Changes in Plasma Bile Acid Levels Following Challenge Test for Drug Suspected to Cause Liver Injury and Their Clinical Significance in Drug-Induced Liver Injury

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In this paper, changes in total bile acid levels in comparison with serial results of conventional blood biochemical analyses in the clinical course after a challenge test for a drug suspected of causing liver injury in five patients with drug-induced liver injury were described and the clinical significance was discussed. On the basis of this investigation, it can be concluded that the estimation of bile acid levels in plasma in the clinical course after the challenge test increases the diagnostic and discriminatory capacities of liver function tests in drug-induced liver injury, i.e., total and basic bile acid levels in plasma promptly reflect altered hepatic cell function after the challenge test.

(Key Words: Drug-induced Liver Injury, Total Bile Acid Level, Basic Bile Acid Level, Challenge Test, Lymphocyte Stimulation Test)

INTRODUCTION

In drug-induced liver injury, the challenge test, lymphocyte stimulation test (blastoid transformation reaction), macrophage migration inhibition test and leucocyte migration inhibition test for drugs thought to cause liver injury, are utilized as diagnostic procedures. Among these diagnostic tools, the challenge test for drugs inducing liver injury is regarded as the most sensitive and reliable diagnostic procedure while the others are somewhat less sensitive although they are diagnostically effective in practice. The challenge test must be performed carefully because the drug inducing liver injury is given again to the patient.

Previously, the author pointed out that bile acid levels in plasma can be utilized as a diagnostic procedure not only in inflammatory liver diseases and fatty liver but also in drug-induced liver injury \( (4, 5, 7) \) because bile acid metabolism seems to reflect sensitively the state of hepatic cell function.

The challenge test for drugs suspected to cause liver injury results in liver injury to a certain extent if the repeatedly administered drug really induces to the liver disease. It must be clarified that changes of bile acid levels in plasma can be influenced by altered hepatic cell functions following the challenge test no matter whether the changes in hepatic cell function are minute or severe.

This paper describes the changes of bile acid levels in plasma following the challenge test for drugs thought to cause liver injury and their clinical significance in drug-induced liver injury.

MATERIALS AND METHODS

Total bile acid levels in blood plasma in the clinical course after the challenge test for the drug suspected to cause liver injury were estimated in five patients with drug-induced liver injury in the convalescent stage according to the method to Sandberg et al \( (11) \). The blood used for the estimation was collected from these patients on an empty stomach every day in the clinical course after the challenge test until blood biochemical data after the challenge test became constant. Among these five patients, neurotropic agents caused liver injury in two patients, anesthetics in two patients and anti-inflammatory agents in one. In these patients, the challenge test for a single regular dose of the drug thought to cause liver injury was performed. The correlation of bile acid levels in

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plasma with each item in the conventional blood biochemical analyses for liver function diagnosis and percentage of eosinophilic leucocytes in circulating peripheral blood were also investigated. The lymphocyte stimulation test (blastoid transformation reaction) for suspected drug was also performed.

RESULTS

Age and sex distribution as well as total and basic bile acid levels in plasma in these five patients are summarized in Table 1 according to each type of drug in comparison with the estimated total and basic bile acid levels in the plasma of 60 healthy control subjects on admission.

In a 41 year-old female patient and a male patient of the same age, neurotropic agents, i.e., primidone and imipramine hydrochloride, respectively, caused drug-induced liver injury of the hepatitic type and the estimated total and basic bile acid levels in plasma revealed a similar pattern in composition and quantities on admission. In addition, lymphocyte stimulation tests for the suspected drug were positive in the former case and negative in the latter.

In 40 year-old and 63 year-old male patients, an anesthetic, i.e., pentobarbital, caused drug-induced liver injury of the hepatitic type and the estimated basic bile acid levels in plasma revealed similar patterns in composition, whereas the estimated total and basic bile acid levels in plasma were high in the former patient. The stage of the disease might be responsible for the differences in the estimated bile acid levels in the plasma of these two patients. The lymphocyte stimulation test for the suspected drug was positive in the former case and negative in the latter. In these four patients, positive reaction to the challenge test for the drugs suspected of causing liver injury could be confirmed.

In a 23 year-old male patient, an anti-inflammatory agent, i.e., an aspirin- and acetylsalicylic acid combination caused drug-induced liver injury of the cholestatic type and the estimated total and basic bile acid levels in the plasma, in quantity and in composition respectively, were obtained on admission. In this case, the lymphocyte stimulation test for the suspected drug was positive but the challenge test showed no positive reaction.

The serial changes in total bile acid levels, serum transaminase activity and total bilirubin levels in serum in the clinical course after the challenge test for the suspected drug in these five patients are summarized in Figure 1.

In two patients with drug-induced liver injury due to neurotropic agents, serum transaminase activity and total bilirubin level increased gradually from the day after the challenge test reached the highest level, i.e. the third day after the challenge test, and then gradually reached a plateau by the 7th day. Changes of total bile acid levels in plasma were rather remarkable and more rapid than the above-mentioned blood biochemical items, i.e., the estimated total bile acid level reached the highest level on the second day after the challenge test. The maximum level was more striking than that of the other blood biochemical items, and the estimated total bile acid levels in plasma were restored to normal on the 8th day.

In two patients with drug-induced liver injury due to anesthetics, the estimated total bile acid levels and serum transaminase activity underwent a similar transition in the clinical course after the challenge test, while the estimated levels of total bilirubin showed no marked changes. Total bile acid level in plasma and serum transaminase activity were elevated to the highest level on the day after the challenge test for the suspected drug and came down gradually. Eventually, serum transaminase activity was restored to normal on the 7th day and total bile acid level in plasma was normalized by the 10th day after the challenge test. In addition, eosinophilia of 16% in the circulating peripheral blood could be confirmed on the 3rd day after the challenge test in the 63 year-old male patient, while no eosinophilia could be found in the 40 year-old male patient (3).

In the 23 year-old male patient with drug-induced liver injury due to anti-inflammatory agents, in whom the challenge test for the suspected drug showed negative results in spite of the positive reaction to the lymphocyte stimulation test, the estimated total bile acid levels in plasma changed slightly with a similar pattern as the changes of total bilirubin levels in the above-mentioned four patients who showed positive reactions to the challenge test.
In short, it can be said that total bile acid levels in plasma promptly reflect the altered hepatic cell function following a challenge test for suspected drug, because total bile acid levels began to increase promptly after the challenge test and were restored to normal several days later than the normalization of the elevated serum transaminase activity in the patients with drug-induced liver injury.

DISCUSSION

Since the estimation of total and basic bile acid levels in plasma came to be performed in practice, its clinical significance has been discussed. In accordance with some authors, it appears that fasting bile acid levels in plasma were higher in patients with liver diseases than in healthy control subjects and were significantly higher in severe liver diseases than in mild liver diseases, and that bile acid levels in plasma were closely correlated with cytolysis and protein synthesis (1, 2, 6, 7, 9, 10). It should be also stressed that the estimated bile acid levels increase the diagnostic and discriminatory capacities of liver function tests and are more sensitive and discriminatory when blood from patients is obtained on an empty stomach than when it is obtained postprandially (2).

In drug-induced liver injury, diagnosis used to be made on the basis of administration of the suspected drug, the lymphocyte stimulation test, macrophage migration test, leucocyte migration test and conventional blood biochemical analyses. The author prefers to utilize the challenge test and lymphocyte stimulation test because of practical convenience and facilities in the author’s clinic. Positive reaction in the challenge test for suspected drug together with positive reaction in the lymphocyte stimulation test assures a probability of 91% (8). In two out of four patients in whom the challenge test for the suspected drug gave a positive reaction for liver injury, the lymphocyte stimulation test was positive and in the remaining two patients, this diagnostic procedure gave a negative reaction. This inconsistency among the results of these diagnostic procedures did not depend on the quality of the drug. In any case, the challenge test for the drug suspected of causing liver injury was positive in these four patients and changes of total bile acid levels in plasma were more sensitive than the results of conventional liver function tests.

In addition, it was noteworthy that total bile acid levels increased promptly on the day following the challenge test for the suspected drugs, decreased gradually and were normalized by the 10th day, whereas the results of conventional blood biochemical analyses remained within the normal range in a 23 year-old male patient, i.e., in this case, the challenge test result was negative and the lymphocyte stimulation test positive. In spite of this fact, total bile acid levels underwent a transition in challenge test for the drugs suspected of liver injury, i.e., changes of total bile acid levels in plasma were more sensitive than the results of conventional blood biochemical analyses.

Taking into consideration the previously reported data on total and basic bile acid levels in plasma of 20 patients with drug-induced liver injury, it can be concluded that the estimation of bile acid levels in plasma in the clinical course after the challenge test for the drug suspected of causing liver injury increases the diagnostic and discriminatory capacities of liver function tests in drug-induced liver injury, i.e., total and basic bile acid levels in plasma promptly reflect the altered hepatic cell function after the challenge test.

REFERENCES
Table 1  Total and basic bile acid levels in plasma in five patients with drug-induced liver injury on admission and in healthy control subjects.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Age</th>
<th>Sex</th>
<th>Histologic findings</th>
<th>Basic bile acid levels in plasma (ug/ml)</th>
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<tbody>
<tr>
<td>Healthy control group</td>
<td></td>
<td></td>
<td></td>
<td>CDCA</td>
</tr>
<tr>
<td>(n = 60)</td>
<td></td>
<td></td>
<td></td>
<td>0.37 ±</td>
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<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td>Histologic findings</td>
<td>CDCA</td>
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<tr>
<td>Neurotropic agents</td>
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<td></td>
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<td>0.11</td>
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<tr>
<td>Primidone</td>
<td>41</td>
<td>F</td>
<td>hepatic</td>
<td>6.11</td>
</tr>
<tr>
<td>Imipramine hydrochloride</td>
<td>41</td>
<td>M</td>
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<td>5.83</td>
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<td>Penthorane</td>
<td>40</td>
<td>M</td>
<td>hepatic</td>
<td>9.61</td>
</tr>
<tr>
<td>Penthorane</td>
<td>63</td>
<td>M</td>
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<td>6.33</td>
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<tr>
<td>Anti-inflammatory agents</td>
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<td>1.31</td>
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<tr>
<td>Aspirin + Acetoaminofen</td>
<td>23*</td>
<td>M</td>
<td>cholestatic</td>
<td>7.44</td>
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<td>* Icterus (+)</td>
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</table>
Fig. 1  Changes of total bile acid levels in plasma, serum transaminase activity and total bilirubin levels in serum in the clinical course after the challenge test for the drug suspected of liver injury in five patients with drug-induced liver injury.