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ORIGINAL ARTICLE

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Pharmacokinetics of CPT-11 in rhesus monkeys

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Abstract *Purpose*: To examine the pharmacokinetic relationships between humans and monkeys, we studied the disposition of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) and its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), in rhesus monkeys. *Methods*: CPT-11 was administered to a total of six monkeys at doses of 3, 7, 15 and 25 mg/kg by intravenous infusion for 10 min and plasma concentrations and pharmacokinetic parameters of CPT-11 determined. *Results*: Maximum plasma concentrations at 25 mg/kg reached around 10 000 ng/ml, and dropped to 500 ng/ml in 8 h. Plasma concentrations of SN-38 remained between 2 and 10 ng/ml. Mean values of systemic clearance, mean residence time and distribution volume at steady state, the major pharmacokinetic parameters for CPT-11, were 13.3 (ml/min per kg), 192 (min) and 2553 (ml/kg), respectively. The initial plasma concentration ratio of lactone to total CPT-11, 76%, declined to about 20% within 75 min, and the final ratio was about 40% at 8 h; the initial ratio of SN-38 was 72%, dropped to 34% within 70 min and finally recovered to 55% at 8 h. *Conclusion*: Comparison with human data revealed that systemic clearances of CPT-11 and the maximum AUC of SN-38 were not as different between humans and monkeys as between humans and mice, but the metabolic conversion of CPT-11 into SN-38 in monkeys was significantly lower than in humans.

Key words CPT-11 · Pharmacokinetics · Monkey

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Introduction

CPT-11 (irinotecan hydrochloride) is a water-soluble analog of camptothecin, an inhibitor of DNA topoisomerase I. It has clinical therapeutic efficacy against lung, colorectal, cervical and ovarian cancers [4]. CPT-11 is a prodrug which is cleaved into its active metabolite, SN-38, by esterase in the liver and blood [8, 13, 18, 20]. In addition, lactone rings of both CPT-11 and SN-38 undergo nonenzymatic hydrolysis producing biologically inactive carboxylate [12]. The lactone form of SN-38 seems to exert the antitumor and toxic effect when CPT-11 is given.

The pharmacokinetics of CPT-11 have been investigated in mice [8], rats [7], dogs [19] and humans [1, 2, 9, 14–17]. In the present study, we administered CPT-11 at 3, 7, 15 and 25 mg/kg to rhesus monkeys, measured the plasma concentrations of CPT-11 and SN-38 discriminating their lactone and carboxylate forms, and analyzed them pharmacokinetically. Adding these data to those reported previously enabled us to compare the overall findings among several animal species with a special focus upon the pharmacokinetic relationship between monkeys and humans. We empirically compared the ratios of plasma SN-38 to CPT-11, pharmacokinetic parameters and the maximum plasma AUC values among these animal species. Based on these comparisons, we discuss whether the AUC of SN-38 is a common pharmacokinetic parameter related to CPT-11 toxicity.

Materials and methods

Administration of CPT-11 to monkeys

Pure CPT-11 was supplied by Yakulto Honsha Co. (Tokyo, Japan), and was dissolved in sterile saline just before injection.

Female adult rhesus monkeys purchased from Clea Japan (Tokyo) were reared and used in accordance with the animal care and experimental use guidelines of the Central Institute for Experimental Animals, including anesthesia procedures. Monkey chairs were used for handling the monkeys. CPT-11 solution was given at a volume ratio of 2 ml/kg body weight by intravenous infusion using an infusion pump (Terumo Co., Tokyo) for 10 min into the forearms of a total of six monkeys (weight 4.5–5.5 kg), one each at doses of 3, 7 and 15 mg/kg and three at 25 mg/kg.

Preparation of plasma samples

Blood was collected into heparinized tubes 5, 10, 20, 40, 70, 130, 250, 370 and 480 min after initiation of the infusion. When blood samples were not collected as scheduled, the actual time was recorded. Blood was taken from the other forearm until 130 min, and thereafter from a lower hind leg. Plasma was isolated by centrifugation (4000 rpm for 3 min at 4 °C) as soon as possible after blood collection. The plasma was immediately mixed with four volumes of cold methanol, and the mixture was centrifuged under the same conditions. The upper layer was separated and stored at −80 °C until HPLC analysis.

Blood for hematological toxicity testing was taken from a lower hind leg of a monkey anesthetized with ketamine hydrochloride (5 mg/kg) on days 0, 4, 7 and 14.

Determination of plasma concentrations of CPT-11 and SN-38

Lactone and total concentrations of CPT-11 and SN-38 in plasma were determined as described previously [17]. Briefly, 20 µl water for the assay of the lactone form of CPT-11 and SN-38 or 20 µl HCl for the assay of total CPT-11 and SN-38 was added to 200 µl of the separated upper layer obtained as described above and aliquots of 20 µl were applied to a Shimadzu (model LC-10AD) HPLC system with a Hitachi 650-10LC fluorospectrometer and a C_{18} reversed-phase column containing TSK gel ODS-80Ts (4.6 mm ID × 150 mm; Tosoh Co., Tokyo). The mobile phases were tetrahydrofuran/methanol/50 m*M* phosphate, 5 m*M* heptane sulfate (8:32:60 v/v), pH 6.0, for CPT-11 and tetrahydrofuran/50 m*M* phosphate, 5 m*M* heptane sulfate (40:60 v/v), pH 6.0, for SN-38. The flow rate was 1.0 ml/min. The detector was set at an excitation wavelength of 370 nm for CPT-11 and 380 nm for SN-38 and an emission wavelength of 430 nm for CPT-11 and 556 nm for SN-38. The detection limits were 5 ng/ml for CPT-11 and 0.5 ng/ml for SN-38.

Pharmacokinetic analysis

Plasma concentration (Cp) was fitted to the following equations and parameters, then α and V_1 were obtained by a nonlinear least squares regression method (MULTI) [21].

During infusion ($t < \tau$):

$$C_p = \frac{k_0}{\alpha V_1}\{1 - \exp(-\alpha t)\}$$

After infusion ($t \geq \tau$):

$$C_p = \frac{k_0}{\alpha V_1}\{1 - \exp(-\alpha t)\}\exp\{-\alpha(t - \tau)\}$$

where τ and k_0 represent the duration of infusion (10 min) and the infusion rate (dose/min). The area under the plasma concentration-time curve (AUC) from time zero to infinity was calculated by the trapezoidal rule extrapolation. The area from the last point to time infinity was estimated by dividing the last concentration by the terminal rate constant. Standard methods were used to calculate the following pharmacokinetic parameters after constant intravenous infusion: the time-averaged total body clearance (CL_{tot}), area under the first moment of the plasma concentration-time curve (AUMC), mean residence time (MRT), apparent volume of distribution at steady state (Vd,ss).

$$CL_{tot} = \frac{\text{Dose}}{\text{AUC}}$$

$$\text{AUMC} = \int_0^\infty t \times \text{Cpdt}$$

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}}$$

$$\text{Vd,ss} = CL_{tot} \times \text{MRT} - \frac{\tau \cdot \text{Dose}}{2 \cdot \text{AUC}}$$

Results

CPT-11 was administered by 10-min intravenous infusions at 3, 7, 15 and 25 mg/kg to rhesus monkeys; plasma concentrations of both CPT-11 and SN-38 at 25 mg/kg in three monkeys are shown in Fig. 1. Peak plasma concentrations of CPT-11 at this dose reached around 10 000 ng/ml, and dropped to 500 ng/ml in 8 h, while plasma concentrations of SN-38 were maintained between about 10 and 2 ng/ml. In addition, the plasma AUCs of CPT-11 and SN-38 at this dose were 28 700 ± 4500 and 128 ± 48.5 (ng · h/ml), respectively. At a dose of 25 mg/kg of CPT-11, the monkeys showed severe diarrhea, nausea and vomiting resulting in an average 8.5% reduction of body weight, although hematological toxicity was relatively mild. Owing to this severe gastrointestinal toxicity, this dose was taken as the maximum tolerated dose (MTD). Therefore, the plasma concentrations and AUCs observed at this dose

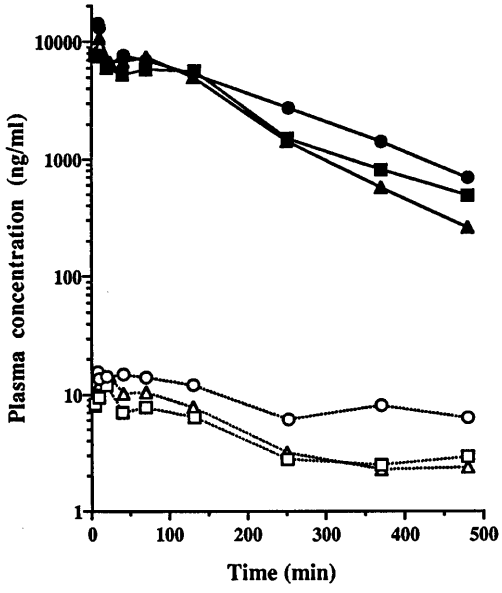

Fig. 1 Plasma concentration-time curves of total CPT-11 and SN-38 in monkeys. CPT-11 (25 mg/kg) was given to three rhesus monkeys as a 10-min infusion, and plasma concentrations of both CPT-11 and SN-38 were measured by HPLC. The different symbols correspond to individual monkeys; closed and open symbols denote CPT-11 and SN-38, respectively

Table 1 Pharmacokinetic parameters of CPT-11 in monkeys

Dose (mg/kg)	α (min^{-1})	V_1 (ml/kg)	AUC (ng · h/ml)	CL_{tot} (ml/min/kg)	MRT (min)	Vd,ss (ml/kg)
3	0.00746	2113	4 420	11.3	133.0	1503
7	0.00649	2446	9 030	12.9	190.3	2455
15	0.00642	2079	22 800	11.0	188.1	2067
25	0.00504	2949	33 800	12.3	238.5	2946
25	0.00578	3514	27 100	15.4	248.8	3832
25	0.00750	2708	25 200	16.6	151.9	2514
Mean	0.00645	2635	28 700[a]	13.3	191.8	2553
SE	0.00096	547	4 500	2.3	45.8	792

[a]Value for dose of 25 mg/kg

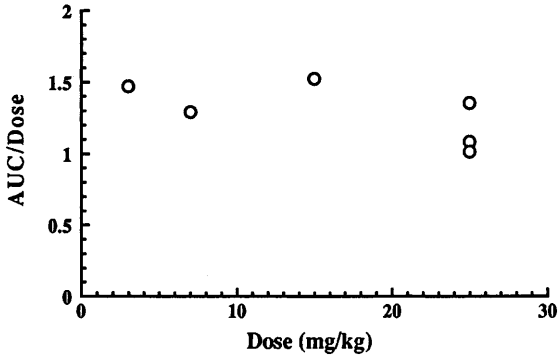

Fig. 2 AUC: dose ratios versus dose of CPT-11 in monkeys. CPT-11 was given to rhesus monkeys at doses of 3, 7, 15 and 25 mg/kg, and the plasma AUC of CPT-11 at each dose was measured. Ratios of AUC: dose (μg · h/ml divided by mg/kg) are plotted against dose

seem to be maximum for monkeys. The major pharmacokinetic parameters were determined (Table 1). The mean values of α, V_1, CL_{tot}, MRT and Vd,ss were 0.00645 (min^{-1}), 2635 (ml/kg), 13.3 (ml/min per kg), 192 (min) and 2553 (ml/kg), respectively. The ratios of AUC to dose of CPT-11 were calculated for the four doses tested, and plotted against CPT-11 dose (Fig. 2). The curve obtained was nearly linear and horizontal against the *x*-axis, indicating linear pharmacokinetics of CPT-11 in the monkey at least within this dose range.

In this study, the lactone plasma concentrations of CPT-11 and SN-38 were measured as well as their total concentrations (Fig. 3). The initial ratio of lactone to total CPT-11 was 76%, but declined to about 20% within 75 min, and the final ratio at 8 h recovered to about 40%. In contrast, for SN-38, this ratio was initially 72%, but dropped to 34% within 70 min and finally recovered to 55% at 8 h. The profiles of both CPT-11 and SN-38 were similar.

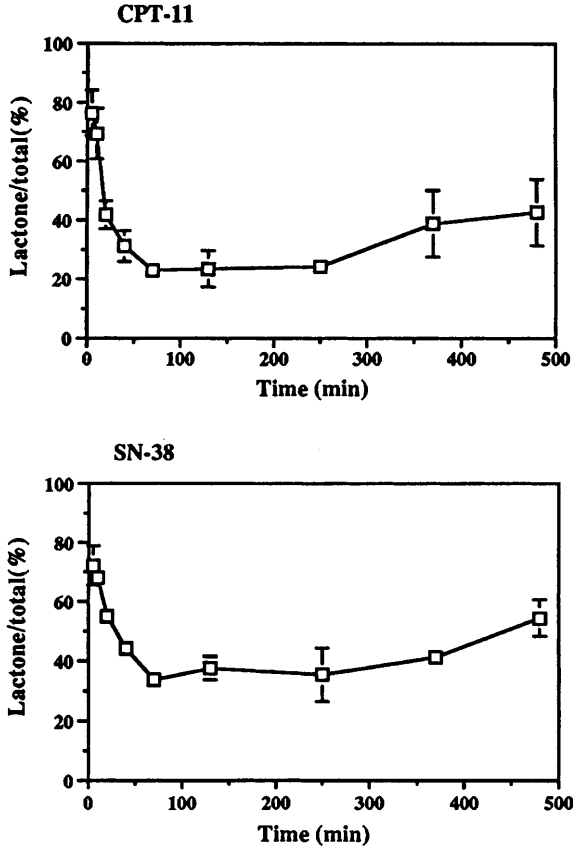

Fig. 3 Changes in lactone/total CPT-11 and SN-38 in plasma over time. CPT-11 was given to three rhesus monkeys at 25 mg/kg, and then the total and lactone forms of CPT-11 and SN-38 were measured. Mean values with standard errors of the ratio (%) of lactone/total concentrations of CPT-11 and SN-38 at various time-points following initiation of a 10-min infusion are plotted

Discussion

In the present study, we examined the pharmacokinetics of CPT-11 in monkeys for the first time and compared them with those of other species, particularly humans. CPT-11 pharmacokinetics is nonlinear in both mice and rats [7, 8]. In human, Negoro et al. [9] have reported a nonlinear increase of AUC, but Rothenberg et al. [14] and Rowinsky et al. [15] have reported a linear relationship between the dose and AUC of CPT-11. In the present study, the infusion time for CPT-11 was 10 min, which was much shorter than the 60–90 min of clinical treatments. Nevertheless, the results in Fig. 2 indicate that the pharmacokinetics of CPT-11 were linear in the monkeys at least in the dose range of 3–25 mg/kg. It suggests that enzymatic conversion of CPT-11 to SN-38 was not saturated under these experimental conditions.

Table 2 Pharmacokinetic parameters of CPT-11 in various species

Species	Dose (mg/kg)	AUC (ng · h/ml)		Cl_{tot} (l/kg · h)	Vd,ss (l/kg)	MRT (h)
		CPT-11	SN-38			
Mice [8]	10	2 960	410	3.38	3.34	–
Rats [7]	10	4 560	245	2.22	3.15	1.43
Monkeys	15	22 800	84	0.66	2.07	3.13
Dogs [19]	10	47 200	91	0.236	1.01	4.3
Humans [15]	9.3	24 440	663	0.446	3.81	12.9

We compared the pharmacokinetic parameters of CPT-11 among mice [8], rats [7], monkeys, dogs [19] and humans [15], at the same dose per body weight, that is 10 mg/kg (the dose for monkeys was a little higher and that for humans was a little lower; Table 2). The human dose was converted from milligrams per meter squared to milligrams per kilogram assuming a ratio of 37. The AUC of CPT-11 is very high in dogs, relatively high in humans and monkeys and low in mice and rats. Reflecting these results, CL_{tot} values were in the following order: mice > rats > monkeys > humans > dogs. It is rational to compare a pharmacokinetic parameter such as CL_{tot} in the dose range showing linear pharmacokinetics. Since the human [15] and monkey dose in Table 2 are within this range, it could be noted that similar levels of CL_{tot} in monkeys and humans indicated their similar pharmacokinetic behavior. The dose of 10 mg/kg in mice and rats is not in the range indicating linear pharmacokinetics, but the respective CL_{tot} for this dose range, which should be lower than 10 mg/kg, would be expected to be the same or higher than the value in Table 2. The only dose studied in dogs was 10 mg/kg [19]. On the other hand, the AUC of SN-38 was highest in humans, relatively high in the mice and rats, and low in monkeys and dogs. The AUC ratios of SN-38 to CPT-11 were 14, 5.4, 2.7, 0.37 and 0.19% for mice, rats, humans, monkeys and dogs, respectively. Although the ratio in humans was significantly lower than in mice, it was one-order higher than in monkeys.

SN-38 is produced by metabolic conversion from CPT-11 in which carboxylesterase in the liver and plasma seems to play a predominant role. Satoh et al. have reported comparative specific activities of several isozymes of this enzyme in the liver of various animal species [18], but these data do not provide total metabolic activities in the liver. Thus, comparative results for the conversion of CPT-11 into SN-38 in the liver and plasma among these animal species have not yet been reported. However, the amount of CPT-11 converted to SN-38 by liver homogenate is similar between humans and monkeys (personal communication, T. Kamataki, Faculty of Pharmaceutical Science, University of Hokkaido). Conversion in the plasma was not detected in either species although the activity was high in mouse plasma. On the other hand, glucuronidation of SN-38 by monkey liver homogenate is significantly higher than that by human material. These results suggest that the lower plasma SN-38 concentration in monkeys than in humans is a consequence of greater glucuronidation of SN-38 rather than of lower production levels.

Considering that the AUC is a pharmacokinetic parameter related to toxicity, the maximum AUCs between mouse and human should be compared. In practice, the maximum AUC is the AUC at 10% of the lethal dose (LD_{10}) or MTD for each animal species. Some experimental evidence led Collins et al. to assert that the human AUC of anticancer drugs at the MTD is equal to the mouse AUC at LD_{10}, allowing the development of a novel method of efficient dose escalation in phase I clinical trials. This was termed 'pharmacokinetically guided dose escalation (PGDE)' [3]. Independently of this, we have found that the cell-killing effects of cell cycle phase-nonspecific agents (type I drugs) are dependent on the AUC and the effects of cell cycle phase-specific agents (type II drugs) are not [10, 11]. From this standpoint the assumption of Collins et al. should be valid for type I drugs, the toxic effects of which are dependent on the AUC. We have retrospectively reviewed the pharmacokinetic data of a number of anticancer drugs, and have found that their assumption is true for many type I drugs, but for far fewer type II drugs [5]. Accordingly, if the AUC is a toxicity-related pharmacokinetic parameter of CPT-11, the mouse AUC of SN-38, a very active metabolite of CPT-11, at the LD_{10} (or MTD) of CPT-11 should approximate the human AUC of SN-38 at the MTD.

To assess the maximum AUC in a single (clinically once in 3–4 weeks) administration schedule only in which the data could be compared, we plotted individual AUC values of CPT-11 and SN-38 in various animal species [7, 8, 15, 19] against CPT-11 doses injected (Fig. 4). In humans [15], when doses are escalated from 100 to 345 mg/m^2 (from 5.4 to 9.3 mg/kg), the AUC of CPT-11 abruptly increases from 4700 to 24 440 (ng · h/ml). In this study, 240 mg/m^2 was regarded as the human MTD and the recommended dose for phase II trials with a schedule every 3 weeks. Therefore, the maximum AUC values of CPT-11 and SN-38 seem to be 15 203 ± 2235 and 274 ± 48, respectively. In mice [8], the AUC of CPT-11 linearly increases between 10 and 40 mg/kg, and that of SN-38 also increases to a lesser degree. Since the MTD for mice in a single injection schedule seems to be around 100 mg/kg, the maximum estimated AUC values of CPT-11 and SN-38 in mice are greater than 23 450 ± 7750 and 1080 ± 110, respectively. Thus, it has been found that the maximum AUC of SN-38 in mice is significantly greater than that in

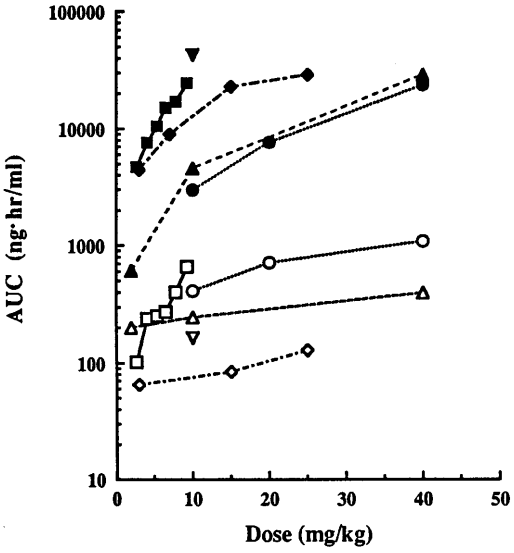

Fig. 4 Comparison of plasma AUC values of CPT-11 and SN-38 among mice, rats, monkeys, dogs and humans. Plasma AUC values of CPT-11 (*closed symbols*) and SN-38 (*open symbols*) at various CPT-11 doses in mice (▲, △) [8], rats (●, ○) [7], monkeys (◆, ◇) (present study), dogs (▼, ▽) [19] and humans (■, □) [15] are plotted against dose

humans. This suggests that the AUC of SN-38 is not related to the toxicity of CPT-11. Kaneda et al. suggested that the maintenance of plasma SN-38 concentrations might be necessary to show antitumor activity in vivo [8]. We analyzed the cell-killing action of camptothecin kinetically and found that it needed a long exposure time and was independent of AUC [6].

The maximum AUC values of CPT-11 and SN-38 in monkeys were 28 656 ± 4511 and 128 ± 48, respectively, since the MTD of CPT-11 was estimated to be 25 mg/kg. Thus, the maximum AUC of SN-38 in monkeys was lower than in humans, although that of CPT-11 in monkeys was higher than in humans. However, the difference in the maximum AUC values between humans and monkeys was minor compared with that between humans and mice. Comparing the plasma elimination curves of SN-38 among mice [8], monkeys (Fig. 1) and humans [1, 2, 9, 14–17], low but effective plasma concentrations of SN-38 were sustained for a long time in humans and monkeys in contrast to its relatively rapid elimination in mice. This is probably at least in part a consequence of the low plasma clearance of CPT-11 in humans and monkeys. The long maintenance of effective concentrations of SN-38 seemed to result in similar AUC levels of SN-38 in humans and monkeys when CPT-11 was administered at each MTD. However, in mice, a very high AUC might be required to produce the relatively long maintenance of an effective concentration of SN-38 because of its rapid elimination.

In some clinical studies, the lactone forms of CPT-11 and SN-38 have been measured [12, 14, 15, 17]. The concentration ratios of lactone to total CPT-11 and SN-38 showed values of 70–90% during the early stages after injection, thereafter rapidly decreasing to lower levels that remained for a very long time. The lower limit of the lactone to total concentration is higher for SN-38 than for CPT-11 [12, 17]. In contrast to these results in humans, the ratios of CPT-11 and SN-38 were similar at every time-point in monkeys (Fig. 3). The hydrolysis of the lactone ring is nonenzymatic and pH-dependent. Therefore, species differences in the plasma concentration ratio of lactone to total drug between humans and monkeys may arise from the relative values of plasma clearance of lactone and carboxylate forms.

In conclusion, the systemic clearance of CPT-11 and the maximum AUC of SN-38 were not as different between humans and monkeys as between humans and mice, but the metabolic conversion of CPT-11 into SN-38 in monkeys was significantly lower than in humans.

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