg, 25 mg and 12.5 mg captopril, respectively. For negative control samples, distilled water was used instead. The biochemical parameters measured included glucose, total protein (TP), urea, creatinine, total cholesterol (TC), triglyceride (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and creatine kinase (CK). These parameters were measured by using Randox kits, and read by spectrophotometry. Each test was performed in triplicate.

The effects of the drug solvent were measured and subtracted from the readings in the presence of the drug. The net effect of the drug on laboratory test was calculated as follow:

Net effect of drug on laboratory test ( Value (serum + drug) - Value (serum + solvent))
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The results were expressed as the mean ± SD. A student t-test was used to examine the difference in the mean of the parameters tested. The p value of less than 0.05 was considered significant. ANOVA was used to evaluate the effects of different concentrations of the drug on the biochemical parameters.

Results

When pooled serum samples were analyzed in the presence of captopril, the tested concentrations of glucose, urea, TC and TG were found to be lower compared to those obtained without the drug. The changes were more pronounced in the presence of 770 ng/ml captopril. The readings of TP and creatinine were also lower when sera were tested in the presence of high doses of captopril but gradually elevated as the captopril dose was decreased to become close to the control levels (Table 1).

Measurements of the serum enzymatic activity revealed that lower doses of captopril increased the AST and ALT levels/readings. The changes were more evident in the presence of 96 ng/ml captopril. In addition, the LDH readings were found to be higher in the presence of captopril concentrations of 770, 385, and 192 ng/ml, but lower in sera containing captopril at the concentration of 96.25 ng/ml. There were significant decreases in the CK activity levels/readings for all the captopril concentrations used, especially with the low captopril concentration of 96.25 ng/ml (Table 1).

Table 1: The in vitro effect of different concentrations of captopril on serum biochemical parameters tested.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>96.25 ng/ml</th>
<th>192.5 ng/ml</th>
<th>385 ng/ml</th>
<th>770 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>96 ± 20.29</td>
<td>87.33 ± 21.73</td>
<td>86 ± 20.66</td>
<td>65.66 ± 21.12</td>
<td>35 ± 15.71</td>
</tr>
<tr>
<td>TP (g/l)</td>
<td>74.33 ± 10.4</td>
<td>76 ± 11.7</td>
<td>70.33 ± 9.4</td>
<td>61.66 ± 12.5</td>
<td>50 ± 10.5</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>29.3 ± 8.7</td>
<td>26.6 ± 9.0</td>
<td>24.3 ± 9.0</td>
<td>12.3 ± 8.0</td>
<td>16.6 ± 6.4</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.093 ± 0.325</td>
<td>1.116 ± 0.345</td>
<td>1.08 ± 0.342</td>
<td>1.03 ± 0.384</td>
<td>0.99 ± 0.305</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>167.66 ± 57.5</td>
<td>160.33 ± 55.36</td>
<td>142.66 ± 57</td>
<td>123.33 ± 1.92</td>
<td>103 ± 62.64</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>110.66 ± 16.65</td>
<td>91.33 ± 18.14</td>
<td>75.33 ± 21.12</td>
<td>70 ± 18.68</td>
<td>50.33 ± 21.07</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>19.66 ± 6.02</td>
<td>29 ± 10.4</td>
<td>25 ± 7.9</td>
<td>21.33 ± 6.05</td>
<td>17.33 ± 4.5</td>
</tr>
<tr>
<td>CK (IU/l)</td>
<td>143.66 ± 16.5</td>
<td>87.66 ± 0.108</td>
<td>95.66 ± 17.55</td>
<td>101.66 ± 16.16</td>
<td>107 ± 15.09</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>159 ± 35.67</td>
<td>123.33 ± 1.18</td>
<td>165.66 ± 4.94</td>
<td>193.33 ± 3.08</td>
<td>208 ± 30.26</td>
</tr>
</tbody>
</table>

TP: total protein; TC: total cholesterol; TG: triglyceride; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CK: creatine kinase; LDH: lactate dehydrogenase.

Discussion

The development of many new therapeutically effective drugs in recent years has resulted in considerable progress in the treatment of numerous diseases. However, considerable reports have surfaced in relation to the interaction of drugs with laboratory assays. For example, aspirin and ascorbic acid have both been reported to cause a false state of hyperglycaemia [13].

The results presented in this study demonstrated clearly that some laboratory findings were altered when tests were performed in sera added with captopril. The data suggest that the antihypertensive agent or its metabolites may have altered the serum levels of glucose, urea, TC, TG, TP and creatinine, or alternatively, interfered in their measurement readings. In the same experiments, captopril, at certain concentrations, had also led to the increase in the levels/readings of serum ALT, AST and LDH in the test, while serum CK levels/readings were lower in its presence. Since all the analytical methods used were based on enzymatic reactions and the issue of drug toxicity does not arise in vitro, the detected changes may have been due to enzymatic, chemical and/or physical interferences caused by the drug or its metabolites.

When drugs are detected as interfering with laboratory results like in the present case of captopril, tests may have to be repeated or the laboratory personnel may need to perform special procedures to eliminate or adjust the interference. Individuals with chronic diseases such as hypertension or diabetes are usually in need for drugs to perform special procedures to eliminate or adjust the interference. When the drug interference is overlooked, the physician may be faced with laboratory results which may not correlate well with the clinical impression of the patient’s state. This, in turn, may lead to more serious consequences, and possibly erroneous therapeutic decisions [14].

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References


