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Research Paper

Altered Pharmacokinetics of Paclitaxel in Experimental Hepatic or Renal Failure

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Purpose. The aim of this study was to investigate the effect of hepatic or renal insufficiency on the pharmacokinetics of paclitaxel in rats.
Methods. Rats were treated with carbon tetrachloride (CCl_4; 0.5 ml/kg) to induce hepatic failure or were subjected to 5/6 nephrectomy (5/6 Nx) to induce renal failure. Paclitaxel (3 mg/kg) was administered intravenously or intraportally. Testosterone 6β-hydroxylase activity, which is a marker of CYP3A activity, was measured in rat liver microsomes from CCl_4-treated or 5/6 Nx rats.
Results. After paclitaxel was administered intravenously, total body clearance was significantly reduced by 73% and 34% relative to each control value in CCl_4-treated and 5/6 Nx rats, respectively (control, 1.82 ± 0.42 vs. CCl_4-treated, 0.49 ± 0.11; sham, 1.54 ± 0.07 vs. 5/6 Nx, 1.01 ± 0.12 L h^{-1} kg^{-1}; mean ± SE, n = 5 to 6). Testosterone 6β-hydroxylase activity was reduced by 92% and 59% relative to each control value in rat liver microsomes from CCl_4-treated and 5/6 Nx rats, respectively. After the intraportal administration of paclitaxel, apparent clearance was reduced by 85% relative to control value in rats with hepatic failure, while that in rats with renal failure was the same as the reduction in systemic clearance.
Conclusions. These results suggested that not only hepatic failure but also renal failure could modify the pharmacokinetics of paclitaxel *in vivo*.

KEY WORDS: hepatic failure; 5/6 nephrectomy; paclitaxel; pharmacokinetics; renal failure.

INTRODUCTION

The taxanes are important anticancer agents that exert their cytotoxicity through an antimicrotubule effect and are active against a wide range of solid tumors including lung and ovarian cancers (1). Paclitaxel is predominantly metabolized by CYP2C8 and CYP3A4 in human liver, but 5–10% of the administered dose is excreted unmetabolized into urine after intravenous administration (2,3). Recently, a relationship between the time above a paclitaxel concentration of 0.05 μM and percent decrease in the absolute neutrophile count was reported (4,5). Moreover, a relationship between the time above a paclitaxel concentration of 0.1 μM and the survival rate was also reported (6). From these reports, control of the paclitaxel plasma concentration is suggested to be important to decrease the adverse effects and increase the effects of paclitaxel in cancer treatment. However, dosage in cancer therapy is usually adjusted according to body surface area, and there are few reports about paclitaxel with which to construct a therapy based on pharmacokinetics and pharmacodynamics.

The pharmacokinetics of drugs mainly metabolized in liver are easily affected by liver disease (7). Recently, cytochrome P450 content and activity were reported to decrease in hepatic cirrhosis (8). In a clinical study, Huizing *et al.* (6) reported that alanine amino transferase negatively correlates with the clearance of paclitaxel, but Panday *et al.* (9) reported that there is only a moderate relationship between liver function and paclitaxel clearance. For docetaxel, the deterioration of liver function and a low level of α_1-acid glycoprotein were reported to have covariate effects on the clearance of docetaxel (10). Therefore, the relationship between liver function and the clearance of paclitaxel requires further examination. On the one hand, although renal failure is considered to affect only the renal elimination of drugs, it has a variety of influences on drug kinetics: it reduces nonrenal elimination, influences protein binding, and alters the volume of distribution of some drugs (11). Recently in rats with chronic renal failure, a downregulation of liver cytochrome P450, especially CYP3A, at the levels of protein and mRNA was reported (12). Dowling *et al.* (13) also reported that in patients with end-stage renal disease, CYP3A activity measured with the erythromycin breath test was 28% lower than that in healthy subjects. Therefore, the clearance of paclitaxel might change with chronic renal failure, although the relationship between renal dysfunction and the pharmacokinetics of paclitaxel has yet to be examined.

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ABBREVIATIONS: AUC, area under the plasma concentration-time curve; HPLC, high-performance liquid chromatography; 5/6 Nx, 5/6 nephrectomy; K_m, Michaelis-Menten constant; V_{max}, maximum velocity.

In this study, to clarify whether hepatic or renal failure affects the pharmacokinetics of paclitaxel, we examined the change of hepatic metabolism *in vivo* and *in vitro* using CCl_4-treated rats or 5/6 nephrectomized rats.

MATERIALS AND METHODS

Materials

Paclitaxel and Taxol were obtained from Bristol-Myers Squibb (Princeton, NJ, USA). Internal standard (4-hydroxybenzoic acid) was purchased from Tokyo Kasei Kogyo Co. Ltd. (Tokyo, Japan). Carbon tetrachloride was obtained from Wako Pure Chemical Co. (Osaka, Japan). Testosterone and 6β-hydroxy testosterone were from Nacalai Tesque Inc. (Kyoto, Japan). All other chemicals used were of the highest purity available.

Induction of Hepatic or Renal Failure

Male Wistar rats weighing 240–260 g and 200–220 g were used for the experiments involving hepatic failure and renal failure, respectively. Hepatic failure was induced by intraperitoneal injection of CCl_4 (0.5 ml/kg) as a 25% v/v olive oil solution (2 ml/kg) 24 h before the experiments (14). Rats were fasted for 18 h before the administration of CCl_4 but allowed free access to water. Rats treated with corn oil (2 ml/kg) served as controls. Chronic renal failure was induced by 5/6 nephrectomy (5/6 Nx) (15). Rats were fasted overnight but given free access to water, and the kidney was exposed under aseptic conditions via a midline incision under anesthesia with sodium pentobarbital (40 mg/kg). The right kidney was removed, and the posterior and anterior apical segmental branches of the left renal artery were individually ligated with 7-0 silk sutures. The abdominal incision was closed with 4-0 silk sutures. In the sham-operated animals, the peritoneal cavity was exposed, and both kidneys were gently manipulated. After surgery, animals were allowed to recover from anesthesia and surgery in cages with free access to water and standard rat chow for 2 weeks until the experiments. Rats were maintained in metabolic cages for 24 h before the *in vivo* experiment to determine urinary output and urinary levels of creatinine, and plasma was obtained from each of the models for the biochemical analysis. The animal experiments were performed in accordance with the *Guidelines for Animal Experiments of Kyoto University*. The experimental protocol was approved by the Animal Research Committee, Graduate School of Medicine, Kyoto University.

Pharmacokinetics of Paclitaxel

Administration solution of paclitaxel was prepared as a dilution of Taxol in saline and filtered through a microfilter (pore size 0.45 μm, Cosmonice Filter W, Japan Millipore Inc., Tokyo, Japan). Paclitaxel was administered via the tail vein for 30 s at a dose of 3 mg/kg (1.2 mg/ml). Blood samples were collected from the tail or jugular vein with heparinized syringes at 5, 15, 30, 60, 120, 240, and 480 min after the injection of paclitaxel.

In a separate experiment, the abdominal cavity was opened via a midline incision and a catheter with a needle (27 G) was carefully inserted with cyanoacrylate glue into the portal vein under anesthesia with sodium pentobarbital (40 mg/kg). The femoral artery was cannulated with polyethylene tubing (SP-31, Natsume Seisakusho, Tokyo, Japan) to collect blood samples. Paclitaxel was infused for 1 h (2.2 ml/h) via the portal vein at a dose of 3 mg/kg. Blood samples were obtained at 30, 60, 65, 75, 90, 120, 180, and 300 min from the start of infusion. The total volume of blood samples from each rat was less than 2 ml. The samples were taken into heparinized tubes and stored at –20°C until the analysis.

Hepatic, Biliary, Renal, and Intestinal Clearance in Rats

The femoral artery and vein were cannulated with polyethylene tubing (PE-50; BD Biosciences, San Jose, CA, USA) filled with heparin solution (100 U/ml) for blood sampling and drug administration, respectively, under light ether anesthesia. The abdominal cavity of rats was opened via a midline incision to gain access to the small intestine. The common bile duct or the urinary bladder was cannulated with PE-10 tubing (BD Biosciences) for bile collection or with PE-50 tubing for urine collection. The whole small intestine starting from the Treitz ligament was used to make an intestinal loop. After washing of the loop with saline to clear the efflux, saline (5 ml) was injected into the loop. Paclitaxel (3 mg/kg) was injected via the femoral vein and blood samples were collected at 2, 5, 15, 30, 45, and 60 min from the femoral artery. After blood sampling was finished, the content in intestine was washed out as completely as possible with 4% bovine serum albumin dissolved in saline to give a volume of 30 ml.

Metabolism of Testosterone in Rat Liver Microsomes

Rat liver microsomes were prepared 24 h after CCl_4 administration or 2 weeks after 5/6 nephrectomy according to a commonly used procedure (16). Testosterone 6β-hydroxylase activity was determined as described (17). Liver microsomal protein (100 μg) was incubated in 200 mM phosphate buffer (pH 7.4) with 6 mM $MgCl_2$, 12 mM glucose 6-phosphate, and 0.25 U of glucose 6-phosphate dehydrogenase. The reaction solution was preincubated for 2 min after the addition of testosterone dissolved in dimethyl sulfoxide. The reaction was started by adding 1.5 mM β-nicotinamide adenine dinucleotide. The total volume was 0.5 ml, and the final concentration of testosterone was 5–150 μM and that of dimethyl sulfoxide was kept at 1%. Incubations were carried out at 37°C in a shaking water bath for 30 min. The concentration of 6β-hydroxy testosterone in the reaction mixture was measured by high-performance liquid chromatography (HPLC). Sample preparation and HPLC analysis were done according to previously reported procedures with slight modifications (18).

In Vitro Plasma Protein Binding

The plasma unbound fraction of paclitaxel was determined by ultrafiltration using a Micropartition System (MPS-1, Amicon, Inc., Beverly, MA, USA). Blood was obtained from sham-operated and 5/6 Nx rats 5 min after administration of paclitaxel at 3 mg/kg via the tail vein. Plasma was placed in an ultrafiltration device equipped with a YMT ultrafiltration membrane (Amicon, Inc.) and centrifuged at $1500 \times g$ for 5 min at 25°C. The cup containing the ultrafiltrate was replaced, and another plasma sample (700 μl) was placed in the same device and centrifuged at $900 \times g$ for 10 min at

25°C. This procedure was needed to prevent the adsorption of paclitaxel by the membranes.

Assays

Paclitaxel was extracted from plasma, bile, urine, and intestinal content using a Sep-pak C_{18} column (Waters, Bedford, MA, USA) as previously described (5). The concentrations of paclitaxel were measured by HPLC according to reported procedures with slight modifications (19). Briefly, the HPLC system was composed of SCL-10 system controller, LC-10AS pump, SIL-10A auto-injector, CTO-10A column oven, SPD-10AV UV-Vis detector (Shimadzu Corporation, Kyoto, Japan) and analytical column (ChemcoPak, Chemcosorb 5-ODS-H 4.6 × 150 mm, Chemco Scientific Co. Ltd., Osaka, Japan). The mobile phase consisted of 40% acetonitrile-10% methanol-50% 20 mM ammonium acetate buffer (pH 5.0) with a flow rate of 1.2 ml/min. The UV detector was set at 227 nm. The lower limit of the assay was 0.01 μM.

The plasma concentration of aspartate amino transferase, alanine amino transferase, bilirubin, albumin, total protein, total bile acid, blood urea nitrogen and creatinine, and the urine concentration of creatinine were measured using assay kits from Wako Pure Chemical Industries (Osaka, Japan). The tests of creatinine in serum and urine and blood urea nitrogen were based on Jaffé method and urease/indophenol method, respectively. The tests of alanine amino transferase and aspartate amino transferase or total bile acid were based on POP·TOOP method or enzyme colorimetry, respectively. The tests of total protein and albumin level in serum were based on bromcresol green method and biuret method, respectively.

Pharmacokinetic Analysis

A conventional two-compartmental analysis was used to examine plasma concentration-time profiles after the intravenous administration of paclitaxel in rats using the nonlinear least squares program NONMEM (double precision NONMEM version IV and PREDPP version III). The parameters, total body clearance, central volume of distribution, intercompartmental clearance, and volume of distribution at a steady-state were calculated. The apparent clearance expressed as the total body clearance divided by bioavailability after intraportal injection was calculated from the dose divided by the area under the plasma concentration-time curve (AUC). The AUC after intraportal administration was calculated using the linear trapezoidal rule and extrapolated to infinity by adding the ratio of the last measurable paclitaxel concentration to the mean terminal disposition rate constant. Biliary, renal and intestinal clearance was calculated as the amount excreted into bile, urine and intestine for 60 min divided by the AUC for 60 min, respectively. Hepatic clearance was calculated by subtracting biliary, renal and intestinal clearance from dose divided by AUC for 60 min.

The kinetic parameters for testosterone 6β-hydroxylase activity in liver microsomes were calculated using the following equation: $V = V_{max} \cdot S/(K_m + S)$, where V is the metabolic rate (nmol/mg protein per 30 min), S is the substrate concentration in the microsome (mM), K_m is the Michaelis-Menten constant (mM), and V_{max} is the maximum velocity by the saturable process (nmol/mg protein per 30 min). The data were fitted to the above equation by nonlinear least squares method.

Statistical Analysis

Values are expressed as the mean ± SE for n experiments. If the variances in each group were similar, the statistical significance of differences between mean values was calculated using the nonpaired t test, otherwise the Mann-Whitney U test was used. Differences were considered significant at $p < 0.05$.

RESULTS

Paclitaxel Pharmacokinetics in Hepatic or Renal Failure

Table I shows the biochemical parameters in CCl_4-treated or 5/6 Nx rats. Marked increases of aspartate amino transferase and alanine amino transferase levels were observed with hepatic failure. The blood urea nitrogen and serum creatinine levels were significantly increased and creatinine clearance was significantly decreased in 5/6 Nx rats. The plasma concentration of paclitaxel was markedly increased in rats with CCl_4-induced hepatic failure (Fig. 1A), and it was also significantly increased at 5, 15, and 30 min after dosing in 5/6 Nx rats (Fig. 1B). The plasma concentrations of paclitaxel after intravenous infusion were better fitted by two-compartment model than one-compartment model. Table II shows the pharmacokinetic parameters of paclitaxel in the rats with hepatic or renal failure and their respective controls. Total body clearance in rats with hepatic failure was reduced by 73% relative to the control value, whereas in 5/6 Nx rats it was reduced by 34% relative to the level in sham-operated

Table I. Biochemical Parameters in CCl_4-Treated or 5/6 Nx Rats and Respective Controls

Parameters	Control	CCl_4-treated	Sham	5/6 Nx
Aspartate amino transferase (IU/l)	98 ± 8	12,400 ± 439*	20 ± 6	9 ± 2
Alanine amino transferase (IU/l)	37 ± 5	2,740 ± 378*	27 ± 7	8 ± 6
Total bile acid (μM)	44 ± 11	121 ± 33	41 ± 11	48 ± 11
Albumin (g/dl)	2.41 ± 0.45	2.17 ± 0.37	2.68 ± 0.27	2.16 ± 0.17
Total protein (g/dl)	4.88 ± 0.26	4.37 ± 0.20	5.21 ± 0.44	5.28 ± 0.03
Blood urea nitrogen (mg/dl)	10.7 ± 1.1	18.9 ± 1.7*	16.8 ± 4.1	61.6 ± 15.9*
Serum creatinine (mg/dl)	0.50 ± 0.01	0.88 ± 0.03*	0.43 ± 0.03	1.04 ± 0.10*
Creatinine clearance (ml min^{-1} kg^{-1})	n.d.	n.d.	7.71 ± 1.18	2.71 ± 0.20*

Each value represents the mean ± SE for four to five rats. n.d., not determined.
* $p < 0.05$, significantly different from respective control.

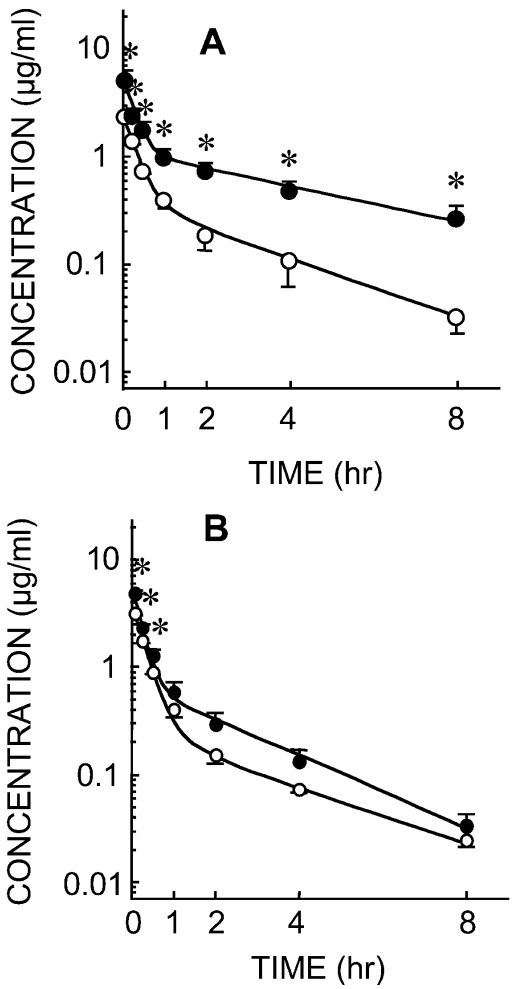

Fig. 1. Effect of CCl_4-treatment (A) or 5/6 Nx (B) on the plasma concentration of paclitaxel after intravenous administration in rats. Paclitaxel was administered as a bolus via the tail vein at a dose of 3 mg/kg to control (○) and CCl_4-treated or 5/6 Nx (●) rats. Blood samples were collected at specified times after the administration. The line shows the fitting curve obtained with the two-compartment model. Each point represents the mean ± SE of five to six rats. *$p < 0.05$, significantly different from control.

rats. The central volume of distribution in CCl_4-treated and 5/6 Nx rats was reduced by 44% and 10% relative to the control value, respectively. The volume of distribution at steady state in 5/6 Nx rats was significantly reduced by 51% relative the control value.

Testosterone 6β-Hydroxylase Activity in Liver Microsomes

Figure 2A shows the liver microsomal activity of CCl_4-treated and control rats, and Fig. 2B shows that of 5/6 Nx and sham-operated rats. Testosterone 6β-hydroxylase activity was significantly decreased in liver microsomes during both hepatic and renal failure. Table III shows the kinetic parameters of testosterone 6β-hydroxylase activity in each model and its control. The apparent K_m value of each model was not significantly different from the control, but V_{max} in hepatic and renal failure was reduced by 92% and 59% relative to the each control value, respectively.

Hepatic, Biliary, Renal, and Intestinal Elimination of Paclitaxel

To evaluate the extrahepatic clearance, we examined the biliary, renal and intestinal clearance of paclitaxel over 60 min in normal and 5/6 Nx rats (Fig. 3). In normal rats, the hepatic, biliary, renal, and intestinal clearance was 96.4 ± 15.4%, 1.8 ± 0.2%, 0.06 ± 0.04%, and 1.8 ± 0.2% (mean ± SE, n = 4) of total body clearance over 60 min, respectively. The biliary clearance in 5/6 Nx rats was significantly increased and extrahepatic clearance was about 2-fold greater than that in normal rats.

Pharmacokinetics of Paclitaxel After Intraportal Administration

Hepatic failure significantly increased the plasma concentration of paclitaxel at all points after the intraportal administration (Fig. 4), corresponding to a marked decrease in the apparent clearance (control, 1.21 ± 0.17; hepatic failure, 0.15 ± 0.02 L h^{-1} kg^{-1}; mean ± SE, n = 4). The apparent clearance values were 1.09 ± 0.14 and 0.77 ± 0.03 L h^{-1} kg^{-1} (mean ± SE, n = 4) in sham-operated and 5/6 Nx rats, respectively, and the plasma paclitaxel concentration was not significantly different at any time point.

Protein Binding of Paclitaxel

The plasma-unbound fraction of paclitaxel was 2.3 ± 0.2% and 3.2 ± 1.3% (mean ± SE, n = 3) in sham-operated and 5/6 Nx rats, respectively. These values were not significantly different.

DISCUSSION

Liver dysfunction often affects the pharmacokinetics of drugs metabolized in the liver, and renal dysfunction sometimes affects drug disposition (7,10). The results presented in this study suggested that not only hepatic failure but also renal failure could affect the pharmacokinetics of paclitaxel in humans.

After intravenous administration of paclitaxel, total body clearance was reduced by 73% and 34% relative to control in rats with hepatic or renal failure, respectively. Choi (20) also reported that total body clearance of paclitaxel was reduced to 54% of the control level in rabbits with CCl_4-induced hepatic failure, which was consistent with our results. It is reasonable that the clearance of paclitaxel decreases with hepatic failure, while there was no information about paclitaxel pharmacokinetics in renal disease. Several other drugs which are mainly excreted via hepatic metabolism, but affected by renal disease, were reported. We previously found that the bioavailability of tacrolimus, which is also a substrate of CYP3A, increased in rats with cisplatin-induced renal failure (21). In that study, we suggested that the hepatic metabolism decreased and the absorption of tacrolimus in the intestine increased (21). Recently, in patients with end-stage renal disease, Dowling *et al.* (13) observed a 28% lower baseline for erythromycin breath test value, an indicator of *in vivo* hepatic CYP3A activity, compared to controls. These findings were consistent with the results of the current study.

To examine whether the reduction of total body clearance in hepatic or renal failure depends on the reduction in hepatic metabolic activity, we measured testosterone 6β-

Table II. Pharmacokinetic Parameters of Paclitaxel After Intravenous Administration to Rats with Hepatic or Renal Failure

Parameters	Control	CCl_4-treated	Sham	5/6 Nx
CL (L h^{-1} kg^{-1})	1.82 ± 0.42	0.485 ± 0.112*	1.54 ± 0.07	1.01 ± 0.12*
Q (L h^{-1} kg^{-1})	1.40 ± 0.23	1.43 ± 0.20	0.919 ± 0.048	0.918 ± 0.075
V_1 (l/kg)	0.968 ± 0.109	0.540 ± 0.102*	0.752 ± 0.032	0.680 ± 0.041*
V_{ss} (l/kg)	2.51 ± 0.23	1.92 ± 0.34	2.59 ± 0.25	1.26 ± 0.18*

CL, total body clearance; Q, intercompartmental clearance; V_1, central volume of distribution; V_{ss}, volume of distribution at steady-state. Each point represents the mean ± SE for five to six rats.
* $p < 0.05$, significantly different from control.

hydroxylase activity in hepatic microsomes. Because paclitaxel is mainly metabolized by CYP3A in rats (22), testosterone 6β-hydroxylase activity was considered to be a proper index of paclitaxel-metabolizing activity. Testosterone 6β-hydroxylase activity was significantly reduced, and kinetic analysis showed that the V_{max} value was reduced by 92% and 59% relative to each control in hepatic and renal failure rats, respectively, but the K_m value did not change. Bastien *et al.* (8) reported that in animal models of cirrhosis induced by bile duct ligation or CCl_4-treatment, protein and activity levels of CYP3A significantly decreased, which was consistent with our results. Leblond *et al.* (12) reported that the protein and mRNA levels of cytochrome P450, especially CYP3A1, were reduced by 85% in 5/6 Nx rats. In addition, the hepatic metabolic activities of cytochrome P450 in rats with renal failure were reported to fluctuate according to the subtype of P450 or etiology of renal failure, and the hepatic metabolic activity of CYP3A was reduced by 66% in 5/6 Nx rats (23). These findings strongly suggest that renal failure in addition to hepatic failure can affect the disposition of drugs metabolized by hepatic CYP3A.

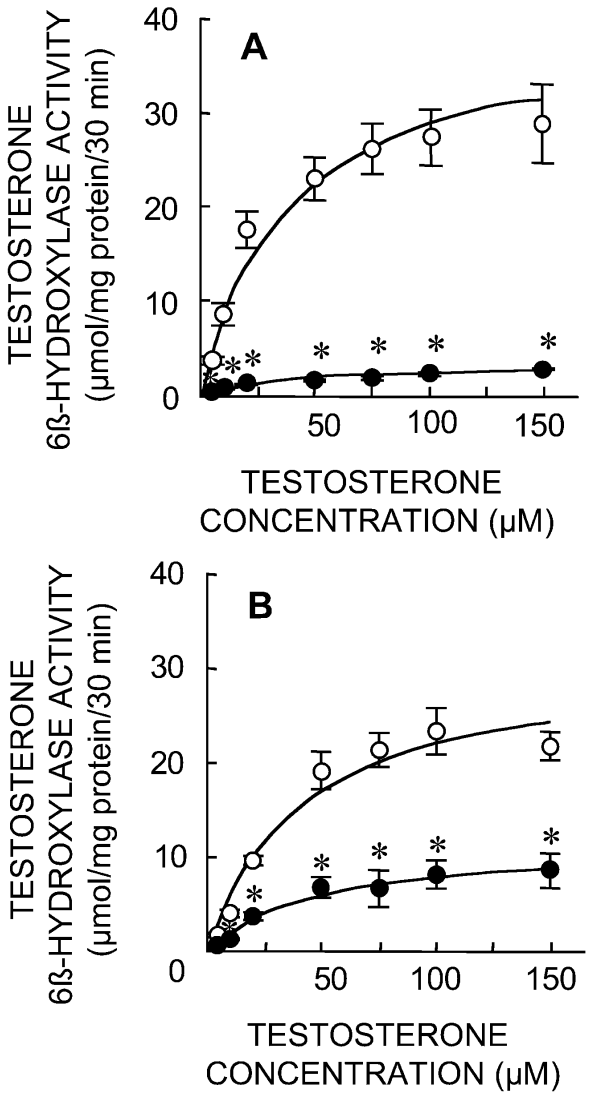

Fig. 2. Testosterone 6β-hydroxylase activity in liver microsomes from CCl_4-treated (A) or 5/6 Nx (B) and respective control rats. Testosterone was incubated in microsomes from CCl_4-treated or 5/6 Nx (●) and control (○) rats. Each line represents the activity estimated with the Michaelis-Menten equation. Each point represents the mean ± SE of three to four rats. *$p < 0.05$, significantly different from control.

In the current study, the reduction in microsomal testosterone 6β-hydroxylase activity did not correspond to the decrease in systemic clearance. Then we considered that the extrahepatic clearance in bile, urine, and intestine might play a key role in paclitaxel clearance. However, the sum of these values was only 3.9% of total body clearance in normal rats, which was consistent with a previous report (24). Because the extrahepatic clearance in 5/6 Nx rats was also about 7.8% of total body clearance, the total body clearance of paclitaxel in rats was approximated using the hepatic clearance in spite of renal failure. The total body clearance of respective controls after intravenous administration (Table II) was almost equal to the hepatic plasma flow rate in rats (27–40 ml min^{-1} kg^{-1}) (25). Therefore, we considered that the extraction of paclitaxel is limited by perfusion, and the decrease in hepatic intrinsic clearance was not fully reflected by the systemic clearance after the intravenous administration.

When drugs, which are mainly eliminated by hepatic metabolism, are administered orally, the apparent clearance is

Table III. Effect of Hepatic or Renal Dysfunction on Testosterone 6β-Hydroxylase Activity in Liver Microsomes

Parameters	Control	CCl_4-treated	Sham	5/6 Nx
K_m (µM)	41.4 ± 5.6	32.3 ± 3.7	39.4 ± 1.9	49.7 ± 14.9
V_{max} (nmol/mg protein per 30 min)	40.7 ± 5.1	3.26 ± 0.23*	30.4 ± 2.7	12.5 ± 3.5*

Each value represents the mean ± SE for three to four rats.
* $p < 0.05$, significantly different from control.

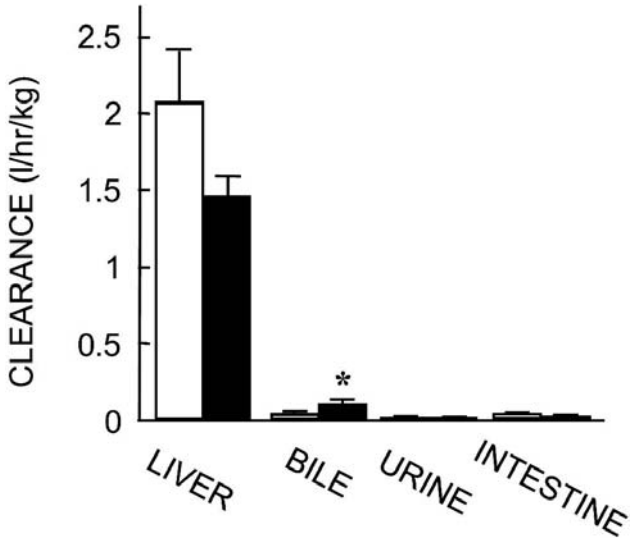

Fig. 3. Hepatic, biliary, renal, and intestinal clearance over 60 min after administration of paclitaxel (3 mg/kg) via the tail vein in normal (open columns) or 5/6 Nx (closed columns) rats. Each column represents the mean ± SE for three to four rats. *$p < 0.05$, significantly different from control.

calculated by the following equation according to the well-stirred model (26):

$$CL/F = f_{ub} \cdot CL_{int}$$

where CL is the total body clearance, F is the bioavailability, f_{ub} is the plasma-unbound fraction of drug, and CL_{int} is the hepatic intrinsic clearance. Therefore, the apparent clearance after oral administration is a function of the plasma-unbound fraction and hepatic intrinsic clearance. Because paclitaxel was extensively metabolized in the intestine after oral administration (24), we examined the apparent clearance after the intraportal administration of paclitaxel to evaluate the effect of altered hepatic metabolic activity on the pharmacokinetics *in vivo*. The apparent clearance was reduced by 85% relative to the control value in the rats with hepatic failure, which almost corresponded to the reduction in metabolic activity estimated from testosterone 6β-hydroxylase activity *in vitro*. However, in 5/6 Nx rats the apparent clearance was reduced by 31% relative to the control value and the reduction was the same with systemic clearance after the intravenous administration. In renal disorders, the serum albumin level is known to decrease (27), although the albumin level was not significantly reduced in our renal failure model. In addition, uremic toxins are reported to exist in the blood of patients with chronic renal disease and inhibit drug protein binding to albumin (28). Indeed, Gugler *et al.* (27) reported that the clearance of diphenylhydantoin or clofibrate, whose protein binding rates are above 90%, increased in patients with nephrotic syndrome. Paclitaxel mainly binds to albumin, and the binding ratio of paclitaxel is high (about 95%) (29,30). Because the unbound fraction of paclitaxel increased moderately in 5/6 Nx rats in this study, we considered that the apparent clearance did not decrease as much as with hepatic intrinsic clearance. As an alternative reason for the inconsistency of the reduction in hepatic metabolic activity *in vitro* and apparent clearance *in vivo* in 5/6 Nx rats, another metabolic enzyme might contribute to paclitaxel metabolism in rats (22).

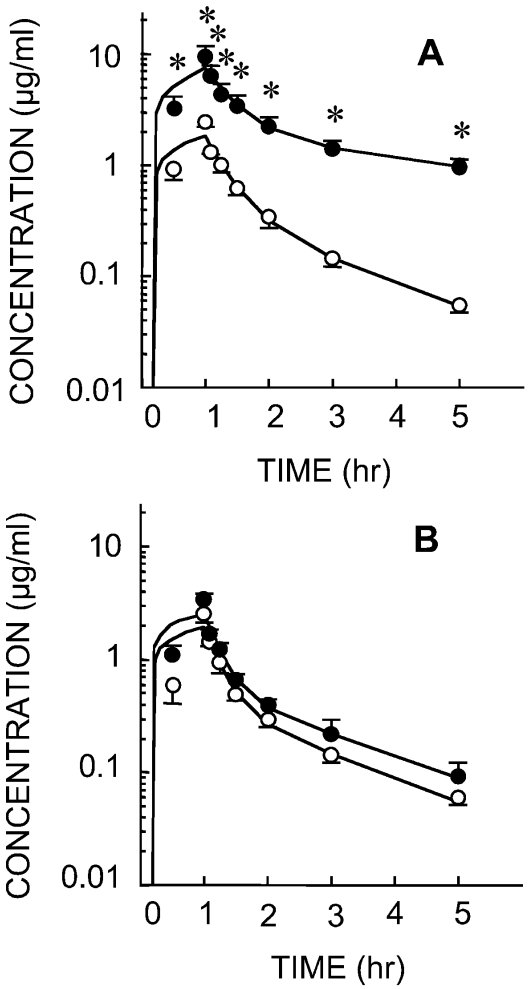

Fig. 4. Plasma concentration of paclitaxel after intraportal administration in CCl_4-treated (A), 5/6 Nx (B) and respective control rats. Paclitaxel (3 mg/kg) was infused for 60 min (2.2 ml/h) via the portal vein to CCl_4-treated or 5/6 Nx (●) and control (○) rats. Blood samples were collected at specified times after the injection. The line shows the fitting curve obtained with the two-compartment model. Each point represents the mean ± SE for four rats. *$p < 0.05$, significantly different from control.

Gianni *et al.* (4) and Ohtsu *et al.* (5) reported a positive relationship between the duration for which the plasma paclitaxel concentration was above 0.05 μM and percent decrease in the absolute neutrophile count. Moreover, Huizing *et al.* (6) observed a positive relationship between time above a threshold paclitaxel concentration of 0.1 μM and drug effect (survival rates) in non-small-cell lung cancer patients. From these reports, it is concluded that the plasma concentration is an important factor in cancer therapy using paclitaxel. Because the metabolism of paclitaxel is dependent on intrinsic hepatic activity in humans (3), not only hepatic failure but also renal failure might increase the blood concentration of paclitaxel. However, if the plasma-unbound fraction of paclitaxel also changes in renal failure, total body clearance might not decrease as much as intrinsic hepatic activity. The current study indicates that attention should be paid to controlling the concentration of paclitaxel when it is administered to patients with not only hepatic failure but also renal failure.

In conclusion, the excretion of paclitaxel is dependent on hepatic blood flow in rats, and total body clearance changed dramatically with hepatic failure, but much less markedly with renal failure.

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