

Nonlinear Pharmacokinetics of CPT-11 in Rats

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ABSTRACT

The pharmacokinetics of a new water-soluble derivative of camptothecin, 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11), and its major metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), was investigated after i.v. administration of 1 to 40 mg/kg of CPT-11 to rats.

The plasma concentration of CPT-11 decreased biexponentially. The area under the concentration-time curve increased nonlinearly as the dose increased. SN-38 was found in the plasma, bile, urine, and feces. The SN-38 level was maintained at 0.06 to 0.08 $\mu\text{g/ml}$ for 0.5 to 5.5 h depending on the dose, followed by exponential decay. Thirty-three to 58% of the CPT-11 was excreted without metabolism into the bile and urine for 24 h. SN-38 was mainly excreted into the bile.

Analysis of the clearance has shown nonlinear pharmacokinetics which was due to metabolic processes such as the conversion of CPT-11 to SN-38.

INTRODUCTION

CPT,² obtained from the Chinese tree *Camptotheca acuminata*, is an alkaloid with a novel ring structure (1). Though camptothecin has shown promising antitumor effects *in vitro* (2, 3) and in animal studies (1, 4), it has not produced favorable results in clinical investigations because of its low therapeutic efficacy and severe toxicity to the intestinal mucosa, bladder, and hematological system (5-9).

Various derivatives of CPT, such as ECPT, have been semi-synthesized (10, 11). As CPT and its derivatives are only slightly soluble in water, they were given i.v. as sodium salts with an open lactone ring structure. Sodium salts have weaker activity than the closed form lactone (12). Therefore we have obtained various water-soluble derivatives without the open lactone ring. Among the derivatives, 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11; Fig. 1) with a closed lactone ring showed stronger antitumor effects *in vivo* than camptothecin derivatives in mice (13, 14) and in rats (15). In this paper, we present pharmacokinetic data on CPT-11 and its major metabolite 7-ethyl-10-hydroxycamptothecin (SN-38; Fig. 1) in rats after i.v. administration.

MATERIALS AND METHODS

Chemicals. All chemicals and reagents used were of analytical grade. CPT-11 and SN-38 were provided by the organic synthesis group at our institute. CPT-11 used in the experiments was checked by HPLC, and its purity was more than 99.5%.

Disposition Studies. Male Wistar rats were purchased from Charles River Japan, Inc. (Atsugi, Japan). Rats weighing 230 to 320 g were used in all experiments except for the determination of the plasma SN-38 profile after i.v. administration of CPT-11, where animals weighing about 150 to 160 g were used. Animals were used without fasting before

all experiments. All the experiments were performed under conditions of free access to water and without food except for the fecal excretion experiments.

For the purpose of determining the plasma profiles of CPT-11, cannulas (Intramedic PE-50; Clay Adams, Parsippany, NJ) were implanted under light ether anesthesia into the right femoral vein and artery through which CPT-11 was administered and blood was collected, respectively. The animals were kept in Bollman cages after the operation, and CPT-11 was administered, followed by flushing with NaCl solution, after they awoke from anesthesia. The volume of drug and NaCl solution injected into each animal was 1 ml. Blood (0.3 ml) was collected 5, 10, 20, 30, and 45 min and 1, 1.5, and 2 h after administration of the drug. The same volume of blood was also collected every hour up to 6 h for the three lowest doses and every 2 h up to 12 h for the three highest doses.

The plasma SN-38 profile after i.v. administration of CPT-11 was determined. CPT-11 was injected into the tail vein, and blood was collected by cardiac puncture 5, 10, and 30 min and 1, 3, and 6 h after injection.

Experiments on excretion of CPT-11 were performed in rats in which a cannula had been implanted into the bile duct or bladder under ether anesthesia. The animals were kept in a Bollman cage, and the drug was administered in the same fashion as in the experiments on plasma concentration of CPT-11. Bile and urine samples were collected over a 24-h period after administration and kept on ice. SN-38 and its glucuronide were stable under these conditions. Feces and urine were collected in the metabolic cage for over 2 days from animals given injections into the tail vein. The animals had free access to an ordinary diet (MF; Oriental Yeast, Tokyo, Japan) and water.

Preparation and Analysis of Samples. Samples of rat plasma for CPT-11 determination were immediately diluted 10-fold with 0.1 N HCl and then serially diluted to give a concentration of about 10 ng/ml. Plasma (2 ml) for SN-38 determination was immediately acidified with 0.2 ml of 1.0 N HCl.

Bile and urine were also serially diluted 10-fold with 0.1 N HCl, and for the determination of SN-38 glucuronide, the samples were incubated with β -glucuronidase as follows. One-tenth ml of bile or urine was added to 0.6 ml of 0.1 M phosphate buffer (pH 6.0) containing 1000 Sigma units of β -glucuronidase (*Escherichia coli*, type IX; Sigma Chemical Co., St. Louis, MO). The mixture was incubated overnight at 37°C and determined as SN-38.

CPT-11 and SN-38 in plasma, bile, and urine were determined by the method described previously (16). Adequately diluted samples were applied under nitrogen gas pressure to a C₁₈ cassette of an advanced automated sample processor (Analytichem International, Harbor City, CA) which was wetted with methanol and water before application, followed by rinsing with 1.5 ml of water. A high-performance liquid chromatograph (LC-4A; Shimadzu Seisakusho, Kyoto, Japan) was linked to the advanced automated sample processor which performed as an autosampler. A C₁₈ reversed-phase column (LiChrosorb RP-18; 7 μm , 25 x 0.4 cm; E. Merck AG, Darmstadt, West Germany) with an RP-18 precolumn was used for chromatography. The mobile phases consisted of acetonitrile/ethanol/0.8% ammonium carbonate (2/1/1, v/v) and acetonitrile/water (1/4, v/v) for CPT-11 and SN-38, respectively. The flow rate and column temperature were 1.0 ml/min and 50°C and 2.0 ml/min and 60°C for CPT-11 and SN-38, respectively. A fluoro-spectromonitor (RF-530; Shimadzu) was set at an excitation wavelength of 373 nm and an emission wavelength of 428 nm for CPT-11 and at 380 nm and 540 nm for SN-38. The peak areas were integrated by a data processor (Chromatopac C-R1BS; Shimadzu). A calibration curve was established with a CPT-11 standard solution in 0.1 N HCl containing 0.1% rat plasma, 0.1% bile, or 1% urine and with an SN-38 standard solution in 0.1 N HCl containing 10% rat plasma or 1% bile or urine. A calibration curve was prepared for each analysis. Accuracy and precision were within 10%. The limits of quantification of CPT-11

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² The abbreviations used are: CPT, camptothecin; ECPT, 7-ethylcamptothecin; HPLC, high-performance liquid chromatography; $t_{1/2}$, half-life of the elimination phase; AUC, area under the plasma concentration-time curve; AUMC, first moment of the plasma concentration-time curve; CL_p, plasma clearance; CL_b, biliary clearance; CL_r, renal clearance; CL_m, metabolic clearance; MRT, mean residence time; V_{dss} , volume of distribution at steady state.

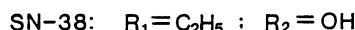
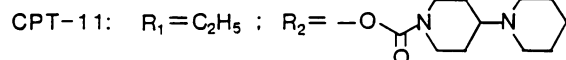
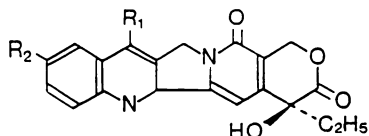


Fig. 1. Structures of CPT-11 and SN-38.

Table 1 Validation of CPT-11 and SN-38 determination

Added (ng)	Intraday (n = 4)			Interday (n = 5)		
	Mean ± SD	CV ^a (%)	% of error	Mean ± SD	CV (%)	% of error
CPT-11						
1.00	1.07 ± 0.05	4.7	+7.0	1.06 ± 0.08	7.5	+6.0
2.00	1.96 ± 0.02	1.0	+2.0	1.98 ± 0.04	2.0	-1.0
5.00	4.86 ± 0.01	0.2	-2.8	4.96 ± 0.08	1.6	-0.8
10.00	9.95 ± 0.08	0.8	-0.5	10.01 ± 0.09	0.9	+0.1
20.00	19.81 ± 0.21	1.1	-1.0	20.23 ± 0.23	1.4	+1.2
SN-38						
20.0	20.5 ± 0.4	2.0	+2.4	21.1 ± 0.9	4.4	+5.5
50.0	49.3 ± 0.7	1.4	-1.4	49.2 ± 0.6	1.2	-1.6
100.0	100.1 ± 0.2	0.2	+0.1	99.4 ± 0.9	0.9	-0.6
200.0	200.1 ± 1.0	0.5	+0.0	200.5 ± 0.5	0.3	+0.3

^a CV, coefficient of variation.

and SN-38 were 1 and 5 ng, respectively. Validations of plasma CPT-11 and SN-38 determination are listed in Table 1. Determinations of CPT-11 and SN-38 in urine and bile were within the same range of variation.

Feces were lyophilized and weighed. Five ml of 0.1 N HCl were added to 1 g of powdered feces, and then the suspension was extracted twice with CHCl₃ for 15 min (20 ml × 2). The organic layer was absorbed by a Sep-Pak silica cartridge (Waters Associates, Inc., Milford, MA), and the cartridge was washed with 10 ml of CHCl₃/methanol (100/1, v/v). Then it was eluted with about 40 ml of CHCl₃/methanol (2/1, v/v), and the volume was made up to 50 ml with CHCl₃. An aliquot was evaporated *in vacuo* and dissolved in methanol for HPLC. An Inertsil ODS column (5 μm, 250 × 4.6 mm; Gasukuro Kogyo, Tokyo, Japan) and a solvent system composed of CH₃CN/0.01 M phosphate buffer, pH 6.8 (2/3, v/v), at 50°C were used for the determination in feces. Other conditions were the same as for the plasma, bile, and urine. Recovery of CPT-11 and SN-38 was about 60% at the concentration of 100 μg/g of feces.

Pharmacokinetic Analysis. Plasma concentration-time curves were analyzed by compartmental and noncompartmental models (17).

AUC was calculated by the trapezoidal rule with estimation of AUC from the last sampling time to infinity by Equation A.

$$\int_{last}^{\infty} Cdt = C_{last}/\text{last log-linear phase slope} \quad (A)$$

The last log-linear phase slope in the AUC calculation of CPT-11 equals β.

CL_p, CL_b, CL_r, and CL_m were calculated as follows.

$$CL_p = \text{dose}/AUC$$

$$CL_b = CL_p \times (\text{ratio of unchanged CPT-11 excreted in bile to dose for 24 h after injection})$$

$$CL_r = CL_p \times (\text{ratio of unchanged CPT-11 excreted in urine to dose for 24 h after injection})$$

$$CL_m = CL_p - CL_b - CL_r$$

MRT was calculated as

$$MRT = AUMC/AUC$$

V_{dss} was calculated by the method of Benet and Galeazzi (18).

$$V_{dss} = \text{dose} \times AUMC/(AUC)^2 \quad (I)$$

Statistical Analysis. All values for doses in the pharmacokinetic studies were compared by one-way analysis of variance. When analysis of variance showed a significant difference at the level of $P < 0.05$, the difference between individual pairs of means was evaluated by Tukey's multiple comparison test at the level of $P < 0.05$. The difference between biliary and fecal excretion was compared by the two-tailed Student *t* test at the level of $P < 0.05$.

RESULTS

Plasma Pharmacokinetics of CPT-11 and SN-38 in Rats. Fig. 2 shows the CPT-11 plasma concentration-time curves after i.v. administration of CPT-11 at doses of 1, 2, 4, 10, 20, and 40 mg/kg. Plasma concentrations *versus* time data were analyzed by compartmental and noncompartmental methods. Using nonlinear weighted (inverse square of the concentration) least-squares regression, a two-compartment model best described the data. The pharmacokinetic parameters of three representative doses are shown in Table 2. *t*_{1/2β} increased from 1.2 h at a dose of 2 mg/kg to 2.4 h at the highest dose, though there was no significant difference among the doses. MRT also increased from 1.3 to 2.9 h, and AUC increased from 0.6 to 28.6 μg·h/ml. CL_p decreased from 3.3 to 1.4 liters/kg·h. A nonlinear increase in AUC and decrease in CL_p were detected by normalization of the dose. V_{dss} was relatively constant from 3.2 to 4.3 liters/kg.

The plasma concentration of SN-38, the major metabolite of CPT-11, after i.v. administration of CPT-11 was determined from different experiments because of the low sensitivity of SN-38 determination. CPT-11 (10, 20, and 40 mg/kg) was given i.v. The SN-38 concentration profiles are shown in Fig. 3. The SN-38 concentration was about 1 to 1.5 μg/ml at 5 min after administration and about 0.05 to 0.07 μg/ml at 30 min. The dose of 10 mg/kg gave a log-linear decrease with a half-life of about 2 h after 30 min. After a dose of 20 mg/kg, SN-38 remained at the concentration of about 0.06 μg/ml for the next 30 min, followed by a log-linear decrease with a half-life of about 4.5 h. At the 40-mg/kg dose, SN-38 remained constant at about 0.06 to 0.07 μg/ml up to at least 6 h after injection. AUC from Time 0 to 6 h was 12.0, 14.7, and 23.7 μg·min/ml for the doses of 10, 20, and 40 mg/kg, respectively. Recently we have been able to determine an SN-38 concentration of 10 ng/ml in 0.1 ml of plasma sample. Similar results for CPT-11 and SN-38 concentration profiles were obtained in the experiments in which plasma CPT-11 and SN-38 concentrations were determined for the same animal.

Excretion of CPT-11. Curves of cumulative biliary and urinary excretion of CPT-11 and SN-38 after i.v. administration of 2, 10, and 40 mg of CPT-11 per kg in rats are presented in Figs. 4 and 5, respectively. Cumulative excretion of CPT-11 and SN-38 into the bile and urine reached a plateau 24 h after administration with the exception that biliary excretion of SN-38 in the 40-mg/kg-treated group was linear up to 24 h. The percentage of the administered dose recovered as CPT-11 increased from 12 to 30% in the bile and from 13 to 27% in the urine as the dose increased from 1 to 40 mg/kg. The percentage of recovery as SN-38 decreased from 8.6 to 2.2% in the bile and from 2.5 to 0.8% in the urine as the dose increased (data not

Fig. 2. Plasma CPT-11 concentration profiles after i.v. administration of CPT-11 to rats. Male Wistar rats were given injections i.v. with 1 (○), 2 (△), 4 (◐), 10 (◑), 20 (▲), and 40 (●) mg of CPT-11 per kg through a cannula implanted in the right femoral vein, followed by flushing with NaCl solution. Blood was collected from a cannula implanted in the right femoral artery. Points, mean of 4 to 6 animals; bars, SD.

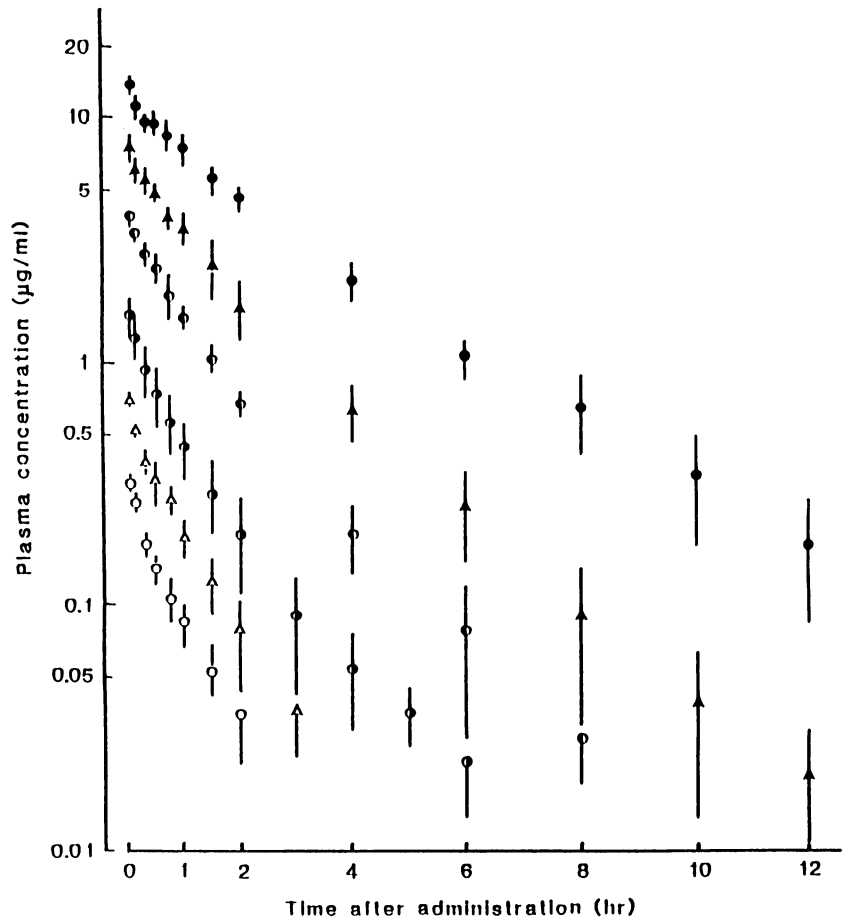


Table 2 Pharmacokinetic parameters of CPT-11 after i.v. administration of CPT-11 to rats

Parameter	Dose (mg/kg)		
	2	10	40
$t_{1/2\beta}$ (h) ^a	1.15 ± 0.42 ^b	1.54 ± 0.50	2.40 ± 0.76
MRT (h)	1.30 ± 0.26	1.43 ± 0.09	2.87 ± 0.52 ^c
AUC (µg·h/ml) ^d	0.61 ± 0.10	4.56 ± 0.59	28.60 ± 4.18 ^e
CLp (liter/kg·h)	3.34 ± 0.52 ^e	2.22 ± 0.26	1.42 ± 0.22
V_{area} (liter/kg)	4.26 ± 0.42 ^f	3.15 ± 0.26	4.02 ± 0.49

^a Plasma concentration-time curves were fitted to the biexponential equation.

^b Mean ± SD of five animals.

^c The mean was significantly different from those of the two lower doses ($P < 0.05$).

^d Values from Time 0 to infinity.

^e The mean was significantly different from those of the two higher doses ($P < 0.05$).

^f The mean was significantly different from that of the dose of 10 mg/kg ($P < 0.05$).

shown here). The ratio of excretion of CPT-11 into bile to that excreted into urine was 0.98 to 1.42; therefore CPT-11 was excreted equally into bile and urine. On the other hand, SN-38 was mainly excreted into bile, and the excretion ratio was 2.91 to 3.78.

Urinary and biliary excretion of CPT-11, SN-38, and SN-38 glucuronide for 24 h and fecal excretion of CPT-11 and SN-38 are listed in Table 3. From 23.6 to 59.9% of the dose was excreted as CPT-11 for 48 h in the feces as the dose increased from 2 to 40 mg/kg. In contrast, as SN-38 was decreased in dosage the percentage of the dose excreted decreased from 35.8 to 11.5%. CPT-11 excretion in the feces for 48 h after administration was higher than that observed in the bile. SN-38 excretion decreased from 8.4 to 2.4%, while the dose increased from 2 to 40 mg/kg, and these values were much lower than

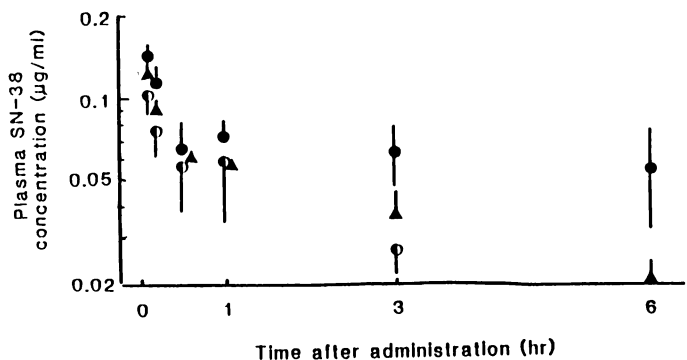


Fig. 3. Plasma SN-38 concentration profiles after i.v. administration of CPT-11 to rats. Male Wistar rats weighing about 150 to 160 g were given injections with 10 (○), 20 (△), and 40 (●) mg of CPT-11 per kg in the tail vein. Blood was collected by cardiac puncture under ether anesthesia. Points, mean of 9 to 12 animals; bars, SD.

those observed in the feces, suggesting the existence of metabolites other than SN-38 in the bile. Treatment with β -glucuronidase increased SN-38 concentration; however, enzyme treatment with the inhibitor β -1,4-saccharolactone did not. Therefore SN-38 glucuronide was thought to be present. SN-38 was mainly excreted as glucuronide into the bile and urine. The total SN-38 content decreased from 11.4 to 3.7% in the urine and from 38.0 to 10.2% in bile, while the dose increased from 2 to 40 mg/kg. The total SN-38 content (SN-38 and its glucuronide) in bile was in good agreement with that found in feces over 48 h after administration, except for the 10-mg/kg group. The SN-38 glucuronide/SN-38 ratios were 3 and 5 in the bile and the urine, respectively.

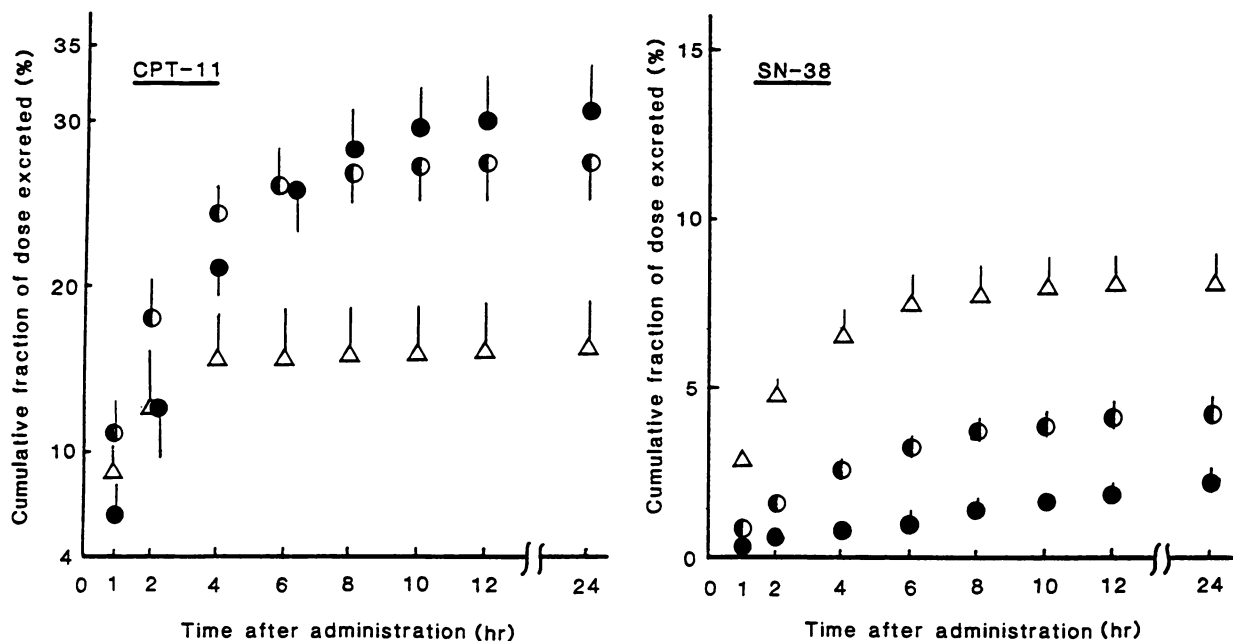


Fig. 4. Cumulative biliary excretion of CPT-11 and SN-38. Male Wistar rats with a bile duct cannula were given 2 (Δ), 10 (\circ), and 40 (\bullet) mg of CPT-11 per kg through a femoral vein cannula. Cumulative percentages of the injected dose excreted as CPT-11 and as SN-38 are shown (left and right, respectively). Points, mean of 4 to 6 animals; bars, SD.

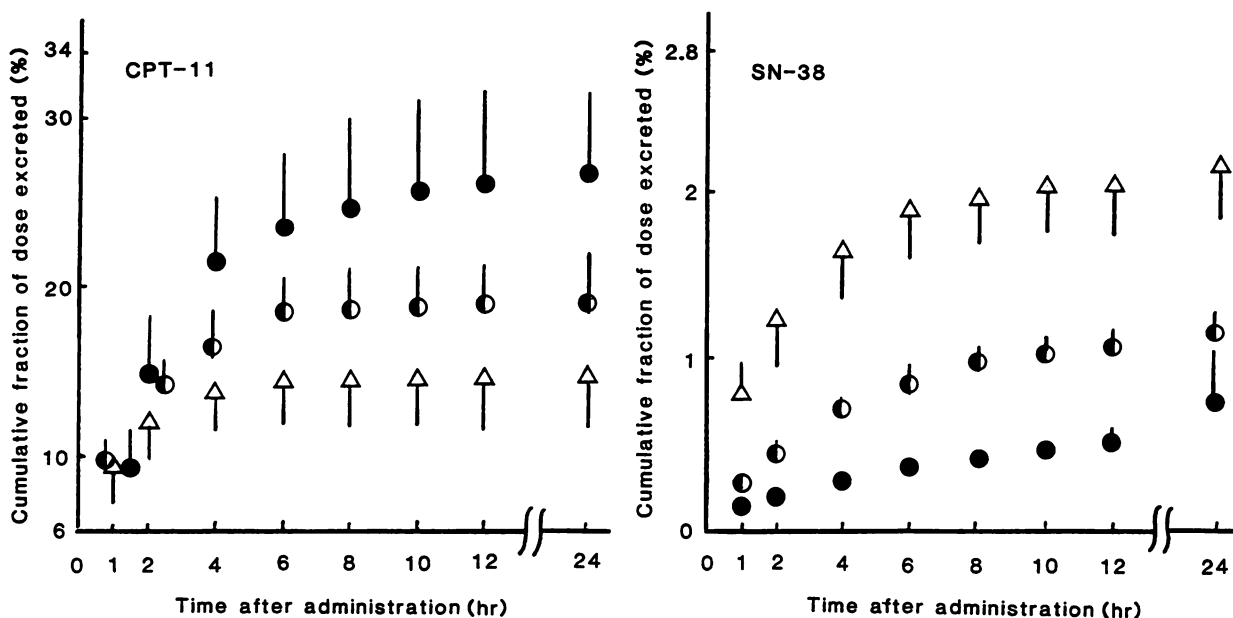


Fig. 5. Cumulative urinary excretion of CPT-11 and SN-38. Male Wistar rats with a bladder cannula were given 2 (Δ), 10 (\circ), and 40 (\bullet) mg of CPT-11 per kg through a femoral vein cannula. Cumulative percentages of the injected dose excreted as CPT-11 and SN-38 are shown (left and right, respectively). Points, mean of 4 to 6 animals; bars, SD.

Renal, biliary, and metabolic clearance was calculated to analyze the nonlinearity of CPT-11 plasma concentration profiles (Table 4). Renal and biliary clearances were relatively constant, ranging from 0.38 to 0.50 and from 0.43 to 0.61 liters/kg·h, respectively. Only metabolic clearance decreased from 2.93 to 0.61 liters/kg·h as the dose increased. The ratio of CL_m to CL_p decreased from 75 to 43% with an increase in dose.

DISCUSSION

The water-soluble derivative of CPT, CPT-11, enabled administration by various routes without opening the lactone ring

which was reported to be related to the activity. Readily available sodium salts of camptothecins are relatively unstable in solution and form a precipitate with a closed lactone ring. CPT-11 shows potent antitumor activity against Walker 256 sarcoma in rats by various routes of administration (15) as has also been reported for mice (13, 14).

Plasma concentration profiles of CPT-11 after i.v. injection (Fig. 2) were quite different at all doses from those of CPT or ECPT. The concentrations of CPT and ECPT decline after i.v. administration rapidly in the distribution phase and relatively slowly in the elimination phase (10). This apparent difference in plasma concentration-time curves was considered to be mainly due to the lipophilicity of the drugs. CPT and ECPT

Table 3 Excretion of CPT-11, SN-38, and SN-38 glucuronide into bile and urine and CPT-11 and SN-38 into feces after i.v. administration of CPT-11 to rats

Route of excretion	% of dose excreted at		
	2 mg/kg	10 mg/kg	40 mg/kg
Urine ^a			
CPT-11	17.5 ± 3.1 ^{b, c}	26.4 ± 3.2	35.1 ± 4.4
SN-38	1.9 ± 0.4 ^d	1.3 ± 0.2 ^c	0.6 ± 0.2
SN-38 glucuronide	9.5 ± 2.0 ^e	6.5 ± 0.8 ^e	3.1 ± 0.7 ^e
Bile ^a			
CPT-11	16.0 ± 3.1 ^d	32.5 ± 4.5	33.7 ± 3.6
SN-38	8.4 ± 0.4 ^d	4.8 ± 0.8	2.4 ± 0.3
SN-38 glucuronide	29.6 ± 2.0 ^d	13.2 ± 0.6	7.3 ± 1.1
Feces ^a			
CPT-11	23.6 ± 3.1 ^{d, f}	45.6 ± 6.4 ^f	59.9 ± 9.2 ^f
SN-38	35.8 ± 0.4 ^e	24.8 ± 4.6 ^{e, g}	11.5 ± 2.0 ^e
SN-38 glucuronide	Not done	Not done	Not done

^a Urine, bile, and feces were collected from different animals. Urine and bile values are those of 0 to 24 h, and feces values are those of 0 to 48 h.

^b Mean ± SD of 4 to 5 animals.

^c The mean was significantly different from that of the dose of 40 mg/kg ($P < 0.05$).

^d The mean was significantly different from those of the two higher doses ($P < 0.05$).

^e The means were significantly different from each other ($P < 0.05$).

^f The means were significantly different from those in bile.

^g The mean was significantly different from the sum of SN-38 and its glucuronide excreted in bile.

Table 4 Clearance of CPT-11 after i.v. administration of CPT-11 to rats

Clearance (liters/kg·h)	Dose (mg/kg)		
	2	10	40
Plasma	3.34 ± 0.52 ^{a, b}	2.22 ± 0.26	1.42 ± 0.22
Renal	0.50 ± 0.10	0.49 ± 0.15	0.38 ± 0.09
Biliary	0.54 ± 0.12 ^c	0.61 ± 0.04	0.43 ± 0.04
Metabolic	2.30	1.12	0.61

^a Mean ± SD of 4 or 5 animals.

^b The mean was significantly different from those of the two higher doses ($P < 0.05$).

^c The mean was significantly different from that of the dose of 40 mg/kg ($P < 0.05$).

are easily excreted because of their high hydrophilicity, which results in their rapid disappearance from plasma. The relative lipophilicity of CPT-11 might slow down the excretion rate and make distribution easier than in the case of CPT or ECPT.

The difference found in the excretion of CPT-11 in bile and feces suggests the possibility that there exist other excretion routes into the gastrointestinal tract, such as gastric or intestinal excretion of CPT-11 other than biliary excretion. The difference in SN-38 excretion found in bile and feces suggests the existence of a metabolite other than SN-38 (Table 3). Incubation of bile from drug-treated animals with a cecum extract from an untreated animal increased the SN-38 content.³ Therefore the metabolite SN-38 glucuronide is believed to be deconjugated by intestinal microflora to SN-38.

Nonlinear plasma pharmacokinetics of CPT-11 was observed (Fig. 2; Table 2). The analysis of clearance showed that metabolic clearance decreased, while renal and biliary clearance remained constant as the dose increased (Table 4). It is likely that metabolic clearance contributed to the nonlinear pharmacokinetics of CPT-11. The ratio of metabolic clearance among the doses was about 4:2:1 for the doses of 2, 10, and 40 mg/kg. This ratio showed a good correlation with total SN-38 excretion (free SN-38 and SN-38 glucuronide) as shown in Table 3, that is, 39:18:10 in bile and 11.4:7.8:3.7 in urine. About 86% of the dose was excreted as SN-38 and its glucuronide in bile and

³ Unpublished data.

urine 24 h after i.v. administration of 40 mg of SN-38 per kg.³ On the assumption that the excretion of SN-38 and its glucuronide is almost complete within 24 h after administration, the total SN-38 excreted equals the total SN-38 formed from CPT-11. The total SN-38 excreted was about 49% at a dose of 2 mg of CPT-11 per kg, and the expected value from the metabolic clearance was 69%, which was the ratio of metabolic clearance to plasma clearance.

Another main factor affecting nonlinear pharmacokinetics is plasma protein binding. The plasma protein binding of CPT-11 could not be measured because of its metabolism in plasma and serum. It was difficult to measure the protein binding of CPT-11 without the effects of SN-38 caused by metabolism. Therefore the contribution of plasma protein binding to the nonlinear plasma decay of CPT-11 remains unclear.

In this paper we showed the nonlinear pharmacokinetics of CPT-11 after i.v. administration to rats. The metabolism of CPT-11 to SN-38 is suggested as one of the reasons for the nonlinear plasma profiles of CPT-11.

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