Elevated Serum Transaminase Values in Volunteers after Administration of Placebo in a Phase I Study

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Serum transaminase (AST and ALT) values were monitored after administration of placebo to 104 healthy male volunteers for a phase I study. Both values remained within normal ranges in most of them. However, AST or ALT was above the normal range in 13 volunteers (12.5%). Their clinical features were ALT>AST, high serum γ-glutamyl transpeptidase, high serum triglyceride, high obesity index, or a combination of any of the four. We concluded that AST or ALT is likely elevated in volunteers showing these clinical signs; this should be noted in the evaluation of drug toxicity in future phase I studies.

Key words: phase I study, serum transaminase, serum γ-GTP, serum triglyceride, obesity index

Introduction

Phase I studies of new drugs typically include "healthy" male volunteers in whom all clinical examination results are within normal ranges. Placebos or pharmacologically inactive compounds are also administered as the control in these studies. However, we found that serum AST (aspartate aminotransferase, GOT) or ALT (alanine aminotransferase, GTP) was above the normal range in some volunteers after the administration of placebo. These enzyme levels might have a wide intra-individual variation in volunteers under physiological or normal conditions.

We investigated the clinical characteristics of these volunteers in whom AST or ALT was elevated to determine whether or not this elevation could be predicted from any clinical tests.

Subjects and Methods

We studied 104 male volunteers who received a single or multiple (maximum 7 times) administration of placebo for phase I studies in the Kitasato University East Hospital. All of the volunteers gave informed consent, and the studies were permitted by the Institutional Review Board.
Clinical examinations such as urine examination, blood examination, electrocardiogram and vital signs of the volunteers were taken 4 weeks before the administration of placebo. The volunteers who gave any abnormal results at these preliminary examinations were excluded from the study. Blood was collected for examination one hour before the first administration, and one and 7 days after the final administration. When AST or ALT was above the normal range even 7 days after the final administration, blood was collected for tests until the value returned to the normal range. The blood was always collected before breakfast.

**Results**

In most of the volunteers, the serum transaminase values were within the normal range after the administration (91/104=87.5%). Thirteen volunteers (13/104=12.5%) gave high AST (≥28 IU/L) or high ALT (≥35 IU/L) once or more times after the administration. The clinical features of the “transaminase elevated group” were compared with those of the “non-elevated group”. Figure 1 shows the time courses of AST and ALT of each group. Mean values of both AST and ALT of the elevated group were higher than those of the non-elevated group even before the administration. After the administration, AST rose to 25.8±5.4 IU/L (mean±S.D., range 18~33; highest value was taken for the calculation from several measurements of each volunteer), and that of the non-elevated group remained at 16.5±4.6 (range 8~27 IU/L). ALT of the elevated group rose to 45.1±13.3 (range 34~77), and that of the non-elevated group remained at 13.9±7.7 (range 3~33 IU/L).

Figure 1 shows that the mean AST value was also greater than the mean ALT value (AST>ALT) in the non-elevated group. In contrast, the mean ALT value was greater (ALT>AST) in the elevated group. The same tendency is shown in Table 1 as: AST≥ALT in the majority of the non-elevated group (76.9% four weeks before and 73.6% one hour before the administration), ALT>AST in all in the elevated group (100% four weeks before and 100% one hour before the administration).

The age, obesity index, serum γ-glutamyl transpeptidase (γ-GTP), and serum triglyceride levels
Tab. 1 Number of the Subjects with AST≥ALT before the Placebo Administration

<table>
<thead>
<tr>
<th>Group</th>
<th>4 weeks before</th>
<th></th>
<th>1 hour before</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AST≥ALT</td>
<td>AST&lt;ALT</td>
<td>AST≥ALT</td>
</tr>
<tr>
<td>Non-elevated group (n=91)</td>
<td>76.9% (n=70)</td>
<td>23.1% (n=21)</td>
<td>73.6% (n=67)</td>
</tr>
<tr>
<td>Elevated group (n=13)</td>
<td>0% (n=0)</td>
<td>100% (n=13)</td>
<td>0% (n=0)</td>
</tr>
<tr>
<td>p &lt;0.01</td>
<td>p &lt;0.01</td>
<td>p &lt;0.01</td>
<td>p &lt;0.01</td>
</tr>
</tbody>
</table>

Tab. 2 Age, Obesity Index, Serum γ-GTP and Serum Triglyceride 4 Weeks before the Placebo Administration

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (year)</th>
<th>Obesity index&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>γ-GTP&lt;sup&gt;b&lt;/sup&gt; (IU/L)</th>
<th>Triglyceride&lt;sup&gt;c&lt;/sup&gt; (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-elevated group (n=91)</td>
<td>29.1±6.23</td>
<td>-0.195±9.64</td>
<td>19.0±10.1</td>
<td>88.5±40.0</td>
</tr>
<tr>
<td>Elevated group (n=13)</td>
<td>32.2±8.08</td>
<td>7.95±9.60</td>
<td>34.5±19.7</td>
<td>127.8±66.6</td>
</tr>
<tr>
<td>p &lt;0.01</td>
<td>p &lt;0.01</td>
<td>p &lt;0.01</td>
<td>p &lt;0.01</td>
<td>p &lt;0.01</td>
</tr>
</tbody>
</table>

<sup>a</sup>) obesity index (%)=(body weight−standard body weight)/(standard body weight)×100
<sup>b</sup>) standard body weight=(height−100)×0.9; weight in kg and height in cm
<sup>c</sup>) normal range of γ-GTP: 6~60 IU/L
<sup>c</sup>) normal range of triglyceride: 20~160 mg/dl

are shown in Table 2. The age was not significantly different between the two groups. The obesity index of the elevated group was significantly higher than that of the non-elevated group (p<0.01). The γ-GTP value of the elevated group 4 weeks before administration was significantly higher than that of the non-elevated group (p<0.01). The median values in the elevated group were 11.5% for the obesity index, 32 IU/L for γ-GTP and 122 mg/dl for triglyceride, which might be used as the cutoff values. No significant differences were found (p>0.01) in all the other tests such as lactate dehydrogenase, cholinesterase, alkaline phosphatase, glucose, cholesterol, albumin and total protein.

**Discussion**

The result in the present report was in accordance with that of our previous report<sup>1</sup>). The volunteers in our previous study took a non-toxic dose of pharmacologically active drugs, but it was possible that the elevation of AST or ALT was due to the active drugs. In the present study the volunteers took placebos which were inactive pharmacologically and toxicologically. Therefore, the elevation of AST or ALT could not be the result of the toxicity of the given compound, but might be the result of a change in environmental, physiological, or pathological factors. According to Kanamaru et al.<sup>2</sup>), ALT elevation during a Phase I study was due to the imbalance of energy supply and consumption,
that is, gain of food intake and lack of physical exercise. The elevation of the serum enzymes observed in some volunteers in the present report might also be due to energy imbalance.

It has been reported that the AST value is higher than the ALT value in most healthy subjects\(^5\).\(^6\). Therefore, some volunteers with AST < ALT might not be healthy even though these value are within the normal range. ALT fluctuated more widely than AST in the present report, and elevation of ALT was more frequently seen than that of AST. These results are in accordance with the fact that ALT in the liver cell leaks into blood with slight damage of the liver cell membrane, whereas AST leaks only in gross cellular necrosis or in chronic liver damage\(^5\).\(^6\).

The obesity index and the triglyceride concentration of the elevated group were higher. This result was supported by the following results: 1) hepatic fatty change was associated with a high obesity index and high triglyceride concentration\(^7\)\(^9\), 2) ALT was slightly high and greater than AST in obese subjects\(^10\)\(^11\).

It is well known that \(\gamma\)-GTP rises after drinking alcohol and immediately returns to the normal level and that \(\gamma\)-GTP remains high in heavy drinkers\(^5\)\(^12\). Since alcohol drinking was prohibited and controlled in the present study, the high \(\gamma\)-GTP values obtained were not considered to be the result of alcohol intake.

The following characteristics appear to indicate a possible elevation of AST or ALT: ALT > AST, high obesity index (>11.5%), high \(\gamma\)-GTP (>32 IU/L), and high triglyceride (>122 mg/ml). The cutoff values described in parentheses are the median in the elevated group. We conclude that these factors should be considered in the evaluation of AST or ALT elevation in Phase I studies.

References