Development of Dosage Design of Hepatic Metabolizing Drugs Using Serum Albumin Level in Chronic Hepatic Failure

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We have previously reported good correlations among serum aminotransferase (AST) activity, metabolic enzyme activity of CYPs, and total clearance (CL tot) of probe drugs in rats with acute hepatic failure induced by CCl 4 . In this study, we searched for new biochemical indicators that correlate with hepatic function and tried to simulate appropriate drug dosage in chronic hepatic failure. Model rats were prepared by administration of CCl 4 (1 ml/kg, s.c., 3 times/week) and used after 48 h after the last administration. Serum albumin concentration was time-dependently decreased and correlated well with 3 major biologic determinants of drug clearance, hepatic blood flow (HBF), intrinsic clearance (CL i� ), and the unbound fraction of drugs in plasma (f u ) after intravenous administration of cyclophosphamide, tolbutamide, zonisamide, and chlorzoxazone (as probe drugs for low hepatic extraction) and propranolol and lidocaine (as high-hepatic extraction drugs). By calculating these parameters based on prediction equations by the level of albumin, CL i� was obtained. As a result of having evaluated this model using administration of cyclosporin, there was a statistically significant relationship between predicted CL i� and observed CL i� . In conclusion, the value of serum albumin level is a useful parameter that correlates well with chronic hepatic function. We have shown that this quantitative administering design using serum albumin level can predict appropriate dosages of hepatic metabolizing drugs in chronic hepatic failure.

Key words dosage design; serum albumin concentration; chronic hepatic failure; disposition kinetics; low/high-hepatic extraction drug

To achieve optimum drug therapy, it is important to take into account changes of disposition kinetics under diseased physiological conditions. In patients with renal failure, serum creatinine level and creatinine clearance are useful indicators for optimum dosage design. On the other hand, we should also consider that the kinetics of many drugs are altered in patients with liver diseases, such as hepatitis, hepatocirrhosis, and hepatocarcinoma, but there is no useful indicator and procedure of dosage design for patients with hepatic failure. The capacity of the liver to metabolize drugs depends on hepatic blood flow (HBF) and liver enzyme activities, and both can be changed in liver failure. Drug disposition kinetics should also be considered influenced by the drug’s binding capacity to plasma proteins and protein concentration.

Clinically, it is important to establish appropriate drug therapy by predicting the metabolic ability in individual patients with liver disease. Dynamic tests of liver function have long been used. Such tests include the aminopyrine breath test and measurement of the elimination capacity for indocyanine green (ICG), galactose, and sorbitol. Furthermore, various probe drugs have been used as quantitative tests of liver function and degree of liver impairment, especially in relation to cytochrome P450 (CYP), which plays a major role in drug metabolism in the liver. However, it is not easy to utilize these procedures to determine dosage design in patients with hepatic impairment. Another method widely used is the Child Pugh classification for quantitative evaluation of cirrhotic patients, but this does not provide an accurate evaluation of hepatic impairment.

Therefore we considered that laboratory data might be useful to evaluate hepatic function and might be available as predictors of hepatic drug clearance. We previously reported that serum aspartate aminotransferase (AST) concentration appears a promising candidate as indicator to predict appropriate dose modification of drugs for patients with acute hepatic failure in rat model. The purpose of this study is to construct predicting equations for determination of total clearance of various drugs using laboratory data that reflect hepatic function. In this report, we show that quantitative dosage design of hepatic metabolizing drugs in rats treated with CCl 4 as a model of chronic hepatic failure is possible.

MATERIALS AND METHODS

Chemicals Lidocaine hydrochloride and chlorzoxazone were purchased from Sigma-Aldrich Co., Ltd. (MO, U.S.A.). Tolbutamide and CCl 4 were purchased from Wako Pure Chemicals Co., Ltd. (Osaka, Japan). Zonisamide was provided by Dainippon Pharmaceutical Co., Ltd. (Osaka, Japan). Cyclophosphamide (Endoxan™, containing 100 mg cyclophosphamide per vial) was purchased from Shionogi Pharmaceutical Co., Ltd. (Osaka, Japan). Propranolol (Indera™, containing 2 mg propranolol per 2 ml ampoule) was purchased from AstraZeneca Japan Co., Ltd. (Osaka, Japan). Cyclosporin A (Sandimmun™, containing 250 mg cyclosporin per 5 ml ampoule) was purchased from Fujisawa Pharmaceutical Co., Ltd. (Tokyo, Japan). Other chemicals were of reagent grade.

Animal Experiments All animal experiments were performed in accordance with guidelines of the Institutional Animal Care and Use Committee of the University of Kanazawa. Model rats for chronic hepatic failure were pre-
pared by subcutaneous administration of CCl₄ and used at 
48 h after the last administration. CCl₄ was dissolved in corn 
and administered at a dose of 1 ml/kg to male Wistar rats 
(4 weeks old, Nippon SLC Co., Ltd., Hamamatsu, Japan). 
Administration interval was 3 times/week (Monday, Wednes-
day, and Friday), maintained for 4, 8, or 12 weeks (1, 2, or 
3 months). Untreated control consisted of 4-week-old rats 
receiving corn oil alone. A 100 µl aliquot of chlorozoxane 
(10 mg/kg) and tolubutamide (10 mg/kg) dissolved in 7% 
NaHCO₃, zonisamide (10 mg/kg) dissolved in 50% ethanol, 
cyclophosphamide (90 mg/kg), propranolol (2 mg/kg), lidoc-
aine (10 mg/kg) or cyclosporin (10 mg/kg) in distilled water 
was injected via the femoral vein. Blood samples (350 µl 
each) were collected at designated time intervals from the 
jugular vein under light ether anesthesia. Plasma was sepa-
rated by centrifugation at 3000×g for 10 min and stored at 
−30 °C. HPLC assays for chlorozoxane,⁷ tolubutamide,⁸ 
zonisamide,⁹ cyclophosphamide,¹⁰¹¹ lidocaine,¹²¹³ cyclo-
sporine,¹⁴ and propranolol¹⁵ were carried out by means of 
the cited methods.

**Determination of Laboratory Data**  
Blood samples for laboratory data were collected from the jugular vein under light ether anesthesia and plasma was separated by centrifugation and stored at −30 °C. Measurements of laboratory data were conducted at SRL Co., Ltd. (Tokyo, Japan). Items of laboratory data examined in this work included activities of AST, alanine aminotransferase (ALT), and alkaline phosphatase (ALP) and concentration of albumin, total-bilirubin, and albumin/globulin ratio (A/G ratio) in plasma.

**Histological Examination**  
Samples from all lobes of the liver were immersed-fixed in 10% buffered formalin. Samples were embedded in paraffin and stained with silver at SRL Co., Ltd. (Tokyo, Japan).

**Determination of Hepatic Blood Flow**  
HBF was estimated by a modification of the reported procedure.¹⁶ ICG (5 mg/kg loading dose and 1.25 mg/h/kg maintenance dose) was given by injection into the femoral vein under light ether anesthesia. Plasma was obtained from blood samples taken from the hepatic artery and vein at 40 min after administration of ICG. ICG concentration in plasma was measured by BioSpec-1600 Spectrophotometer (Shimadzu, Kyoto, Japan) at a wavelength of 805 nm after 3-fold dilution.

**Determination of Serum Protein Binding of Drugs**  
To separate the free and protein-bound fractions, 900 µl of each serum sample was transferred to a centrifuge tube (Centrfree MPS, Millipore, Inc., Billerica, MA, U.S.A.) and centrifuged at 1000×g at 37 °C for 10 min. A 100 µl aliquot of the free fraction was obtained and stored at −20 °C until analysis; 100 µl of serum sample containing protein-bound and free drug was also stored at −20 °C until assay.

**Data Analysis**  
Pharmacokinetics parameters were estimated according to model-independent moment analysis as described by Yamaoka et al.¹⁷ The data were analyzed by Student's t-test to compare the unpaired mean values of two sets of data. The number of determinations is noted in each table and figure. Regression analysis was performed to determine whether the probability of predicted values was significantly related to observed values. A value of p<0.05 was taken to indicate a significant difference between sets of data.

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### Table 1. Biochemical Data in Vehicle Control and CCl₄-Treated Rats

<table>
<thead>
<tr>
<th>Control</th>
<th>CCl₄ treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>for 1 month</td>
</tr>
<tr>
<td>AST (IU/l)²</td>
<td>81±6</td>
</tr>
<tr>
<td>ALT (IU/l)³</td>
<td>41±6</td>
</tr>
<tr>
<td>ALP (IU/l)⁴</td>
<td>957±170</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.65±0.17</td>
</tr>
<tr>
<td>A/G ratio⁵</td>
<td>2.15±0.25</td>
</tr>
<tr>
<td>Total-bilirubin (mg/dl)</td>
<td>0.16±0.04</td>
</tr>
</tbody>
</table>

Data were measured at 48 h after treatment with several subcutaneous administration times of CCl₄ (1.0 ml/kg, 3 times/week) in rats. Each value represents the mean±S.D. (n=3–20).  
a. Aspartate aminotransferase.  
b. Alanine aminotransferase.  
c. Alkaline phosphatase.  
d. Albumin/globulin ratio.  
* ** Significantly different from vehicle control at p<0.05, p<0.01.

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### RESULTS

**Laboratory Data in Rats with Chronic Hepatic Failure**  
Table 1 shows serum biochemical parameters associated with liver function in rats treated with 1.0 ml/kg CCl₄ 3 times/week for 1, 2, or 3 months. AST, ALT, and ALP levels increased at 1—2 months after treatment with CCl₄ but subsequently decreased. Furthermore, total bilirubin time-dependently elevated during administration of CCl₄. In contrast, serum albumin level and A/G ratio were gradually but significantly decreased. Histopathological assessment of liver revealed that severity of fibrosis, formation of bridging fibrosis, and regenerating nodules were increased in a CCl₄ administration period-dependent manner (Fig. 1). Hence these results indicated that the rat after CCl₄ administration of this schedule is a good model of chronic hepatic failure.

**Changes of HBF and Relation to Serum Albumin Concentration**  
Figure 2 shows changes of HBF in the chronic hepatic failure rats. In the control group, HBF showed values of 83.2±17 ml/min/kg. In rats with chronic hepatic failure, HBF at 1, 2, and 3 months was significantly reduced to 47.5±17, 32.0±14, and 30.9±8.0 ml/min/kg, respectively.

Figure 3 indicates that there was a positive correlation between HBF and serum albumin concentration in control rats and CCl₄-treated rats. The predicted value of HBF (Qₚₑᵣ) can be expressed by serum albumin concentration (alb) as follows:

\[
Q_{p}=Q_{c} \cdot 9.34 \exp(0.655 \cdot \text{alb})/100
\]

where Qₚₑᵣ is the control value of HBF, i.e. 83.2 ml/min/kg.

**Changes of Serum Protein Binding and Relation to Serum Albumin Concentration**  
The unbound fraction of drugs in plasma (fₑ) was measured in control and CCl₄-treated rats by ultrafiltration system. In control rats fₑ values ≤0.2 and >0.2 were classified as sensitive-binding drug and insensitive-binding drug, respectively. As shown in Fig. 4, some insensitive-binding drugs (cyclophosphamide, zonisamide, and lidocaine) were not influenced by decrease of serum albumin concentration. On the other hand, some sensitive-binding drugs (tolbutamide, chlorozoxaze, and propranolol) were negatively correlated with serum albumin concentration. In the case of sensitive-binding drugs, the predicted value of fₑ (fₑ₋ₚₑᵣ) can be expressed by serum albumin concentration as follows:
i) Sensitive-binding drugs ($f_{p,N} \leq 0.2$)

$$f_{p,pre} = f_{p,N} \cdot 12.1 \exp(-0.689 \cdot alb)$$

(2)

where $f_{p,N}$ is the observed value of $f_p$ in control rats. In the case of insensitive-binding drugs, $f_{p,pre}$ can be expressed as Eq. 3.

ii) Insensitive-binding drugs ($f_{p,N} > 0.2$)

$$f_{p,pre} = f_{p,N}$$

(3)

Plasma Concentration–Time Course of Various Drugs

Control rats and rats at 48 h after administration of 1.0 ml/kg CCl$_4$ were intravenously given chlorzoxazone (10 mg/kg), tolbutamide (10 mg/kg), cyclophosphamide (90 mg/kg), zonisamide (10 mg/kg), propranolol (2 mg/kg), or lidocaine (10 mg/kg). The plasma concentrations of these drugs in rats treated with CCl$_4$ were all higher than those in control rats (Fig. 5). Pharmacokinetics parameters of these drugs are listed in Tables 2 and 3. Values of area under the plasma concentration–time curve from 0 time to infinity ($AUC$) in CCl$_4$-treated rats were significantly larger for all the drugs tested than those in control rats. The values of total clearance in plasma ($CL_{tot}$) of all the drugs in CCl$_4$-treated rats were also smaller than those in control rats. Values of elimination of half-life ($t_{1/2}$) in CCl$_4$-treated rats were gradually increased for all drugs except tolbutamide and lidocaine.

Changes in Intrinsic Clearance ($CL_{int}$)

As shown in Fig. 6, although the degree of decrease of intrinsic clearance ($CL_{int}$) was different among probe drugs, $CL_{int}$ values were decreased in a CCl$_4$ administration period-dependent manner.

Correlation between $CL_{int}$ and Serum Albumin Concentration

We used a well-stirred model to describe the hepatic metabolism of each drug to estimate $CL_{int}$. Since all
**Table 2.** Pharmacokinetic Parameters of Various Drugs after Intravenous Administration in Vehicle Control and CCl₄-Treated Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chlorzoxazone</th>
<th>Tolbutamide</th>
<th>Cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>CCl₄ treatment</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>for 1 month</td>
<td>for 2 months</td>
<td>for 3 months</td>
</tr>
<tr>
<td>AUC (µg·h·ml⁻¹)</td>
<td>57.8±6.9</td>
<td>89.5±13.8**</td>
<td>127±1.9**</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>2.25±0.23</td>
<td>5.06±0.94**</td>
<td>5.53±0.49**</td>
</tr>
<tr>
<td>Vdₚ (l/kg)</td>
<td>0.38±0.02</td>
<td>0.56±0.05**</td>
<td>0.44±0.03*</td>
</tr>
<tr>
<td>Clₚ (ml/min/kg)</td>
<td>2.80±0.30</td>
<td>1.90±0.32*</td>
<td>1.32±0.02**</td>
</tr>
<tr>
<td>T½ (h)</td>
<td>1.23±0.08</td>
<td>3.63±0.73**</td>
<td>4.00±0.37**</td>
</tr>
<tr>
<td>f₂</td>
<td>0.04±0.05</td>
<td>0.64±0.010*</td>
<td>0.13±0.03**</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.D. (n=3). ** significantly different from vehicle control at p<0.01. a) Area under the blood concentration-time curve from zero to 24 h. b) Mean residence time from 0 to 24 h. c) Distribution volume at steady state. d) Total clearance. e) Elimination half-life. f) Free fraction in plasma.

**Table 3.** Pharmacokinetic Parameters of Various Drugs after Intravenous Administration in Vehicle Control and CCl₄-Treated Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zonisamide</th>
<th>Propranolol</th>
<th>Lidocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>CCl₄ treatment</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>for 1 month</td>
<td>for 2 months</td>
<td>for 3 months</td>
</tr>
<tr>
<td>AUC (µg·h·ml⁻¹)</td>
<td>78.7±2.5</td>
<td>100±5.3**</td>
<td>137±45</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>9.03±0.22</td>
<td>11.4±1.3*</td>
<td>20.4±4.2*</td>
</tr>
<tr>
<td>Vdₚ (l/kg)</td>
<td>1.15±0.05</td>
<td>1.35±0.13</td>
<td>1.45±0.18*</td>
</tr>
<tr>
<td>Clₚ (ml/min/kg)</td>
<td>2.12±0.07</td>
<td>1.67±0.09*</td>
<td>1.30±0.38*</td>
</tr>
<tr>
<td>T½ (h)</td>
<td>6.39±0.17</td>
<td>7.87±0.94</td>
<td>14.2±3.0*</td>
</tr>
<tr>
<td>f₂</td>
<td>0.71±0.07</td>
<td>0.81±0.08</td>
<td>0.69±0.08*</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.D. (n=3). ** significantly different from vehicle control at p<0.01. a) Area under the blood concentration-time curve from zero to 24 h. b) Mean residence time from 0 to 24 h. c) Distribution volume at steady state. d) Total clearance. e) Elimination half-life. f) Free fraction in plasma.
drugs in this study are hepatically metabolized drugs, $CL_{tot}$ can be expressed as Eq. 4.

$$CL_{tot} = \frac{Q \cdot CL_{int} \cdot f_p}{Q + CL_{int} \cdot f_p}$$

(4)

Furthermore, $CL_{int}$ is obtained from Eq. 4 as follows:

$$CL_{int} = \frac{Q \cdot CL_{tot} \cdot f_p}{(Q - CL_{int}) \cdot f_p}$$

(5)

$CL_{int}$ can be calculated from Eq. 5 using the value of $Q$ as utilized as the value of albumin concentration in Eq. 1 in control or CCl$_4$-treated rats.

Figure 7 shows the correlation between $CL_{int}$ values of probe drugs and serum albumin concentration in control or CCl$_4$-treated rats. There was a good positive correlation between values. The predicted value of $CL_{int}$ ($CL_{int,pre}$) can be expressed by serum albumin concentration as follows:

$$CL_{int,pre} = CL_{int,N} \cdot 1.08 \cdot \exp(1.18 \cdot alb)/100$$

(6)

where $CL_{int,N}$ is $CL_{int}$ of control rats.

**Prediction of Decreased $CL_{tot}$ after Administration of Cyclosporin A in Rats with Chronic Hepatic Failure**

Control rats and rats treated with CCl$_4$ were intravenously
Eq. 4. Finally, it is necessary to correct the predicted ratios with chronic hepatic failure.

indicators that correlate with decreased clearance of drugs in col for hepatically metabolized drugs using new biochemical administration.

tolbutamide, chlorzoxazone, propranolol, cyclophosphamide, zonisamide, or lidocaine (LID) (10 mg/kg), or propranolol (PRO) (2 mg/kg). □, vehicle control; ▪, 1 month; ■, 2 months; □, 3 months. Each column with a bar represents the mean ± S.D. of 3 rats. * Significantly different from vehicle control at p<0.05. ** Significantly different from vehicle control at p<0.01.

given cyclosporin A (CyA, 10 mg/kg). CL\textsubscript{tot} in blood (CL\textsubscript{tot,b}) of CyA in the twelve rats were calculated by model-independent moment analysis from the blood concentration–time course. Then, CL\textsubscript{tot,B} was converted into CL\textsubscript{tot} using the blood to plasma concentration ratio (RBP, 1.25).\textsuperscript{19} Next, CL\textsubscript{int,N} was calculated using the observed Q\textsubscript{pre}, CL\textsubscript{tot}, and the reported f\textsubscript{P,N} (83.2 ml/min/kg, 7.31 ml/min/kg, and 0.05\textsuperscript{19}) based on Eq. 5. The CL\textsubscript{int,N} value was 160 (ml/min/kg). Q\textsubscript{pre}, f\textsubscript{P,pre} and CL\textsubscript{int,pre} of CyA were calculated using serum albumin concentration based on Eqs. 1, 2, and 6. CL\textsubscript{tot} of CyA predicted using the obtained values of Q\textsubscript{pre}, f\textsubscript{P,pre}, and CL\textsubscript{int,pre} based on Eq. 4. Finally, it is necessary to correct the predicted CL\textsubscript{tot} to CL\textsubscript{tot,B} using RBP and comparing with the observed CL\textsubscript{tot} of CyA (Fig. 8). Regression analysis revealed that there was a statistically significant relationship between predicted and observed CL\textsubscript{tot,B} of CyA (r=0.713; p<0.01).

The CCl4-treated rat is frequently used as an experimental model to study hepatic disease. Here, we administered 1.0 ml/kg CCl4 for 1, 2, or 3 months three times/week. When treated with CCl4 for 1 month, the liver exhibited periporal fibrosis and linking vascular structures. After administration of CCl4 for 3 months, dense fibrous septa dividing the hepatic parenchyma into multiple discrete nodules was observed giving a macroscopically nodular liver surface. This state was recognizable as cirrhosis. Hence rats treated with CCl4 for >1 month were recognized as models of chronic hepatic failure (Fig. 1).

Serum albumin concentration might serve as a marker of the degree of chronic hepatic failure because it decreased time-dependently during the administration period of CCl4 (Table 1). This was accounted for by de novo albumin synthesis, and depended on the decrease of hepatocyte function in chronic hepatic failure. Furthermore, the increasing level of total bilirubin might be due to cholestatic injury in rats treated with CCl4. Levels of ALT and AST did not reliably reflect the severity of disease because these levels dropped during the study period. The reason for this may be that AST, and ALT leaked into the blood from hepatocytes acutely damaged by CCl4. Therefore we examined the relationship between albumin level and 3 major biologic determinants of hepatic drug clearance, HBF, f\textsubscript{P}, and CL\textsubscript{tot}.

At first, we examined the change of HBF using ICG in control or CCl4-treated rats. ICG is highly extracted by the liver (70—90%), not recoverable from the urine, is 95% bound to circulating albumin, and cleared by hepatic uptake, conjugation, and excretion into bile.\textsuperscript{20} We found that with moderate hepatic fibrosis after 1 month of CCl4 treatment, HBF was about 60% of the control. After 2 or 3 months of CCl4 treatment, HBF of cirrhosis was decreased by about 40% from the control value (Fig. 2). On the other hand, we have reported that there were no significant differences in the degree of HBF in acute hepatic failure.\textsuperscript{6} In chronic hepatic failure rats, it was indicated that the change of HBF was influenced by the severity of hepatic disease. There was a positive correlation between HBF and serum albumin concentration (Fig. 3). As shown in Eq. 1, we indicated that the pre-
dicted value of HBF (Qpre) could be expressed by serum albumin concentration.

We also examined whether there was any relation between increase of unbound drug for binding-sensitive drugs and decrease of serum albumin concentration as liver injury advanced. As shown Tables 2 and 3, f∞ of tolbutamide, chlorzoxazone, and propranolol became significantly greater as liver injury progressed, whereas f∞ of cyclophosphamide, zonisamide, and lidocaine hardly changed. It has been reported that albumin affinity changes during progression of liver injury due to increased bilirubin levels.21) Bratlid and Bergan reported that the effect of bilirubin to displace drugs from their binding sites on albumin was most pronounced with compounds that had the highest degree of protein binding, i.e. those bound >80% by albumin.22) Therefore we recognized tolbutamide, chlorzoxazone, and propranolol as sensitive-binding drugs because the observed values of f∞ were ≤0.2 in control rats. On the other hand, cyclophosphamide, zonisamide, and lidocaine were recognized as insensitive-binding drugs because the observed value of f∞ was >0.2 in control rats. For sensitive-binding drugs, the increase of f∞ correlated well with decreased serum albumin levels, while the f∞ of insensitive drugs was constant regardless of the level of albumin (Fig. 4). Thus we surmised that the predicted value of f∞ (UPpre) could be expressed by serum albumin concentration as Eq. 2 or 3.

We investigated the changes of plasma concentration of drugs using four specific probe drugs with low hepatic extraction, cyclophosphamide for CYP2B10) tolbutamide for CYP2C11,8) zonisamide for CYP3A223) and chlorzoxazone for CYP2E124) and two drugs with high hepatic extraction, propranolol and lidocaine, in control or CCl4-treated rats. Several drugs showed delay of drug metabolism in CCl4-treated rats versus control rats (Fig. 5). Some studies have indicated age-dependent changes of the levels of CYP 25), but in this study, enzymatic activities of CYP isoforms were significantly decreased by about 10—30% of control at 1—3 months after CCl4 treatment (data not shown). It was suggested that drug metabolism chiefly might reflect the decrease of activities of CYP isoforms as liver damage by CCl4 progressed. The decrease rate of CLtot of several drugs differed greatly from about 2/3 to 1/11 (Tables 2, 3). Elimination from the body of drugs metabolized in the liver is considered dependent on HBF, bile excretion, renal excretion of metabolites, and other factors. When we examined the relation between serum albumin concentration and CLtot of several drugs, that of CLtot of tolbutamide to albumin level was not good (r=0.61), while good correlation of the other 5 drugs tested was observed (r=0.85—0.92) (data not shown). The correlation coefficient of chlorzoxazone was 0.85, but CLtot decreased until 2 months after CCl4 treatment and did not change thereafter. This phenomenon observed with tolbutamide and chlorzoxazone, shows that hepatic metabolism-limited elimination is explained by an increase of f∞ of drugs in serum; that is, CLint is assumed only slightly changed due to mutual cancellation of reduced CLint and increased unbound drug concentration as liver damage advanced. Thus CLtot was converted into CLint in consideration of f∞ and HBF. We found that CLint of each of the 6 drugs was decreased as liver damage progressed (Fig. 6). In addition, the level of albumin was correlated with CLint in control rats and CCl4-treated rats. There was a good correlation between these (Fig. 7). We indicated that the predicted value of CLint (CLint,pre) could be expressed by serum albumin concentration as shown in Eq. 6.

Finally, using calculated parameters: Qpre, f∞,pre, and CLint,pre, CLint was obtained. That is, it might be possible to predict appropriate drug dosage of unknown basic drugs in chronic hepatic failure. We evaluated this predicting model using CyA, and noted that good prediction had been obtained (Fig. 8).

Clinically, pharmacokinetics parameters of f∞,N and CLtot,N in prescription drugs in healthy persons are available on the prescribing information, and it is reported that the value of QN is 20 ml/min/kg.26) Because CLtot,N can be exchanged with CLint,N using Eq. 5, we can estimate parameters of QN, f∞,N and CLtot,N in healthy persons. Therefore if data on serum albumin concentration in patients with chronic hepatic failure are obtained, it may be possible to predict CLtot of drugs using this model. Although it has been reported that dosage adjustment of drugs should be individually based on biochemical markers such as AST,27) the advantage of our model might be that it might be used for all heptatically metabolized drugs, either with high or low hepatic extraction in patients with chronic hepatic failure.

In conclusion, we have developed a novel model for predicting CLtot of heptatically metabolized drugs in rats with chronic hepatic failure from the serum albumin values. Serum albumin level may be useful for predicting dosage adjustments of drugs in patients with chronic hepatic failure.

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