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Pharmacokinetics of Paclitaxel in Rabbits with Carbon Tetrachloride-Induced Hepatic Failure

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The pharmacokinetic of paclitaxel (1 mg/kg, i.v.) was investigated in rabbits with carbon tetrachloride-induced hepatic failure. The area under the plasma concentration-time curve (AUC) of paclitaxel was significantly ($p<0.01$) increased in severe carbon tetrachloride-induced hepatic failure rabbits (1364.54 ± 382.07 ng/ml · hr) compared to that of normal rabbits (567.52 ± 141.88 ng/ml · hr), but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits (803.1 ± 208.81 ng/ml · hr). The volume of distribution (Vd) (6.25 ± 1.56 L) and the elimination rate constant(β) (0.09 ± 0.025 hr^{-1}) of paclitaxel in severe carbon tetrachloride-induced hepatic failure rabbits were significantly ($p<0.05$) decreased compared to those of normal rabbits (11.65 ± 2.91 L, 0.12 ± 0.030 hr^{-1}), but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits (9.46 ± 2.37 L, 0.10 ± 0.026 hr^{-1}). Total body clearance (CL_t) of paclitaxel in severe carbon tetrachloride-induced hepatic failure rabbits (0.733 ± 0.183 L/hr/kg) was significantly ($p<0.01$) decreased compared to that of normal rabbits (1.762 ± 0.440 L/hr/kg), but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits (1.245 ± 0.311 L/hr/kg). The half-life(t1/2) of paclitaxel in severe carbon tetrachloride-induced hepatic failure rabbits (7.71 ± 2.16 hr) was significantly ($p<0.05$) increased compared to that of normal rabbits (5.75 ± 1.44 hr), but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits (6.77 ± 1.76 hr). This results could be due to inhibition of paclitaxel metabolism in liver disorder rabbits since paclitaxel is essentially metabolized in liver. The findings suggest that the dosage regimen of paclitaxel should be adjusted when the drug would be administered in patients with liver disorder in a clinical situation.

Key words: Paclitaxel, Pharmacokinetics, Carbon tetrachloride-induced hepatic failure

INTRODUCTION

Paclitaxel (Taxol®) is an antineoplastic agent that is derived from the bark of the Pacific yew tree (*Taxus brevifolia)* (Wan *et al.,* 1971). In contrast to Vinca alkaloids, the anticancer action of taxol is thought to be mediated by the inhibition of cellular growth by promotion and stabilization of microtubule assembly by noncovalent interaction with tubulin, thereby blocking cell replication in the late G_2 mitotic phase of the cell cycle (Kumar, 1981, Manfredi *et al.,* 1984). Because of its poor water solubility, paclitaxel is currently formulated in taxol and a mixture of polyoxyethyleneglycerol triricinoleate 35 (Cremophor EL) and dehydrated ethanol USP (1 : 1, v/v).

It has been reported that the human toxicity of paclitaxel included myelosuppression, emesis, weight loss, hepatic dysfunction and increases in total plasma lipids, cholesterol and triglyceride (Rowinsky *et al.,* 1993). Paclitaxel has been clinically used in patients with ovarian carcinoma, breast carcinoma, leukemia, melanoma, and prostate carcinoma, ovarian and breast carcinoma being the clinical target for the agent (Rowinsky *et al.,* 1990, McGuire *et al.,* 1989, Sarosy *et al.,* 1992, Holmes *et al.,* 1991).

Oral administration the paclitaxel has been problematic; it has poor absorption because of poor solubility and low permeability across the intestinal epithelium. The drug has been reported to be a substrate for the multidrug transporter P-gp, an efflux transporter, which is abundantly present in the gastrointestinal tract. Therefore, this drug is mainly used for intravenous administration (Sparreboom *et al.,* 1997). Paclitaxel has a very large volume of distribution in the body, and is highly bound by plasma protein, primarily albumin (95-98%) (Wiernik *et al.,* 1987). Especially the tissue distribution is much higher for the liver

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(Hiroshi *et al.,* 1994). Less than 5 to 10% of administered paclitaxel was recovered as unchanged drug in the urine of treated patients (Wiernik *et al.,* 1987, Wiernik and Einzig *et al.,* 1987, Brown *et al.,* 1991). Paclitaxel is mainly metabolized through the liver and undergo biliary excretion (Cresteil *et al.,* 1994, Kumar *et al.,* 1994, Rahman *et al.,* 1994, Sonnichsen *et al.,* 1995), as evidenced by the fact that, in humans, the total fecal excretion is approximately 70% of paclitaxel dose, with 6-hydroxypaclitaxel being the major metabolite (Walle T *et al.,* 1995).

In cancer patients, it has been reported that liver dysfunction may be one of the most common complications. Since the liver dysfunction is likely to be associated with the reduced ability of hepatic biotransformation of drugs (Donelli *et al.,* 1998), the drugs that are primarily eliminated by the route may have clinically implications in patients with cancer. Indeed, it have been reported that pharmacokinetics of doxorubicin (Brenner *et al.,* 1984) and vincristine (Van den Berg *et al.,* 1982) has been affected in liver disorder. Unfortunately, however, alteration in paclitaxel pharmacokinetics has not been systematically studied in liver disorder. Considering the fact that the toxicity (especially myelosuppression) of paclitaxel is related to plasma paclitaxel concentrations and duration time (Sonnichsen *et al.,* 1994, Gianni *et al.,* 1995 and Grem *et al.,* 1987), any alteration in paclitaxcel is likely to have a clinical impact. The purpose of this study, therefore, was to investigate the pharmacokinetic changes of paclitaxel after intravenous administration of paclitaxel in normal rabbits and moderate and severe carbon tetrachloride-induced hepatic failure rabbits in order to develop the optimal dosage regimen of paclitaxel in patients with liver disorder in a clinical situation.

MATERIALS AND METHODS

Materials

Paciltaxel was purchased from Brystol-Myers Squibb Co. (NY, USA). Saline (0.9% NaCl injectable solution) was purchased from Choongwae Co. (Seoul, Korea). Acetonitrile, methanol, ether and ammonium acetate were purchased from Merck Co.(Darmstadt, Germany). n-Butyl p-amino-benzoate (Butamben) was purchased from Sigma Chemical Co. (St. Louis, MO, USA). Phosphoric acid was purchased from Junshei Co. (Tokyo, Japan). The other chemicals were of reagent grade and were used without further purification. HPLC (Waters 1515 isocratic HPLC Pump, Waters 717 plus autosampler, Waters 2487 Dual λ absorbance detector, Waters Co., Milford, MA, USA), syringe pump (Model M361, Sage Instruments, MA, USA), vortex mixer (Scientific Industries, Korea), sonication chamber (Dhihan Co., Korea) and centrifuge (Abbot Co., USA) were used in this study.

Animals

The white male New Zealand rabbits (body weight 2.0~2.5 kg) were fasted at least 24hr before experiment and were given water freely. Moderate and severe hepatic failure rabbits induced with carbon tetrachloride (CCl_4: olive oil = 20:80,v/v) 1.2 ml/kg and 2.0 ml/kg subcutaneous injection, respectively. Under 25% urethane (3 ml/kg) anesthesia, the right femoral artery was cannulated with polyethylene tubing (PE-50, Intramedic, Clay Adams, USA) for blood sampling at room temperature.

Drug administration

Diluted paclitaxel [with saline (0.9% NaCl injectable solution), final dose; 1 mg/kg] was given to rabbits intravenously. Blood samples (1.2 ml) were withdrawn from the catheter connected to femoral artery at 7, 15, 30 min, 1, 2, 4, 6, 9, 12 hr after the paclitaxel administration. Plasma samples were obtained by centrifugation of 13,000 rpm for 5 min. 0.5 ml Plasma were collected and stored at -70°C until the HPLC analysis. Urine samples were collected between 0-2, 2-4, 4-6, 6-12 hr after administration of the drug. After measuring the total volume of each collection, the a 0.5 ml aliquot of urine samples was stored at -30°C until HPLC analysis of paclitaxel. Saline (0.9% NaCl injectable solution) was infused at the rate of 1.5 ml/hr to ear vein to replace the loss of blood volume induced by blood sampling using infusion pump (Model M361, Sage instruments, MA, USA). Each rabbit was kept in supine position throughout the experiment period.

Assay and HPLC conditions

Plasma concentrations of paclitaxel were determined by high performance liquid chromatography assay. The method of Catalin *et al.,* (1998) and Mase *et al.,* (1994) was slightly modified and used in this study. Briefly, 0.1 ml of n-butyl p-aminobenzoate (internal standard) solution (1 μg/ml), 0.2 ml of 0.2 M ammonium acetate buffer (pH 5.0) and 4 ml of ether were added to a 0.5 ml of plasma and urine samples. It was then mixed for 15 min and centrifuged at 3000 rpm for 10 min. 3.5 ml Of organic layer was transferred to a clean test tube and evaporated to dryness under a stream of nitrogen at 40°C. The residue was then dissolved in 0.3 ml of mobile phase (ACN:MeOH:2 mM phosphate buffer (pH 5.0), 38:22:40) and centrifuged 13,000 rpm for 5 min and a 100 μl aliquot of the mixture was injected onto the HPLC system.

The HPLC system consisted of Waters 1515 isocratic HPLC Pump, Waters 717 plus autosampler, Waters 2487 Dual λ absorbance detector (Waters Co., Milford, MA, USA) and an intergrater. The detection wavelength was set at 227 nm. The separation was carried out in a Symmetry C18 column (4.6 ± 150 mm, 5 μm, Waters Co., USA). Mixtures of acetonitrile : methanol : 2 mM phsphate buffer

(pH 5.0) (38:22:40 v/v/v) were used as the mobile phase at a flow rate of 1.2 ml/min. The mobile phase was filtered by passing through a 0.45 μm pore size membrane filter. The retention times for the internal standard and paclitaxel were 4.5 minutes and 7.7 minutes, respectively.

Pharmacokinetic analysis

Pharmacokinetic parameters calculated assuming a two compartment open model with a nonlinear least square regression using a MULTI program (Yamaoka *et al.*, 1981) and simplex algorithm. The parameter value was obtained when the AIC (Akaike's information criterion) value reached the minimum. The area under the plasma concentration-time curves (AUC) was calculated by trapezoidal rule. Total body clearance (CLt) was calculated by the moment analysis.

Statistical analysis

All means were presented with their standard deviation (mean ± S.D.). Unpaired Student's t-test was utilized to compare mean values. $P<0.05$ was accepted as denoting a significance difference between the normal and moderate and severe carbon tetrachloride-induced hepatic failure rabbits.

RESULTS AND DISCUSSION

Clinical laboratory data

Clinical laboratory data in carbon tetrachloride-induced hepatic failure rabbits were shown in Table I. AST and ALT in moderate and severe carbon tetrachloride-induced hepatic failure rabbits increased significantly ($p<0.01$ in both cases) compared to those of normal rabbits. Bilirubin in moderate and severe carbon tetrachloride-induced hepatic failure rabbits increased significantly ($p<0.05$ and $p<0.01$, respectively) when compared with the normal rabbits.

Plasma concentrations of paclitaxel

The plasma concentration-time curve for paclitaxel after the intravenous administered (paclitaxel, 1 mg/kg) was shown in Fig. 1. The plasma concentration of paclitaxel in moderate and severe carbon tetrachloride-induced hepatic failure rabbits increased significantly ($p<0.05$ and $p<0.01$, respectively) compared to that of normal rabbits.

Table I. Laboratory data in moderate and severe carbon tetrachloride-induced hepatic failure rabbits.

Lab. data	Normal	Moderate hepatic failure	Severe hepatic failure
AST (unit/dl)	28 ± 3.8	168 ± 24.5**	292 ± 48.0**
ALT (unit/dl)	22 ± 3.5	196 ± 28.5**	314 ± 52.4**
Bilirubin (mg/dl)	0.25 ± 0.043	0.34 ± 0.064*	0.46 ± 0.076**

Mean ± S.D. (n = 6) *p<0.05, **p<0.01
AST; aspartate amino transferase
ALT; alanine amino transferase

Cumulative urinary excretion of Paclitaxel

The amount of cumulative urinary excretion of paclitaxel was showed in Fig. 2. The amount of cumulative urinary excretion of paclitaxel in moderate and severe carbon tetrachloride-induced hepatic failure rabbits increased compared to that of normal rabbits, but not significantly.

Pharmacokinetic parameters

The pharmacokinetic parameters of paclitaxel in normal rabbits and moderate and severe carbon tetrachloride-induced hepatic failure rabbits were listed in Table II. The volume of distribution (Vd) (6.25 ± 1.56 L) and the slope of the terminal phase (β) (0.09 ± 0.025 hr^{-1}) of paclitaxel in severe carbon tetrachloride-induced hepatic failure rabbits

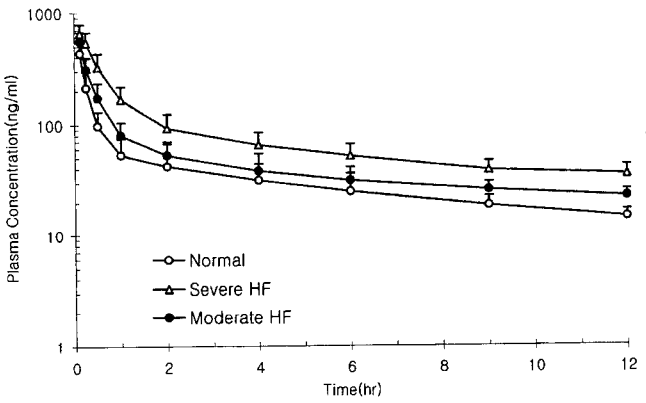

Fig. 1. Mean plasma concentration of paclitaxel after intravenous administration (1 mg/kg) of the drug in moderate and severe carbon tetrachloride-induced hepatic failure rabbits. Bars represent standard deviation.

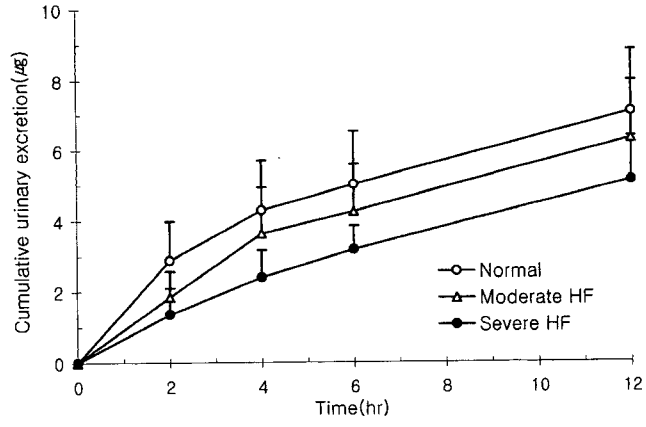

Fig. 2. Mean cumulative urinary excretion (μg) of paclitaxel after intravenous administration (1 mg/kg) of the drug in moderate and severe carbon tetrachloride-induced hepatic failure rabbits. (n = 6, each). Bars represent standard deviation.

Table II. Mean (±S.D.) Pharmacokinetic parameters of paclitaxel after intravenous administration (1 mg/kg) of the drug in moderate and severe carbon tetrachloride-induced hepatic failure rabbits.

Parameters	Normal	Moderate hepatic failure	Severe hepatic failure
β (hr^{-1})	0.12 ± 0.030	0.10 ± 0.026	0.09 ± 0.025*
$t_{1/2}$ (hr)	5.75 ± 1.44	6.77 ± 1.76	7.71 ± 2.16*
Vd (L/kg)	11.65 ± 2.91	9.46 ± 2.37	6.25 ± 1.56*
CLt (L/hr/kg)	1.762 ± 0.440	1.245 ± 0.311	0.733± ± 0.183**
AUC (ng/mlhr)	567.52 ± 141.88	803.10 ± 208.81	1364.54 ± 382.07**

Mean ± S.D. (n = 6), *p<0.05, **p<0.01 compared to control
β, terminal phase slope; $t_{1/2}$, half life; Vd, volume of distribution; CLt, total clearance; AUC^{0}_{12}, area under the plasma concentration-time curve from 0 to 12 h

were significantly ($p<0.05$) decreased compared to that of normal rabbits (11.65 ± 2.91 L and 0.12 ± 0.030 hr^{-1}, respectively), but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits (9.46 ± 2.37 L and 0.10 ± 0.026 hr^{-1}, respectively). Total body clearance (CL_t) of paclitaxel in severe carbon tetrachloride-induced hepatic failure rabbits (0.733 ± 0.183 L/hr/kg) was signi-ficantly ($p<0.01$) decreased compared to that of normal rabbits (1.762 ± 0.440 L/hr/kg), but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits (1.245 ± 0.311 L/hr/kg). The half-life (t1/2) of paclitaxel in severe carbon tetrachloride-induced hepatic failure rabbits (7.71 ± 2.16 hr) was significantly ($p<0.05$) increased compared to that of normal rabbits (5.75 ± 1.44 hr), but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits (6.77 ± 1.76 hr). The area under the plasma concentration-time curve (AUC) of paclitaxel was significantly ($p<0.01$) increased in severe carbon tetrachloride-induced hepatic failure rabbits (1364.54 ± 382.07 ng/mlhr) compared to that of normal rabbits (567.52 ± 141.88 ng/ml · hr), but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits (803.1 ± 208.81 ng/ml · hr).

A great number of anticancer drugs are now available for clinical use. These agents show vast differences with respect to their pharmacokinetic properties and anticancer actions. According to Cresteil *et al.,* 1994 and Kumar *et al.*, 1994 and others, it has been reported that the primary route of elimination for paclitaxel is via hepatic metabolism and biliary excretion. Therefore, it can be expected that hepatic dysfunction will have a major impact on the pharmacokinetics of paclitaxel. In consistent with the expectation, we have demonstrated that, in an animal model, a severe hepatic dysfunction has a significant impact on the pharmacokinetics of paclitaxel. In cancer patients, liver dysfunction may be important because of changes in the metabolism of anticancer drugs which undergo hepatic biotransformation, either producing active metabolites or resulting in detoxified products (Donelli *et al.,* 1998). Reports of Nannan panday *et al.,* 1997 and Venook *et al.,* 1998 are as pharmacokinetic studies of paclitaxel in liver dysfunction. Considering the fact that the toxicity (especially myelosuppression) of paclitaxel is related to plasma paclitaxel concentrations and duration time (Sonnichsen *et al.,* 1994, Gianni *et al.,* 1995 and Grem *et al.,* 1987), the pharmacokinetic alteration for paclitaxel is likely to have a clinical implication.

In this study, the AUC of paclitaxel were significantly increased in severe carbon tetrachloride-induced hepatic failure rabbits, but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits. The volume of distribution (Vd) and the elimination rate constant(β) and total body clearance (CL_t) of paclitaxel were significantly decreased in severe carbon tetrachloride-induced hepatic failure rabbits, but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits. The half-life (t) of paclitaxel in severe carbon tetrachloride-induced hepatic failure rabbits was significantly increased compared to control rabbits, but not significantly in moderate carbon tetrachloride-induced hepatic failure rabbits. Underlying mechanism for the changes of pharmacokinetic charac-teristics for paclitaxel during the severe hepatic damage is not directly studied. However, the fact that both the distribution and the elimination of the drug are affected suggested that hepatic metabolism as well as the permeability of the drug to the tissue (e.g., the liver) may be altered during the experimental hepatic damage. Therefore, the finding of the study suggests that the dosage regimen of paclitaxel should be adjusted when the drug would be administered in cancer patients with a severe liver disorder.

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