which were divided into 4 groups, the control group (7 rats) received distilled water, the other three treatment groups each group (14 rats) were divided into two subgroups T1 & T2 according to the following oral daily dosing regimen (aspirin subgroup 2 and 4 mg/kg, captopril, 6 and 12 mg/kg and aspirin + captopril (2 + 6 mg/kg and 4 + 12 mg/kg) respectively.

The following biochemical and hematological results were recorded during the experiment:

Aspartate Transaminase: significant increase (p < 0.05) were observed in the serum of rats treated subgroups T1 & T2 of captopril and captopril + asprin after 3 month while aspirin showed a significant increase in serum AST level started from 1.5 months for T2 group.

Alanine Transeaminase: Captopril, asprin and captopril + asprin treated rats showed significant increase (P < 0.05) in serum ALT level in both T1 & T2 subgroups at the period of 1.5 & 3 months treatment positively proportional with the dose and treatment period.

Alkaline Phosphatase: Captopril, asprin and captopril + asprin treated rats showed highest levels with significant increase (P < 0.05) in serum AP levels in both T1 & T2subgroup at the period of 1.5 & 3 months treatment positively proportional with the dose and treatment period.

Introduction

Both aspirin (acetylsalicylic acid) and captopril (ACE inhibitors) are often used concomitantly, especially in patients with both heart failure and ischaemic heart disease (1).

Controversy commenced as to whether there is a negative interaction between angiotensin-converting enzyme inhibition and acetylsalicylic acid. Since one of the most important underlying causes of congestive heart failure is coronary artery disease, this question is of utmost clinical importance. The fact that this topic is still relevant > 10 years after the initiation of the controversy indicates the difficulty inherent in resolving the question (2).

Aims

Monitoring biochemical in different orally dosed rat groups as following AST, ALT and AP

Materials and Methods

Determination of aspartate and alanine transaminase activities

Principle

Aspartate transaminase (AST) or glutamate oxaloacetate transaminase (GOT) catalyzed the irreversible transfer of an amino group from aspartate to α-oxoglutarate forming glutamate
and oxaloacetate.

\[
\begin{align*}
\text{\textit{\(\alpha\)-oxoglutarate}} & + \text{L-aspartate} \\
\text{L-glutamate} & + \text{oxaloacetate}
\end{align*}
\]

Aspartate transaminase is measured by monitoring the concentration of decarboxylated pyruvate that react with 2-4 DNPH (2,4-dinitrophenyl-hydrazine) forming the colored hydrazone.

\[
\begin{align*}
\text{\textit{\(\alpha\)-oxoglutarate}} & + \text{L-alanine} \\
\text{L-glutamate} & + \text{pyruvate}
\end{align*}
\]

Alanine transaminase is measured according to the method of Reitman and Frankel, 1957. The absorbance was read against blank at 540 nm by using visible spectrophotometer.

\[
\text{Calculation (IU/L)} = \frac{\text{Test} - \text{Control}}{\text{Stand} - \text{Blank}}
\]

**Determination of Alkaline phosphatase activity:**

**Principle**

Colorimetric determination Alkaline phosphatase activity was achieved according to the following reaction:

\[
\begin{align*}
\text{Phenyl phosphate} & \rightarrow \text{phenol} + \text{phosphate}
\end{align*}
\]

The phenol liberated is measured in the presence of 4-amino-antipyrine and potassium ferricyanide. ALP activity was measured in serum and supernatant according to the method of Belfield and Goldberg, 1971(3) in which absorbance of colored mixture was
measured spectrophotometrically at 510 nm according the equation:

\[
\text{Calculatio } n \ (\text{IU/L}) = \frac{\text{Test} - \text{Control}}{\text{Standard} - \text{Blank}} \times n
\]

\[n = 142 \ \text{IU/L}\]

**Results**

**AspartateTransaminase**: significant increase \((P < 0.05)\) were observed in the serum of rats treated subgroups T1&T2 of captopril and captopril + aspirin after 3 months while aspirin showed a significant increase in serum AST level started from 1.5 months for T2 group. (Table 1,2,3)

*Table -1- Effect Of Different Doses Of Captopril On The Serum AST Level IU/L In Different Experimental Groups & Treatment Periods*

<table>
<thead>
<tr>
<th>Group/period</th>
<th>Pretreatment Mean ± SE</th>
<th>1.5 months Mean ± SE</th>
<th>3 months Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control n=7</td>
<td>20.3 ± 0.88</td>
<td>23.2±1.9</td>
<td>24.14±1.3</td>
</tr>
<tr>
<td>T1 n=7</td>
<td>22.1 ± 0.87</td>
<td>25.2±1.3</td>
<td>35.50±1.6</td>
</tr>
<tr>
<td>T2 n=7</td>
<td>24.16±0.93</td>
<td>25.8±1.4</td>
<td>33.84 ± 2.8</td>
</tr>
</tbody>
</table>

\(T1 = 6 \text{ mg/kg B.W.}\)

\(T2 = 12 \text{ mg/kg B.W.}\)

Different capital letters means, there are significant differences within groups at \(P < 0.05\).

Different small letters means, there are significant differences between groups at \(P <0.05\).

\(n = \text{number of animals}\)

*Table -2- Effect Of Different Doses Of Aspirin On The Serum AST Level IU/L In Different Experimental Groups & Treatment Periods.*

<table>
<thead>
<tr>
<th>Group / period</th>
<th>Pretreatment Mean ± SE</th>
<th>1.5 months Mean ± SE</th>
<th>3 months Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control n=7</td>
<td>20.3 ± 0.9</td>
<td>23.2±1.9</td>
<td>24.14 ±1.3</td>
</tr>
</tbody>
</table>
Different capital letters means, there are significant differences within groups at \( P < 0.05 \).
Different small letters means, there are significant differences between groups at \( P < 0.05 \).

Table -3- Effect Of Different Doses Of Aspirin And Captopril On The Serum AST Level IU/ L Of Different Experimental Groups & Treatment Periods

<table>
<thead>
<tr>
<th>Group/ period</th>
<th>Pretreatment Mean ± SE</th>
<th>1.5 months Mean ± SE</th>
<th>3 months Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Aa 20.3 ± 0.88</td>
<td>Aa 23.2 ± 1.9</td>
<td>Aa 24.14 ± 1.3</td>
</tr>
<tr>
<td>n=7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Aa 24.6 ± 5.2</td>
<td>Aa 27.3 ± 2.5</td>
<td>Bb 38.4 ± 2.3</td>
</tr>
<tr>
<td>n=7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Aa 25.71 ± 4.70</td>
<td>Aa 24.6 ± 0.7</td>
<td>Bb 32.04 ± 1.7</td>
</tr>
<tr>
<td>n=7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( T1 = 2 \text{ mg/kg B.W.} \)  
\( T2 = 4 \text{ mg/kg B.W.} \)

Different capital letters means, there are significant differences within groups at \( P < 0.05 \).
Different small letters means, there are significant differences between groups at \( P < 0.05 \).

Table -4- Effect Of Different Doses Of Captopril On The Serum ALT Level IU/ L In Different Experimental Groups & Treatment period

<table>
<thead>
<tr>
<th>Group/ period</th>
<th>1.5 months Mean ± SE</th>
<th>3 months Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Aa 23.2 ± 1.9</td>
<td>Aa 24.14 ± 1.3</td>
</tr>
<tr>
<td>n=7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Aa 27.3 ± 2.5</td>
<td>Bb 38.4 ± 2.3</td>
</tr>
<tr>
<td>n=7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Aa 24.6 ± 0.7</td>
<td>Bb 32.04 ± 1.7</td>
</tr>
<tr>
<td>n=7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( T1 = (\text{captopril 6 + aspirin 2}) \text{ mg/kg. B.W.} \)  
\( T2 = (\text{captopril 12 + aspirin 4}) \text{ mg/kg. B.W.} \)

Different capital letters means, there are significant differences within groups at \( P < 0.05 \).
Different small letters means, there are significant differences between groups at \( P < 0.05 \).

Alanine Transaminase: Captopril, aspirin and captopril + aspirin treated rats showed significant increase (\( P < 0.05 \)) in serum ALT levels in both T1&T2 subgroups at the period of 1.5 & 3 months treatment positively proportional with the dose and treatment period. (Table 4,5,6)
### Table -5- Effect Of Different Doses Of Aspirin On The Serum ALT Level IU/L In Different Experimental Groups & Treatment Periods

<table>
<thead>
<tr>
<th>Group / period</th>
<th>Pretreatment Mean ± SE</th>
<th>1.5 months Mean ± SE</th>
<th>3 months Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Aa 4.3 ± 0.9</td>
<td>Aa 4.4 ± 0.5</td>
<td>Aa 5.7 ± 0.9</td>
</tr>
<tr>
<td>T1</td>
<td>Aa 4.1 ± 0.6</td>
<td>Bb 6.5 ± 0.4</td>
<td>Bb 20.9 ± 6.9</td>
</tr>
<tr>
<td>T2</td>
<td>Aa 4.3 ± 0.6</td>
<td>Bb 7.4 ± 0.8</td>
<td>Bb 13.4 ± 0.7</td>
</tr>
</tbody>
</table>

T1 = 6 mg/kg B.W.  
T2 = 12 mg/kg B.W.  
Different capital letters means, there are significant differences within groups at P < 0.05.  
Different small letters means, there are significant differences between groups at P <0.05.  
n = number of animals

T1 = 2 mg/kg B.W.  
T2 = 4 mg/kg B.W.  
Different capital letters means, there are significant differences within groups at P < 0.05.  
Different small letters means, there are significant differences between groups at P < 0.05.
Table -6- Effect Of Different Doses Of Aspirin And Captopril On The Serum ALT Level IU/L In Different Experimental Groups & Treatment Periods

<table>
<thead>
<tr>
<th>Group/ period</th>
<th>Pretreatment Mean±SE</th>
<th>1.5 months Mean±SE</th>
<th>3 months Mean±SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=7</td>
<td>Aa 4.3 ± 0.9</td>
<td>Aa 4.4 ± 0.5</td>
<td>Aa 5.7 ± 0.9</td>
</tr>
<tr>
<td>T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=7</td>
<td>Aa 4.8 ± 0.8</td>
<td>Bb 7.9 ±1.7</td>
<td>Bb 13.3 ± 0.9</td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=7</td>
<td>Aa 4.40 ± 0.6</td>
<td>Bb 7.10 ± 0.8</td>
<td>Bb 13.8 ±1.3</td>
</tr>
</tbody>
</table>

T1 = (captopril 6 + aspirin 2) mg/kg B.W.
T2 = (captopril 12 + aspirin 4) mg/kg B.W.

Different capital letters mean there are significant differences within groups at P < 0.05.
Different small letters mean there are significant differences between groups at P < 0.05.

Alkaline Phosphatase: Captopril, aspirin and captopril + aspirin treated rats showed highest levels with significant increase (P < 0.05) in serum AP levels in both T1&T2 subgroup at the period of 1.5 & 3 months treatment positively proportional with the dose and treatment period.

Table -7- Effect Of Different Doses Of Captopril On The Serum AP Level IU/L In Different Experimental Groups & Treatment Periods

<table>
<thead>
<tr>
<th>Group/ period</th>
<th>Pretreatment Mean ± SE</th>
<th>1.5 months Mean ± SE</th>
<th>3 months Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=7</td>
<td>Aa 70.9 ± 2.9</td>
<td>Aa 71.7 ± 1.9</td>
<td>Aa 75.06 ± 2.3</td>
</tr>
<tr>
<td>T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=7</td>
<td>Aa 72.7 ± 3.0</td>
<td>Bb 163.3 ± 3.7</td>
<td>Cb 243.7 ± 2.0</td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=7</td>
<td>Aa 72.4 ± 4.2</td>
<td>Bb 142.7 ± 2.0</td>
<td>Cc 261.1 ± 1.2</td>
</tr>
</tbody>
</table>

T1 = 6 mg/kg B.W.
T2 = 12 mg/kg B.W.

Different capital letters mean there are significant differences within groups at P < 0.05.
Different small letters means, there are significant differences between groups at $P < 0.05$

**Table -8- Effect Of Different Doses Of Aspirin On The Serum AP Level IU/L In Different Experimental Groups & Treatment Periods**

<table>
<thead>
<tr>
<th>Group / period</th>
<th>Pretreatment Mean ± SE</th>
<th>1.5 months Mean ± SE</th>
<th>3 months Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control n=7</td>
<td>Aa 70.9 ± 2.9</td>
<td>Aa 68.6 ± 1.5</td>
<td>Aa 75.06 ± 2.3</td>
</tr>
<tr>
<td>T1 n=7</td>
<td>Aa 76.7 ± 0.5</td>
<td>Bb 168.03 ± 1.4</td>
<td>Cb 188.06 ± 0.8</td>
</tr>
<tr>
<td>T2 n=7</td>
<td>Aa 77.3 ± 0.8</td>
<td>Bb 153.5 ± 1.5</td>
<td>Cc 207.0 ± 0.9</td>
</tr>
</tbody>
</table>

T1 = 2 mg/kg B.W.
T2 = 4 mg/kg B.W.

Different capital letters mean, there are significant differences within groups at $P <0.05$.
Different small letters mean, there are significant differences between groups at $P < 0.05$.

**Table -9- Effect Of Different Doses Of Aspirin And Captopril On The Serum AP Level IU/L In Different Experimental Groups & Treatment Periods**

<table>
<thead>
<tr>
<th>Group/period</th>
<th>Pretreatment Mean±SE</th>
<th>1. 5 months Mean±SE</th>
<th>3 months Mean±SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control n=7</td>
<td>A a 70.9 ± 2.9</td>
<td>A a 71.7 ± 1.9</td>
<td>A a 75.06 ± 2.3</td>
</tr>
<tr>
<td>T1 n=7</td>
<td>Aa 74.1 ± 0.9</td>
<td>Bb 139.0 ± 0.8</td>
<td>Bb 143.1 ± 1.8</td>
</tr>
<tr>
<td>T2 n=7</td>
<td>Aa 75.4 ± 0.8</td>
<td>Bb 140.4 ± 1.06</td>
<td>Bb 145.3 ± 2.9</td>
</tr>
</tbody>
</table>
T1 = (captopril 6 + aspirin 2) mg/kg B.W.
T2 = (captopril 12 + aspirin 4) mg/kg B.W.

Different capital letters means, there are significant differences within groups at
P < 0.05.
Different small letters means, there are significant differences between groups at
P< 0.05.

Discussion

Aspartate transaminase

significant increase in the level of serum AST in both T1&T2 groups were noticed after 3 months treatment period in comparison with the period before. This finding is similar to that of Patrick and Kamath, (1996)\(^4\), who found that many medication cause increases in AST level, one of which is ACE inhibitor.

Different doses of aspirin causes a significant increase in serum AST level started from 1.5 months for T2 group. This finding is similar to Patrick and Kamath, (1996)\(^4\), Ebong, et al., (1998)\(^5\) and in a study done by Fries, et al., (1992)\(^6\). Elevated levels of AST was most frequent in patients with rheumatoid arthritis taking salicylates and methotrexate.

Also the same significant increase was seen for the effect of aspirin and captopril together in T1&T2 group. This finding is similar to that reported by Patrick and Kamath, (1996)\(^4\).

Alanine transaminase

Significant increase in serum ALT levels in both T1&T2 captopril group in the period of 1.5 & 3 month in comparison with pretreatment period and control group. This finding is similar to that of in Patrick and Kamath, (1996)\(^4\).

The transaminase increase could be due to the hypotensive effect of captopril in healthy animals causing ischemic hepatitis as reported in the study done by Abd El-Aziz, et al., (2001)\(^7\).

Same significant increase was seen in serum ALT after treatment with aspirin in aspirin treated groups, this finding is similar to that of Ebong, et al., (1998)\(^5\). Besides a significant increase in serum ALT levels after aspirin and captopril treatment, due to hepatitis induced by these drugs were observed by Fries, et al., (1992)\(^6\) and Stolz and Kaplowitz, (1990)\(^8\).

ALT is more sensitive clinical enzyme than AST as indicator about liver function and liver damage due to disease or toxicity (Cheng and Harris, 2004)\(^9\). The increase in ALT enzyme levels positively proportional with increase in dosing with aspirin and captopril or both drugs as well as the treatment period that indicate, there is either increase in physiology of liver function or liver cell damage due to the long runuse of these drugs (coles, 1974)\(^10\).

Alkaline Phosphate

The present results indicate significant increase in serum AP levels for different doses of captopril at 1.5 months period and higher one at 3 months period in T1&T2 groups in comparison with that of the control group and experimental periods. This finding is similar to that of Parker, (1984)\(^11\). who reported high serum AP levels in captopril dosed old black female that developed secondary hepatic dysfunction.

The same significant increase was noticed in the effect of aspirin in T1 & T2 groups at different treatment periods. This finding is similar to Das and Dasgupta, (1997)\(^12\).
Also a significant increase in serum enzyme levels noticed in both aspirin + captopril dosed groups, positively proportional with the doses and treatment periods and this may be due aspirin and Captopril-induced hepatitis. AP is a good clinical enzyme indicator about the damage in skeletal muscle disorder, bone disease and intestinal empty. The increase in AP enzyme level in experimental groups positively proportional with the doses and treatment periods suggest such changes.

Reference


Abstract:

Transient Synovitis Versus Septic Arthritis of The Hip: The Value of Esr & Wbc Count

Ibrahim H. Witwit

Babil Medical College