Drug Metabolizing Activity in Chronic Liver Disease: A Study Using Ultrasonically-Guided Needle Biopsy

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Key words: drug metabolizing activity, chronic liver disease, ultrasonically-guided liver biopsy, cytochrome P-450, elimination half-life of theophylline, liver function tests

Summary
Drug metabolizing activity in chronic liver disease was examined. In 53 patients with chronic liver disease, 7-methoxycoumarin (7-MC) O-demethylase and 7-ethoxycoumarin (7-EC) O-deethylase activities in liver specimens obtained by ultrasonically-guided liver biopsy were measured and compared with the elimination half-life (T1/2) of theophylline and biochemical liver function tests. Both the O-dealkylase activities toward 7-MC and 7-EC in the liver were gradually decreased with progressive histological impairment of the liver to 32.8% and 39.6% of the control level, respectively, in patients with liver cirrhosis. Both the O-dealkylase activities toward 7-MC and 7-EC in the liver inversely and exponentially correlated with the T1/2 of theophylline. These two O-dealkylase activities correlated well with serum albumin content (Alb), cholinesterase (ChE), prothrombin time (PT), heparastintest (HPT), cholesterol ester ratio (E/T), zinc sulfate turbidity test (ZTT), the ratio of branched chain amino acids to aromatic amino acids (BCAA/AAA) or indocyanine green test (ICG), but not with GPT, LAP or total cholesterol. These findings indicate that the activity of drug metabolizing enzymes reflect hepatic functional capacity, and the measurement of these activities in specimens obtained by liver biopsy is useful for the clinical estimation of liver functions.

Introduction
The liver is the major site of drug metabolism. Many hydrophobic compounds, including drugs, chemicals, environmental pollutants and carcinogens, are biotransformed into more hydrophilic metabolites in liver microsomes. In rats with chronic liver injury induced by carbon tetrachloride (CCl4) and a choline-deficient diet, the drug metabolizing activity in liver microsomes is known to be impaired with progressive histological impairment of the
liver.

On the other hand, the drug metabolizing activity in patients with chronic liver disease has been investigated mainly by means of the elimination half-lives of several drugs, such as theophylline and antipyrine, which are chiefly metabolized in the liver. The drug metabolizing activity in human liver microsomes has been reported using specimens obtained by autopsy and during operations; however, there have been few reports involving specimens obtained by liver biopsy.

In recent years, ultrasonically-guided (US-guided) needle biopsy has been widely used in Japan because of its safety and simplicity; it has been reported that 7-alkoxycoumarin O-dealkylase activities can be measured using 10 mg of a liver specimen.

In the present study, 7-methoxycoumarin (7-MC) O-demethylase and 7-ethoxycoumarin (7-EC) O-deethylase activities in the liver obtained by US-guided biopsy were measured in patients with a variety of chronic liver diseases and compared with the degree of histological impairment of the liver. The elimination half-life (T1/2) of theophylline and biochemical liver function tests were also investigated in each patient and compared with the drug metabolizing activity in the liver.

Materials and Methods

Subjects

US-guided liver biopsy by a fine needle was performed on a total of 53 patients with chronic liver disease. The patients consisted of 20 females and 33 males and their average age was 48.1 years old. A part of the liver tissue obtained was used for the assay of drug metabolizing activity and the remains were fixed in formalin for histological examination. Informed consent had been obtained from each patient.

The degrees of histological impairment of the liver were classified into four grades according to the classification by the European Association for the Study of the Liver (1968): 12 patients with chronic persistent hepatitis (CPH), 11 patients with chronic aggressive hepatitis (moderate) (CAH 2A), 8 patients with chronic aggressive hepatitis (severe) (CAH 2B) and 20 patients with liver cirrhosis (LC). In two patients, histological findings of the liver were revealed to be normal: a patient with elevated serum transaminases who was finally diagnosed as polymyositis, and a patient on whom liver biopsy was performed in order to deny a liver tumor.

None had significant cardiac decompensation and renal functions of all the patients were normal. Some of the patients were taking drugs, such as furosemide, but none was receiving compounds known to induce or reduce the activity of drug metabolizing enzymes.
smokers (over 1 pack per day) and patients with obvious alcoholic liver disease were excluded.

**Assays of drug metabolizing activity in the liver**

A piece (about 10 mg wet weight) of the liver tissue was immediately homogenized in 0.8 ml of 20 mM potassium phosphate buffer (pH 7.4) containing 15% glycerol at 0—4°C. 7-MC O-demethylase and 7-EC O-deethylase activities were determined by a direct fluorometric measurement of 7-hydroxycoumarin produced according to the method of Ullrich and Weber\(^1\). The substrates, 7-EC and 7-MC, were dissolved in 1 M Tris-HCl buffer (pH 7.6) to give \(10^{-3}\) M solutions. The incubation mixture consisted of whole liver homogenate, \(10^{-4}\) M substrate and \(10^{-4}\) M NADPH in 1.0 ml of 0.1 M Tris-HCl buffer (pH 7.6). The reaction was started by adding NADPH (10 \(\mu\)l, \(10^{-2}\) M) and the mixture was incubated aerobically at 37°C. The increase in the fluorescence intensity with time was measured at 460 nm with an excitation of 372 nm using a fluorescence spectrophotometer (Hitachi, 650-60). 7-EC and 7-MC were purchased from Nakarai Chemicals (Kyoto) and Aldrich Chemical Co. (Milwaukee, WI, U.S.A.), respectively.

**Elimination half-life (T1/2) of theophylline**

The patients abstained from xanthine-containing foods and drinks (e.g. coffee, tea, cola, chocolate) for 2 days prior to blood sampling.

Each patient received a single intravenous infusion of 250 mg theophylline ethylenediamine (Neophylline®, Eisai Co., Tokyo) in 230 ml 5% glucose in water, over a period of 60 min at a constant rate. Blood samples were collected from the contralateral arm at 0.5, 1, 2, 4, 7 and 11 hr after the end of the infusion. Serum theophylline concentrations were determined by an enzyme immunoassay (EMIT\(^1\))\(^7\). The T1/2 of theophylline was read from the linear part of the time concentration curve on a semilog graph.

**Blood biochemistry**

Blood samples for liver function tests were taken after an overnight fast. Liver function tests investigated were as follows: glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), alkaline phosphatase (ALP), leucine aminopeptidase (LAP), serum albumin content (Alb), cholinesterase (ChE), prothrombin time (PT), heparplastin-test (HPT), total cholesterol (T-Chol), cholesterol ester ratio (E/T), zinc sulfate turbidity test (ZTT), the ratio of branched chain amino acids to aromatic amino acids (BCAA/AAA), and indocyanine green test (15 min retention rate, ICGR\(_{15}\) and plasma disappearance rate, KICG). Each was measured by routine clinical methods.

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Statistical analysis
Significance of difference was determined by Wilcoxon rank sum test.

Results

Drug metabolizing activity in the liver of patients with chronic liver disease

The 7-MC O-demethylase and 7-EC O-deethylase activities (/g liver) in the liver of patients with chronic liver disease are shown in Figs. 1 and 2. The ratio of 7-EC O-deethylase to 7-MC O-demethylase activity in each group is shown in Table 1.

The mean value of the two patients with normal livers were taken as the control (100%). The 7-MC O-demethylase activities in patients with CPH, CAH 2A, CAH 2B and LC were

7-MC demethylation

Fig. 1 7-methoxycoumarin (7-MC) O-demethylase activity in the liver of patients with normal liver and chronic liver disease. The degrees of histological impairment of the liver were classified into four grades: chronic persistent hepatitis (CPH), chronic aggressive hepatitis (moderate) (CAH 2A), chronic aggressive hepatitis (severe) (CAH 2B) and liver cirrhosis (LC). Vertical bars represent the mean±S.D.
7-EC deethylation

Fig. 2 7-ethoxycoumarin (7-EC) O-deethylase activity in the liver of patients with normal liver and chronic liver disease. The degrees of histological impairment of the liver were classified into four grades: chronic persistent hepatitis (CPH), chronic aggressive hepatitis (moderate) (CAH 2A), chronic aggressive hepatitis (severe) (CAH 2B) and liver cirrhosis (LC). Vertical bars represent the mean±S.D.

Gradually decreased to 90.3%, 74.7%, 50.4% and 32.8% of the control level, respectively. No significant difference was observed among patients with normal liver, CPH and CAH 2A. The activity in patients with CAH 2B was significantly lower than in patients with normal liver, CPH and CAH 2A. In patients with LC, the activity was much lower and significantly different from any other group.

Similarly, the 7-EC O-deethylase activities in patients with CPH, CAH 2A, CAH 2B and LC were gradually decreased to 80.3%, 67.5%, 53.7% and 39.6% of the control level, respectively. No significant difference was observed between patients with normal liver and CPH. The activity in patients with CAH 2A was significantly lower than that in patients with normal liver, but no significant difference was observed between patients with CPH and CAH 2A. The activity in patients with CAH 2B was significantly lower than in
Table 1  A comparison of 7-methoxycoumarin (7-MC) O-demethylase and 7-ethoxycoumarin (7-EC) O-deethylase activities in the liver of patients with normal liver and chronic liver disease

<table>
<thead>
<tr>
<th></th>
<th>7-MC</th>
<th>7-EC</th>
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<tbody>
<tr>
<td></td>
<td>O-demethylation</td>
<td>O-deethylation</td>
</tr>
<tr>
<td></td>
<td>(nmol/g liver/min)</td>
<td>(nmol/g liver/min)</td>
</tr>
<tr>
<td>Normal (N)</td>
<td>17.06 ± 0.81</td>
<td>5.08 ± 0.55</td>
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<tr>
<td></td>
<td>(1.00)</td>
<td>(0.30)</td>
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<tr>
<td>CPH</td>
<td>15.40 ± 3.56</td>
<td>4.08 ± 1.24</td>
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<tr>
<td></td>
<td>(1.00)</td>
<td>(0.26)</td>
</tr>
<tr>
<td>CPH/N×100 (%)</td>
<td>90.3</td>
<td>80.3</td>
</tr>
<tr>
<td>CAH 2A</td>
<td>12.74 ± 3.09</td>
<td>3.43 ± 0.77</td>
</tr>
<tr>
<td></td>
<td>(1.00)</td>
<td>(0.27)</td>
</tr>
<tr>
<td>CAH 2A/N×100 (%)</td>
<td>74.7</td>
<td>67.5</td>
</tr>
<tr>
<td>CAH 2B</td>
<td>8.59 ± 2.52</td>
<td>2.73 ± 0.61</td>
</tr>
<tr>
<td></td>
<td>(1.00)</td>
<td>(0.32)</td>
</tr>
<tr>
<td>CAH 2B/N×100 (%)</td>
<td>50.4</td>
<td>53.7</td>
</tr>
<tr>
<td>LC</td>
<td>5.59 ± 2.21</td>
<td>2.01 ± 0.98</td>
</tr>
<tr>
<td></td>
<td>(1.00)</td>
<td>(0.36)*</td>
</tr>
<tr>
<td>LC/N×100 (%)</td>
<td>32.8</td>
<td>39.6</td>
</tr>
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</table>

The degrees of histological impairment of the liver were classified into four grades: chronic persistent hepatitis (CPH), chronic aggressive hepatitis (moderate) (CAH 2A), chronic aggressive hepatitis (severe) (CAH 2B) and liver cirrhosis (LC). Each value represents the mean±S.D. *significantly different from the values in CPH and CAH 2A (P<0.05).

patients with normal liver, CPH and CAH 2A. In patients with LC, the activity was much lower and significantly different from any other group.

The ratios of 7-EC O-deethylase to 7-MC O-demethylase activity in patients with normal liver, CPH, CAH 2A, CAH 2B and LC were 0.30±0.03, 0.27±0.05, 0.27±0.05, 0.33±0.07 and 0.35±0.08 (mean±S.D.), respectively. The ratio in patients with LC was significantly different from those in patients with CPH and CAH 2A.

Theophylline T1/2 in patients with chronic liver disease

As shown in Fig. 3, the theophylline T1/2 in patients with normal liver was 5.9 ± 2.0 hr; those in patients with CPH, CAH 2A, CAH 2B and LC were gradually prolonged to 5.9 ± 1.4, 7.3 ± 2.0, 9.9 ± 3.3 and 17.3 ± 6.7 hr, respectively. No significant difference was observed among patients with normal liver, CPH and CAH 2A. The theophylline T1/2 in patients with CAH 2B was significantly longer than that in patients with CPH, but no significant difference was observed between patients with CAH 2A and CAH 2B. In patients with LC, the theophylline T1/2 was markedly prolonged and significantly different from any other group.
Fig. 3 The elimination half-life of theophylline in patients with normal liver and chronic liver disease. Theophylline ethylenediamine (250 mg) was administered intravenously over 60 min at a constant rate. The degrees of histological impairment of the liver were classified into four grades: chronic persistent hepatitis (CPH), chronic aggressive hepatitis (moderate) (CAH 2A), chronic aggressive hepatitis (severe) (CAH 2B) and liver cirrhosis (LC). Vertical bars represent the mean±S.D.

Fig. 4 Correlations between the elimination half-life (T1/2) of theophylline and 7-methoxycoumarin (7-MC) O-demethylase (A) or 7-ethoxycoumarin (7-EC) O-deethylase (B) activity in the liver.

Correlation between theophylline T1/2 and drug metabolizing activity in the liver

The theophylline T1/2 was gradually prolonged with the decreases in 7-MC O-demethylase (Fig. 4A) and 7-EC O-deethylase (Fig. 4B) activities in the liver. Good logarithmic correlations were observed between the theophylline T1/2 and the 7-MC O-demethylase or 7-EC O-deethylase activity in the liver with coefficient values of −0.841 and −0.696, respectively.

Relationship between drug metabolizing activity in the liver and biochemical liver function tests

There were no significant correlations between the 7-MC O-demethylase activity in the liver and serum GPT or LAP, and weak correlations were observed between this enzyme activity and GOT or ALP (Fig. 5). In contrast, fair correlations were observed between the 7-MC O-demethylase activity in the liver and Alb, ChE, PT or HPT with coefficient values

![Graphs showing correlations between 7-methoxycoumarin (7-MC) O-demethylase activity in the liver and four biochemical liver function tests: glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), alkaline phosphatase (ALP), and leucine aminopeptidase (LAP).](image)

Fig. 5 Correlations between 7-methoxycoumarin (7-MC) O-demethylase activity in the liver and four biochemical liver function tests: glutamic oxaloacetic transaminase (GOT) (A); glutamic pyruvic transaminase (GPT) (B); alkaline phosphatase (ALP) (C); leucine aminopeptidase (LAP) (D).
Fig. 6 Correlations between 7-methoxycoumarin (7-MC) O-demethylase activity in the liver and four biochemical liver function tests: serum albumin content (Alb) (A); cholinesterase (ChE) (B); prothrombin time (PT) (C); hepatoplastintest (HPT) (D).

of 0.565, 0.657, 0.520 and 0.621, respectively (Fig. 6). There was no significant correlation between the 7–MC O-demethylase activity in the liver and T–Chol, but fair correlations were observed between this enzyme activity and E/T, ZTT or BCAA/AAA with coefficient values of 0.642, −0.618 and 0.637, respectively (Fig. 7). On the other hand, there were good logarithmic correlations between the 7–MC O-demethylase activity in the liver and ICGR15 or KICG with coefficient values of −0.700 and 0.759, respectively (Fig. 8).

As shown in Table 2, a similar tendency was observed concerning the relationships between the 7–EC O-deethylase activity in the liver and the liver function tests investigated; the correlation coefficients, however, were slightly smaller than those of the 7–MC O-de- methylase activity in the liver.
Fig. 7 Correlations between 7-methoxycoumarin (7-MC) O-demethylase activity in the liver and four biochemical liver function tests: total cholesterol (T-Chol) (A); cholesterol ester ratio (E/T) (B); zinc sulfate turbidity test (ZTT) (C); the ratio of branched chain amino acids to aromatic amino acids (BCAA/AAA) (D).
Fig. 8 Correlations between 7-methoxycoumarin (7-MC) O-demethylase activity in the liver and indocyanine green tests: 15 min retention rate (ICGR$_{15}$) (A) and plasma disappearance rate (KICG) (B).

### Table 2 Relationship between 7-ethoxycoumarin (7-EC) O-deethylase activity in the liver and biochemical liver function tests

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<tbody>
<tr>
<td>GOT (IU/l)</td>
<td>$-0.367^*$</td>
<td>HPT (%)</td>
<td>$0.447^*$</td>
</tr>
<tr>
<td>GPT (IU/l)</td>
<td>$0.033$</td>
<td>T-Chol (mg/dl)</td>
<td>$0.197$</td>
</tr>
<tr>
<td>ALP (IU/l)</td>
<td>$-0.254$</td>
<td>E/T (%)</td>
<td>$0.486^*$</td>
</tr>
<tr>
<td>LAP (IU/l)</td>
<td>$0.023$</td>
<td>ZTT (U)</td>
<td>$-0.585^*$</td>
</tr>
<tr>
<td>Alb (g/dl)</td>
<td>$0.420^*$</td>
<td>BCAA/AAA</td>
<td>$0.584^*$</td>
</tr>
<tr>
<td>ChE (IU/l)</td>
<td>$0.500^*$</td>
<td>ICGR$_{15}$ (%)</td>
<td>$-0.609^{**}$</td>
</tr>
<tr>
<td>PT (%)</td>
<td>$0.419^*$</td>
<td>KICG</td>
<td>$0.651^{**}$</td>
</tr>
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</table>

Abbreviations for liver function tests are the same as shown in Figs. 5 ~ 8. r: correlation coefficients. *significant correlation (P<0.01). *logarithmic correlation,
Discussion

Many investigators have reported in vivo studies in which the elimination of drugs metabolized in the liver was impaired in chronic liver disease\(^3\text{-}^5\)\). Since the rate of drug elimination from the blood is dependent not only on drug metabolizing enzymes in the liver but also on other factors, such as blood flow, binding to plasma proteins and liver size, the investigation of drug metabolizing activity in liver microsomes and a comparison with drug elimination in vivo are also important for estimating drug metabolizing activity in chronic liver disease.

In this study, both the \(O\)-dealkylase activities toward 7-MC and 7-EC per g liver were gradually decreased with progressive histological impairment of the liver; especially, the activities in patients with CAH 2B and LC were obviously lower than those in patients with CPH. Schoene et al.\(^1\text{0}\) reported similar results in which the content of cytochrome P-450 (P-450), and aminopyrine \(N\)-demethylase and p-nitroanisole \(O\)-demethylase activities in the liver were lowered only in severe hepatitis and LC. Kratz\(^1\text{1}\) also demonstrated that in patients with LC, chronic fatty (alcoholic) hepatitis and CAH, coumarin-7-hydroxylase activity in the liver was significantly lower, but there was no significant difference between patients with subacute viral hepatitis or CPH and normal controls. However, neither study referred to drug elimination in vivo. On the other hand, some investigators have reported that drug metabolizing activity in the liver was enhanced in chronic alcoholic liver damage\(^1\text{8},^1\text{9}\); in this study, patients with obvious alcoholic liver disease were excluded.

In these experiments, drug metabolizing activity in the liver was expressed per g liver, so that the decreases in the \(O\)-dealkylase activities toward 7-MC and 7-EC, especially in patients with CAH 2B and LC, may have reflected the relative decrease in the number of liver cells following the development of hepatic fibrosis as well as the reduction in the function of individual liver cells. In fact, in rats with chronic liver injury induced by \(CCl_4\), the content of P-450 and four substrate-metabolizing activities per g liver were reported to be 5—10\% lower than those per mg microsomal protein\(^1\text{1}\). There are two reasons why drug metabolizing activity in the liver were expressed per g liver in these experiments. First, the preparation of microsomes from a small amount of specimen obtained by liver biopsy is difficult by routine methods; \(O\)-dealkylase activities toward 7-MC and 7-EC can be measured using not only liver microsomes but also whole liver homogenates, as Matsubara et al.\(^2\text{0}\) already reported. Secondly, the drug metabolizing activity expressed per g liver is considered to be clinically more beneficial than that of individual liver cells; for example, if a liver volume can be determined by imaging techniques, the drug metabolizing activity of the total liver can be calculated from that per g liver.
P-450, which is a key enzyme in the mixed-function oxidase system in liver microsomes, consists of multiple species\(^1\); various physiological and pathological conditions affect the population of P-450 species. It was reported that some type(s) of P-450 species may have been selectively reduced in rats with chronic liver injury induced by CCl\(_4\)\(^1\) and a choline-deficient diet\(^2\). Recently, Okuno et al.\(^1\) demonstrated that the ratios of 7-EC O-deethylase and 7-propoxycoumarin (7-PC) O-depropylase to 7-MC O-demethylase activity in rats treated with six inducers were clearly different from each other. They emphasized that the measurement of 7-alkoxycoumarin O-dealkylase activities should be extremely useful for the routine determination of the molecular species of P-450. Kasahara et al.\(^2\) investigated the effects of D-galactosamine and CCl\(_4\) on 7-alkoxycoumarin O-dealkylase activities in rat liver microsomes. They reported that the ratio of 7-EC O-deethylase and 7-PC O-depropylase to 7-MC O-demethylase activity was not altered by D-galactosamine treatment, but decreased with CCl\(_4\) treatment, although all these activities were reduced by either treatment. In this study, both the O-dealkylase activities toward 7-MC and 7-EC were gradually decreased to similar extents with progressive histological impairment of the liver. However, the ratio of 7-EC O-deethylase to 7-MC O-demethylase activity in patients with LC was slightly but significantly different from those in patients with CPH and CAH 2A, so that there might be a possibility that some type(s) of P-450 species was selectively altered in human LC. Farrell et al.\(^1\) demonstrated that aryl hydrocarbon hydroxylase activity was lower in patients with severe hepatitis or active cirrhosis than in controls, but ethylmorphine demethylase activity was unchanged in the patients, and proposed the heterogeneity of P-450 species affected by human liver disease. Their report supports the observations in this study.

Theophylline is known to be metabolized chiefly in the liver. Its elimination from the blood is dependent mainly on drug metabolizing activity in liver microsomes; other factors such as hepatic blood flow and binding to plasma proteins are generally recognized to have little influence on theophylline elimination\(^2\). In this study, the theophylline T1/2 was gradually prolonged with progressive histological impairment of the liver, and was inversely correlated with the 7-MC O-demethylase and 7-EC O-deethylase activities in the liver. The correlation between them was not linear but exponential; the theophylline T1/2 was markedly prolonged in patients with LC. These findings indicate that the rate of theophylline elimination in patients with chronic liver disease is not dependent on the microsomal mixed-function oxidase system alone, and that other factors affect theophylline metabolism in the liver; for example, porto-systemic collaterals in LC should result in marked shunting and diminished effective liver perfusion, which results in reduced and delayed supply of theophylline to the liver. In fact,
Kimura⁴ reported that the theophylline T1/2 was significantly longer in cirrhotic patients with, rather than without, extrahepatic shunting (esophageal varices) evaluated by fiberscope. Sotaniemi et al.¹² demonstrated that the replacement of hepatic parenchyma by fibrous tissue resulted in decreases both in antipyrine clearance rate in vivo and P-450 content in the liver. They also reported that there was a logarithmic correlation between the kinetic parameters of antipyrine and the P-450 content in the liver, but they did not investigate substrate-metabolizing activities in liver microsomes.

In this study, neither the O-dealkylase activities toward 7-MC nor 7-EC in the liver correlated to serum GPT, LAP or total cholesterol, but good correlations were observed between these activities and the liver function tests which represent the protein-synthesizing ability of liver cells or ICG test. These findings indicate that drug metabolizing activity in the liver also reflects hepatic functional capacity, although from a different point of view. Kimura⁴ reported the relationship between theophylline elimination in vivo and liver function tests; Sotaniemi et al.¹² also reported the correlation between antipyrine T1/2 or P-450 content in the liver and some liver function tests, but neither of them referred to the substrate-metabolizing activities in liver microsomes.

Liver biopsy is indicated for every patient with liver disease in order to confirm the diagnosis. The specimens obtained are usually used for histological examination alone, but there might be a discrepancy between histological findings and liver cell functions. The enzyme assay reported here is very simple; results can be obtained within 30 min, if needed. Moreover, since this method requires only a small amount (about 10 mg) of liver specimen, it is possible to determine both the activity of drug metabolizing enzymes and hepatic histology with the same specimen. As was confirmed in this study, the activity of drug metabolizing enzymes in the liver reflect hepatic functional capacity; therefore, the measurement of drug metabolizing activity in specimens obtained by liver biopsy is extremely useful for the clinical estimation of liver cell functions.

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