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International Journal of Pharmaceutics 293 (2005) 137–144
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Cremophor EL releases cyclosporin A adsorbed on blood cells and blood vessels, and increases apparent plasma concentration of cyclosporin A

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Received 11 October 2004; received in revised form 15 December 2004; accepted 17 December 2004

Abstract

We examined the influence of cremophor EL (crEL) on the disposition kinetics of CyA in rats. A dose of 10 mg/kg of CyA in a volume of 750 μL containing 4.3, 16 or 30% concentration of crEL was intravenously administered over 1 min to rats. The values of distribution volume at the steady-state (Vd_{ss}) and total clearance (CL_{tot}) of CyA in the presence of increasing amounts of crEL were decreased to about 1/3–1/5 of those with 4.3% crEL, in a crEL concentration-dependent manner. The values of blood to plasma concentration ratio (RBP) and the apparent tissue to plasma concentration ratio ($K_{p,app}$) of CyA with 30% crEL were both only about 1/2 of those of CyA with 4.3% crEL. Next, rats were intravenously given 30% crEL solution at 30 min after an intravenous administration of CyA (10 mg/kg) with 4.3% crEL. Subsequently, the blood and plasma concentrations of CyA rose significantly to 2.4 and 4.7 times those seen when i.v. 30% crEL was not given, respectively. In an in vitro study, we found that the uptake of CyA by red blood cells is inhibited by crEL, and that CyA adsorbed on the inner surface of blood vessels after the administration of CyA is released by crEL. The disposition kinetics of CyA is altered by i.v. administration in combination with the surfactant vehicle crEL, in a crEL concentration-dependent manner.

Keywords: Cyclosporin A; Disposition kinetics; Adsorption; Blood vessel; Blood cells; Cremophor EL

1. Introduction

Although cyclosporin A (CyA) is widely used in immunotherapy, it is frequently difficult to control the blood concentration effectively owing to interactions

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doi:10.1016/j.ijpharm.2004.12.023

with other drugs. However, the mechanisms involved remain to be fully established.

We have reported that the blood CyA concentration decreased after high-dose steroid therapy because of significant induction of P-glycoprotein and CYP3A in the liver and intestine (Yokogawa et al., 2002). As CyA is a very hydrophobic drug, its disposition kinetics is influenced by drugs and foods, which affect the activities and/or functions of P-glycoprotein and CYP enzymes (Takanaga et al., 2000; Yokogawa et al., 2002). Moreover, as the drug is poorly soluble in various solvents, it is dissolved as micelles in a surfactant vehicle, such as cremophor EL (crEL), for clinical use (e.g., Sandimmun® injection). However, crEL has been reported to inhibit the intestinal absorption and tissue permeability of paclitaxel (Ellis and Webster, 1999; Gelderblom et al., 2002; Bardelmeijer et al., 2002; Yokogawa et al., 2004). These reports suggest that crEL may modify the uptake or adsorption of the drug by cells and tissues.

In this study, we examined the influence of crEL upon the disposition kinetics of CyA after intravenous (i.v.) administration and tried to clarify the mechanism of the interaction.

2. Methods

2.1. Materials

Sandimmun®, Taxol®, Florid-F® and Juvela® injections were purchased from Novartis Pharma Ltd. (Tokyo, Japan), Bristol-Myers Squibb Ltd. (Tokyo, Japan), Mochida Pharma Ltd. (Tokyo, Japan) and Eisai Ltd. (Tokyo, Japan), respectively. Cremophor EL (crEL) was purchased from Sigma Co. (St. Louis, MO). For use, Sandimmun injection (CyA 250 mg) is dissolved in 5 mL of 65% crEL, Taxol injection (paclitaxel 30 mg) in 5 mL of 50% crEL, Florid-F injection (miconazole 200 mg) in 20 mL of 10% crEL, and Juvela injection (tocopherol acetate 100 mg) in 2 mL of 10% crEL.

2.2. Animal experiments

Eight-week-old male Wistar rats (251 ± 8 g; mean ± S.D., Japan SLC Co., Hamamatsu, Japan) were used after having been starved overnight. A dose of 10 mg/kg of CyA in a volume of 750 μL containing 4.3, 16 or 30% crEL was intravenously injected over 1 min. Some rats received additional crEL after CyA administration. Other rats received an i.v. dose of 5, 5 or 2 mg/kg of Taxol, Florid-F or Juvela in a volume of 750 μL of solvent containing 14, 1.67 or 0.133% crEL, respectively, at 30 min after an i.v. administration of 10 mg/kg CyA in 4.3% crEL. Blood samples (100–500 μL) were collected at designated time intervals from the jugular vein under light ether anesthesia. The concentrations of CyA in blood, or red blood cells, and plasma were immediately measured. Rats were killed by decapitation, then the brain, liver, kidney and gut were quickly excised, rinsed well with ice-cold saline, blotted dry, weighed, and stored at −30 °C until assay.

When injected these injection preparations containing crEL in a volume of 750 μL into a rat weighing 250 g, about 15 mL blood, the blood concentration of crEL may be estimated as about 1% for Taxol, 0.1% for Florid-F, and 0.01% for Juvela. Then, these concentrations of crEL were used in the in vitro experiments.

2.3. Assay of CyA in blood, plasma and tissues

The assay for CyA was performed according to Safarcik et al. (2001). Briefly, a sample of blood, plasma or tissue and 1 mL of 0.1 M phosphate buffer (pH 9.2) was added to a glass tube. The tube was vortexed for 15 s, then 4 mL of diethyl ether was added, and the tube was shaken vigorously for 10 min. After centrifugation for 5 min at $3000 \times g$, the organic layer was collected in another glass tube and evaporated for 30 min at room temperature. The residue was taken up in 300 μL of methanol–0.1 M HCl (1:1, v/v) and 1 mL of *n*-hexane, and the tube was shaken for 10 min. The tube was centrifuged for 5 min at $3000 \times g$, then the solvent layer was collected in another glass tube and a 100 μL aliquot was injected into the HPLC system. All samples were analyzed on an HPLC system equipped with a CAPCELL PAK C18 MG column (150 mm × 1.5 mm i.d., Shiseido Co. Ltd., Tokyo, Japan). The absorbance was detected at a wavelength of 205 nm. The mobile phase consisted of acetonitrile:methanol:water (200:80:125) and was pumped at a rate of 0.15 mL/min.

2.4. Uptake of CyA by red blood cells—in vitro study

Rat blood was collected from the jugular artery at 30 min under light ether anesthesia after an intravenous administration of heparin (100 units). The pellet of red blood cells was separated by centrifugation at 1000 × *g* for 10 min, and then washed three times with washing buffer (10 mM Tris, 131 mM NaCl, 5.2 mM KCl, 0.9 mM $MgSO_4$, 0.12 mM $CaCl_2$, 3 mM Na_2HPO_4, pH 7.4). These red blood cells were adjusted to a concentration of 7.5×10^8 cells per 2 mL in incubation buffer (20 mM Tris, 131 mM NaCl, 5.2 mM KCl, 0.9 mM $MgSO_4$, 1.12 mM $CaCl_2$, 3 mM Na_2HPO_4, 5 mM glucose, pH 7.4) and pre-incubated for 3 min at 37 °C. Then, 10 μM of CyA containing 0.01 or 1% crEL was added to 1 mL of red blood cell suspension (10^9 cells), and samples were taken at designated times from 5 to 30 min. Each sample was centrifuged at 4 °C at 1000 × *g* for 5 min, and the concentration of CyA in the supernatant was determined by HPLC. The uptake was measured at both 4 and 37 °C, and the intracellular CyA accumulation was estimated by subtracting the uptake at 4 °C from that at 37 °C, unless otherwise mentioned.

2.5. Adsorption on blood vessels

Rats were given an i.v. dose of 10 mg/kg of CyA containing 4.3% crEL, and after 30 min, about 5–6 cm of the blood vessel from the thoracic aorta to the abdominal aorta was quickly excised. The blood vessel was rinsed twice with 5 mL of saline, and then with 2 mL of saline containing 0, 0.01, 0.1 or 1% crEL, in room temperature. The CyA concentration in the washing saline was determined by HPLC.

2.6. Data analysis

The pharmacokinetic parameters were estimated by means of model-independent moment analysis as described by Yamaoka et al. (1981). The data were analyzed using Student's *t*-test to compare the unpaired mean values of two sets of data. The number of determinations is noted in each table and figure. A value of $P < 0.05$ or 0.01 was taken to indicate a significant difference between sets of data.

3. Results

3.1. Influence of crEL on the blood and plasma concentration–time courses of CyA after an i.v. administration

Fig. 1 shows the concentration-time courses of CyA in whole blood and plasma after an i.v. administration of CyA (10 mg/kg) containing 4.3, 16 or 30% crEL in rats. It is clear that the concentration of CyA in both blood and plasma increased crEL concentration-dependently, and this phenomenon was more marked in the case of plasma.

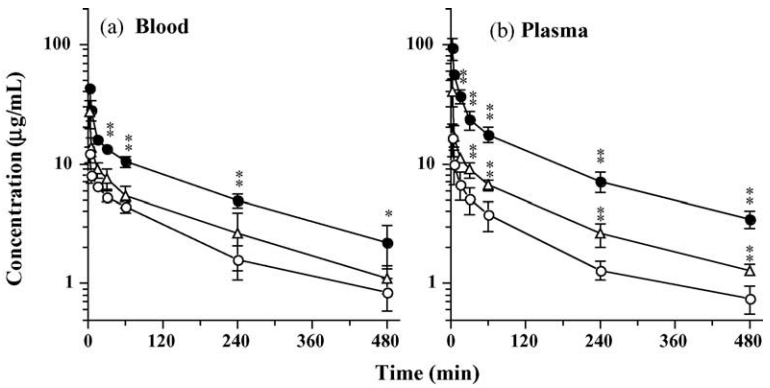

Fig. 1. Concentration–time courses of CyA in whole blood (a) and plasma (b) after an i.v. injection of CyA (10 mg/kg) containing 4.3% (○), 16% (△) or 30% (●) concentration of crEL in rats. Each point with bar represents the mean ± S.D. of four rats. *,** Significantly different from the 4.3% crEL group at $P < 0.05$ and 0.01, respectively.

Table 1
Pharmacokinetic parameters of CyA after an i.v. administration of CyA (10 mg/kg) containing different concentrations of crEL vehicle

Parameters	4.3% crEL		16% crEL		30% crEL	
	Blood	Plasma	Blood	Plasma	Blood	Plasma
AUC (μg min/mL)	1320 ± 135	1270 ± 148	1940 ± 323$^{\#}$	2270 ± 143††	4960 ± 540$^{\#\#}$	5980 ± 860*,††
MRT (min)	232 ± 14	253 ± 62	242 ± 19	232 ± 16	303 ± 18$^{\#\#}$	217 ± 16**
Vd_{ss} (mL/kg)	1750 ± 68	1990 ± 302	1250 ± 101$^{\#\#}$	1020 ± 117*,††	608 ± 126$^{\#\#}$	365 ± 42*,††
CL_{tot} (mL/min/kg)	7.55 ± 0.82	7.90 ± 1.18	5.15 ± 1.05$^{\#}$	4.40 ± 0.28	2.02 ± 0.35$^{\#\#}$	1.67 ± 0.31*,††

Each value represents the mean ± S.D. of four rats.
* Significantly different between blood and plasma at $P < 0.05$.
** Significantly different between blood and plasma at $P < 0.01$.
$^{\#}$ Significantly different from blood in 4.3% crEL at $P < 0.05$.
$^{\#\#}$ Significantly different from blood in 4.3% crEL at $P < 0.01$.
† Significantly different from plasma in 4.3% crEL at $P < 0.05$.
†† Significantly different from plasma in 4.3% crEL at $P < 0.01$.

The pharmacokinetic parameters of CyA are listed in Table 1. The values of the areas under the blood and plasma concentration-time curves (AUC) from zero to infinity in the 16 and 30% crEL groups were significantly larger than those in the 4.3% crEL group. The values of total clearance (CL_{tot}) and distribution volume at the steady-state (Vd_{ss}) of CyA in blood and plasma of the 16 and 30% crEL groups were significantly lower than those in the 4.3% crEL group. In the 30% crEL group, the AUC of plasma was significantly larger than that of blood, whereas the values of CL_{tot} and Vd_{ss} of plasma were significantly smaller than those of blood. In the 4.3% crEL group, there was no significant difference between these parameters in blood and plasma.

3.2. Influence of crEL on the distribution of CyA to red blood cells and tissues

Fig. 2 shows the time course of the ratio of blood to plasma concentration (RBP) of CyA after an i.v. administration of CyA (10 mg/kg) containing 4.3, 16 or 30% crEL in rats. The RBP value reached a plateau about 60 min after administration, and the levels were significantly lowered in a crEL concentration-dependent manner.

Fig. 3 shows the concentrations of CyA in the brain, liver, kidney, gut and plasma, and the values of apparent tissue to plasma concentration ratio ($K_{p,app}$) at 1 h after an i.v. administration of CyA (10 mg/kg) containing 4.3 or 30% crEL in rats. Although the concentrations varied widely among tissues, the concentrations were not significantly different in the 4.3 and 30% crEL groups, even though the plasma concentration in the 30% crEL group was significantly increased to about three times that in the 4.3% crEL group. As a result of the difference in plasma concentration, however, all values of $K_{p,app}$ of these tissues in the 30% crEL group were significantly smaller than those in the 4.3% crEL group.

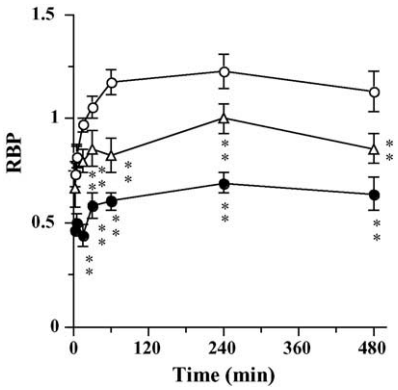

Fig. 2. Time courses of blood to plasma concentration ratio (RBP) of CyA after an i.v. injection of CyA (10 mg/kg) containing 4.3% (○), 16% (△) or 30% (●) concentration of crEL in rats. Each point with bar represents the mean ± S.D. of four rats. **Significantly different from the 4.3% crEL group at $P < 0.01$.

3.3. Influence of additional crEL on the blood and plasma concentration–time courses of CyA

At 30 min after an i.v. injection of CyA (10 mg/kg) containing 4.3% crEL, 750 μL of 30% crEL was addi-

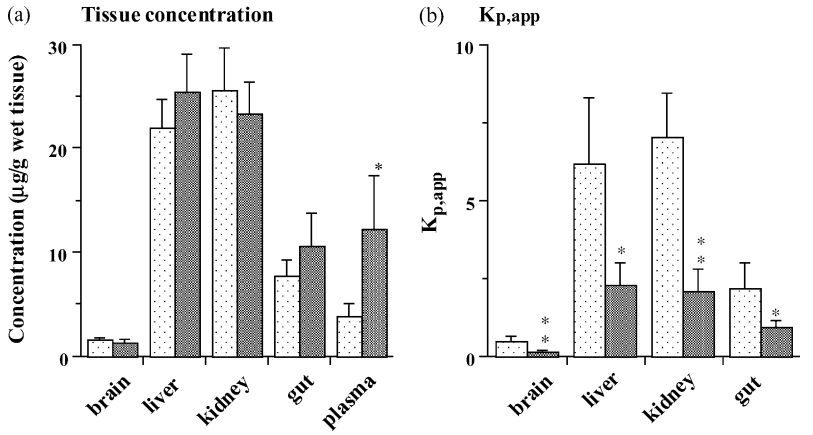

Fig. 3. Tissue and plasma concentration (a) and the apparent tissue to plasma concentration ratio ($K_{p,app}$) (b) of CyA at 1 h after an i.v. injection of CyA (10 mg/kg) containing 4.3% (⬚) or 30% (▩) crEL in rats. Each column with bar represents the mean ± S.D. of four rats. *,** Significantly different from the 4.3% crEL group at $P < 0.05$ and 0.01, respectively.

tionally injected, and the subsequent changes of CyA concentration in blood and plasma are shown in Fig. 4. After additional injection of 30% crEL, the blood and plasma concentrations were significantly increased to about 2.5 and 5 times those of the control, respectively, and the high levels were maintained until 480 min.

Fig. 5 shows the time courses of the RBP calculated from the blood and plasma concentrations of CyA (Fig. 4). The value of RBP at 30 min after administration of 30% crEL was significantly decreased to about 1/2 of the control up to 480 min.

3.4. Influence of crEL on in vitro uptake of CyA into red blood cells

We examined the adsorption and the uptake of CyA (final concentration 10 μM) containing 0.01 or 1% crEL into red blood cells in vitro. Fig. 6 shows the time courses of the uptake of CyA into red blood cells at 4 and 37 °C. At 4 °C, the adsorption of CyA with 1% crEL was about 1/4 of that with 0.01% crEL. The net uptake of CyA was small in the presence of 0.01% crEL, but no apparent net uptake was observed in the presence of 1% crEL. These data indicate that a high

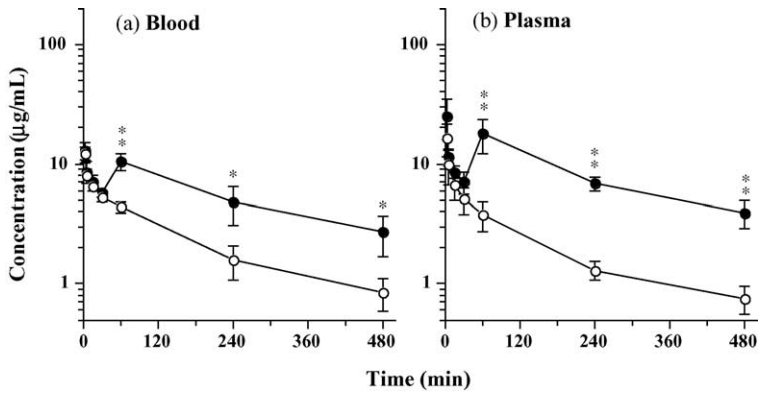

Fig. 4. Influence of crEL on the blood (a) and plasma (b) concentration–time courses of CyA after an i.v. injection of CyA. Rats were intravenously injected with CyA (10 mg/kg) containing 4.3% crEL (◯), and at 30 min after the injection, rats were given additional i.v. crEL 30% (●). Each point with bar represents the mean ± S.D. of four rats. *,** Significantly different from rats in the 4.3% crEL group at $P < 0.05$ and 0.01, respectively.

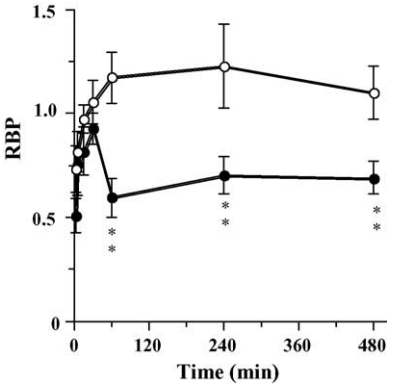

Fig. 5. Time courses of blood to plasma concentration ratio (RBP) of CyA after an i.v. injection of CyA (10 mg/kg) containing 4.3% concentration of crEL in rats. Footnotes and symbols are the same as in Fig. 4. *,** Significantly different from the control at 30 min at $P < 0.05$ and 0.01, respectively.

concentration of crEL inhibits not only adsorption of CyA, but also uptake of CyA into blood cells.

3.5. Recovery of adsorbed CyA from blood vessels

Finally, we examined the effect of crEL upon the adsorption of CyA on blood vessels. Fig. 7 shows the recovery of CyA from a blood vessel removed at 30 min

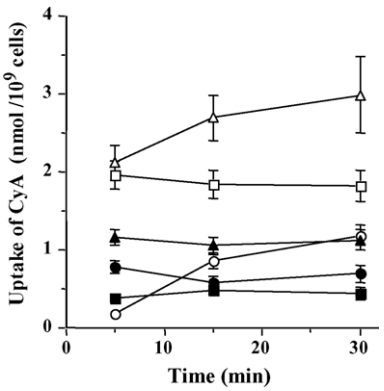

Fig. 6. Time courses of in vitro uptake of CyA into red blood cells in PBS containing 0.01% (open symbol) or 1% crEL (closed symbol). Red blood cells (10^9 cells) were pre-incubated in 1 mL of PBS at 4 °C (squares) or 37 °C (triangles) for 5 min, then 10 μM CyA was added, and the CyA concentration in red blood cells was determined after 5, 15 and 30 min incubation at each temperature. The net uptake of CyA (circles) was obtained by subtracting the concentration at 4 °C from the corresponding value at 37 °C. Each point with bar represents the mean ± S.D. of four experiments.

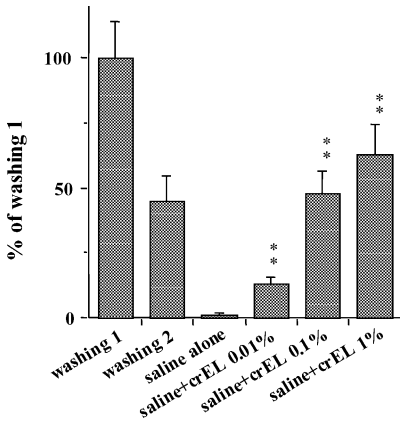

Fig. 7. Release of CyA from the blood vessel by crEL. The blood vessel (5–6 cm) was removed from the thoracic aorta to the abdominal aorta of the rat at 30 min after an i.v. injection of CyA (10 mg/kg). It was washed twice with 5 mL of saline, and then rinsed with 2 mL of saline alone or containing 0.01, 0.1 or 1% crEL. The CyA recovery is presented percentage of the amount of CyA recovered with the first saline wash (washing 1). **Significantly different from saline alone at $P < 0.01$.

after an i.v. administration of CyA in rats. The blood vessel was rinsed twice with 5 mL of saline, and then rinsed with 2 mL of saline, or saline containing 0.01, 0.1 or 1% crEL. The recovery of CyA is presented as a relative percentage with respect to the amount of CyA in the first saline wash (washing 1). After washing with saline twice, only a little CyA was detected in a subsequent saline wash, but a crEL-containing wash recovered 20–60% of the amount in the first washing (washing 1), in a concentration-dependent manner.

3.6. Influence of crEL-containing injections on the blood and plasma concentrations of CyA

Rats were i.v. given Taxol, Florid-F or Juvela injection at 30 min after i.v. administration of CyA (10 mg/kg) containing 4.3% crEL. As shown in Fig. 8, the blood and plasma concentrations of CyA were significantly increased at 30 min after administration of Taxol, Florid-F or Juvela compared with the control (CyA alone). The injection preparations of Taxol, Florid-F and Juvela contained 14, 1.67 and 0.133% crEL, respectively, and the extent of increase of CyA concentration in blood and plasma was dependent upon the content of crEL in these preparations. Moreover, after injection of these drugs, the concentrations of

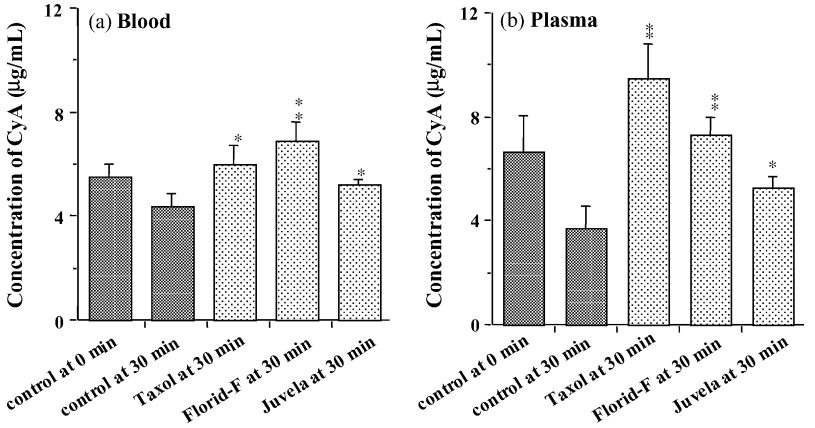

Fig. 8. Influence of various commercial injections containing crEL on the blood (a) and plasma (b) concentrations of CyA. Rats were intravenously injected with CyA (10 mg/kg) containing 4.3% crEL, and at 30 min after the injection, rats were intravenously given saline (control), Taxol (5 mg/kg, 14% crEL), Florid-F (5 mg/kg, 1.67% crEL) or Juvela (2 mg/kg, 0.133% crEL). The CyA concentrations in whole blood and plasma in each group were determined at 30 min after each injection. Each column with bar represents the mean ± S.D. of four rats. *,** Significantly different from the control at 30 min at $P < 0.05$ and 0.01, respectively.

CyA were significantly higher in plasma than in whole blood. This suggests that crEL contained in these drug preparations releases CyA from blood cells into plasma by micellization.

4. Discussion

We found in this study that the injection vehicle crEL significantly influences the disposition kinetics of CyA. The AUC of CyA in whole blood and plasma increased and the values of Vd_{ss} and CL_{tot} decreased in a crEL concentration-dependent manner (Fig. 1, Table 1). The low Vd_{ss} after i.v. injection of CyA in a vehicle containing a high concentration of crEL, may be a consequence of inhibition by crEL of permeation or transport of CyA into tissues and blood cells (Figs. 2, 3 and 6). The low CL_{tot} may also be associated with the inhibition of CyA uptake into hepatocytes. Moreover, we observed an interesting effect of crEL on CyA behavior in blood. When 30% crEL was administered at 30 min after the i.v. injection of CyA, the blood and plasma concentrations of CyA were significantly increased about 2.5- and 5-fold, respectively (Fig. 4) and the RBP value was markedly lowered (Fig. 5), suggesting not only inhibition of CyA uptake into red blood cells, but also mobilization of CyA from some tissues by crEL.

It is well known that CyA is readily adsorbed onto transwell surfaces (Lee et al., 2001) and polyvinyl chloride infusion tubes (Shibata et al., 2000; Yano et al., 2001). Thus, we considered that CyA adsorbed on blood vessels after i.v. injection might be released into plasma following the subsequent administration of crEL. As shown in Figs. 4 and 7, significant amounts of CyA were released or washed out from blood vessels by additional crEL. Therefore, CyA adsorbed on tissues such as blood vessels was presumably released into plasma as a result of micellization by crEL, and the micellization also appeared to inhibit uptake of CyA by tissues. This high drug concentration in plasma is only an apparent increase due to micellization with crEL, and does not represent an increase in free drug which is permeable into tissues.

These results suggest that the disposition kinetics of CyA may be changed by other injection preparations containing crEL. As expected, additional injection of some commercial injection preparations containing crEL increased CyA concentration in plasma more than in whole blood (Fig. 8). Because these injections did not cause hemolysis, the increase of CyA in plasma might have been due to release of adsorbed CyA from the inner surface of blood vessels. The above findings (Figs. 1 and 4) are consistent with the report that crEL remains for a long time in blood (van Zuylen et al., 2001). Since there may be an interaction between crEL and other hydrophobic or highly adsorbed drugs, care is needed when using hydrophobic drugs together with crEL-containing injection prepa-

rations, because unexpectedly high drug concentrations in plasma may cause clinicians to decrease the dosage.

In conclusion, we have identified a new type of drug interaction. The micellization vehicle crEL significantly influenced the disposition kinetics of CyA and increased apparent drug concentrations in plasma, in a crEL concentration-dependent manner. Similar interaction may occur when other hydrophobic or highly adsorbed drugs are administered in combination with injection preparations containing surfactant vehicles such as crEL. This type of drug interaction may result in incorrect dosage planning based on therapeutic drug monitoring in the clinic. This is a new type of drug interaction.

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