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Disposition kinetics of taxanes after intraperitoneal administration in rats and influence of surfactant vehicles

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Abstract

Rats were intraperitoneally administered 40 mg kg^{-1} of paclitaxel or docetaxel dissolved in various drug solutions. The drug solutions were prepared using 20 mL of saline, adding 4.2% Cremophor EL (crEL) for paclitaxel (TXL), and 1.5% Polysorbate-80 (PS-80) (TXT), 7.5% PS-80 (TXT+PS-80) or 4.2% crEL (TXT+crEL) for docetaxel. The apparent first-order absorption rate constant from the peritoneal cavity (k_a) of TXL was about one-twentieth of that of TXT. The ratio of the area under the concentration–time curve of drug in plasma over that in ascites for TXL was about one-third of that of TXT. The values of the above ratio and the k_a of TXT+PS-80 and TXT+crEL were similar to those of TXL. After intraperitoneal administration, the values of the blood-to-plasma concentration ratio in the four groups were similar and independent of time. In the in-vitro study, PS-80 and crEL caused similar, concentration-dependent decreases of drug permeation into red blood cells after a 15-min incubation of rat blood with 10 μg mL^{-1} of TXL. We demonstrated that the disposition kinetics of taxanes after intraperitoneal administration to rats was strongly influenced, in a concentration-dependent manner, by the surfactant vehicle used, crEL or PS-80.

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Introduction

The taxane alkaloids, paclitaxel and docetaxel, are widely used in the treatment of ovarian, breast and lung cancers (Gelmon 1994; Rowinsky 1994). Further, taxanes are effective against advanced gastric cancer (Ajani et al 1998; Ohtsu et al 1998). The anti-cancer activity is related to stabilization and promotion of the assembly of microtubules. When systemically administered, these drugs generally induce dose-dependent side effects, such as leucopenia and neutropenia.

Peritoneal tumour occurs in about 10–15% of cases with gastric cancer and in about 50–60% of relapsed cases after gastrectomy. In general, however, the treatment of peritoneal tumour is ineffective, and the 5-year survival rate is extremely low even after surgical resection, radiotherapy and chemotherapy. Recently, intraperitoneal infusion of taxane anti-cancer drugs has been tried in our hospital to treat peritoneal tumours or dissemination, and is more effective, with fewer side effects, than systemic intravenous administration (Fushida et al 2002a, b). We found in those studies that after intraperitoneal injection at the same dose, paclitaxel gave a much lower concentration than that of docetaxel in the systemic circulation.

Paclitaxel and docetaxel have rather similar chemical and physical characteristics, such as log P (3.7, 3.2) and molecular weight (854, 862), being barely soluble in various solvents. They are therefore used as micellar preparations, Taxol and Taxotere, which are paclitaxel in Cremophor EL (crEL) and docetaxel in Polysorbate-80 (PS-80), respectively.

In this study, we examined the disposition kinetics of docetaxel and paclitaxel after intraperitoneal administration in rats, and we also investigated the influence of the surfactants used in the injection preparations.

Materials and Methods

Materials

Taxol and Taxotere injections were purchased from Bristol-Myers Squibb Ltd (Tokyo, Japan) and Aventis Pharma Ltd (Tokyo, Japan), respectively. Taxol injection contains 30 mg of paclitaxel in 5 mL of 50% crEL. Taxotere injection contains 20 mg of docetaxel in 2 mL of 29.5% PS-80. Paclitaxel and PS-80 were purchased from Wako Pure Chemical Industries (Osaka, Japan). crEL was purchased from Sigma Co. (St Louis, MO). Docetaxel was purchased from LKT Laboratories Inc. (St. Paul, MN).

Animal experiments

All animal experiments were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee of Kanazawa University. Eight-week-old female Donryu rats (Japan SLC Co., Hamamatsu, Japan) were used after having been starved overnight. The peritoneal injection solutions were prepared using commercial preparations, Taxol injection and Taxotere injection, after appropriate dilution with sterile saline. The rats were administered 40 mg kg^{-1} of paclitaxel or docetaxel intraperitoneally in a volume of 20 mL of saline containing 0.2% blue dextran as a volume marker, so that the resulting peritoneal solution contained 4.2% crEL for paclitaxel and 1.5% PS-80 for docetaxel. For examination of the influence of surfactants on the kinetics of docetaxel (40 mg kg^{-1}), the peritoneal solution was prepared by dissolving docetaxel in crEL or PS-80 and diluting to a surfactant concentration of 4.2% or 7.5%. Blood samples (400 μL each) were collected at designated time intervals from the jugular vein under light ether anaesthesia and ascites samples (100 μL each) were similarly collected. The plasma samples were separated by centrifugation and stored at $-30\,^{\circ}$C until assay.

Assay of paclitaxel and docetaxel in blood and ascites fluid

The assays for paclitaxel and docetaxel were performed according to Loos et al (1997). Briefly, a sample of 50–200 μL, 3 mL of acetonitrile–n-butyl chloride (1:4 v/v) and 200 μL of docetaxel or paclitaxel (0.12 μg mL^{-1}) as an internal standard were added to a glass tube. The sample was mixed vigorously for 2 min, followed by centrifugation for 10 min at 3000 *g*. The organic layer was collected in another glass tube and evaporated for 40 min at 55 °C. A volume of 250 μL of methanol–water (1:1 v/v) was added to the residue and after vortex-mixing, 150 μL of the supernatant was injected into the HPLC system. All samples were analysed on an HPLC system equipped with a Shim-pack CLC-ODS column (150 × 6.0 mm i.d.; Shimadzu). The absorbance was detected at a wavelength of 230 nm. The mobile phase consisted of methanol–0.3% phosphoric acid (2:1 v/v) and was pumped at a rate of 1 mL min^{-1}. The limit of quantification was about 0.05 μg mL^{-1} and the linear regression coefficients were 0.985–0.998. The coefficients of variance for the within-run and between-run precisions were below 7%.

Pharmacokinetic calculations

Pharmacokinetic parameters were calculated using the one-compartment model according to Kuzuya et al (1994). The rate of drug loss from the peritoneal cavity can be described by equation 1.

$$\frac{dX_p}{dt} = -k_a \cdot X_p \quad (1)$$

The drug, which enters the systemic circulation at an apparent first-order rate, is likewise eliminated through a first-order process according to equation 2.

$$\frac{dX_s}{dt} = k_a \cdot X_p - k_e \cdot X_s \quad (2)$$

These two equations can then be transformed to equations 3 and 4, respectively.

$$C_p = \frac{X_0}{Vd_p} \cdot e^{-k_a \cdot t} \quad (3)$$

$$C_s = \frac{F \cdot k_a \cdot X_0}{Vd_s(k_e - k_a)} \cdot \left(e^{-k_a \cdot t} - e^{-k_e \cdot t}\right) \quad (4)$$

where F is the fraction of the administered dose (X_0) that is absorbed following peritoneal administration, k_a is the apparent first-order absorption rate constant from the peritoneal cavity to the systemic circulation, k_e is the apparent first-order elimination rate constant from the systemic circulation, X_p and C_p are the amount and concentration, respectively, of drug in the peritoneal cavity, X_s and C_s are the amount and concentration, respectively, of drug in the systemic circulation, X_0 is the amount injected, Vd_p and Vd_s are the apparent volume of distribution in the peritoneal cavity and in the systemic circulation, respectively, and t is time.

To calculate the pharmacokinetic parameters, data were fitted to this model (equations 3 and 4) using the MULTI program (Yamaoka et al 1981). The area under the drug concentration–time curve from 0 to 24 h in ascites ($AUC_{a,\ 0-24\,h}$) or in plasma ($AUC_{p,\ 0-24\,h}$) was estimated by using the trapezoidal method.

Data analysis

The data were analysed using Kruskal–Wallis test to compare variant sets of data. The number of determinations is noted in each table and figure. The criterion of a significant difference between sets of data was taken to be $P < 0.05$.

Results

Ascites and plasma concentration–time courses of taxanes after intraperitoneal administration

Rats were intraperitoneally administered 40 mg kg^{-1} of paclitaxel (4.2% crEL) or docetaxel (1.5% PS-80), and the

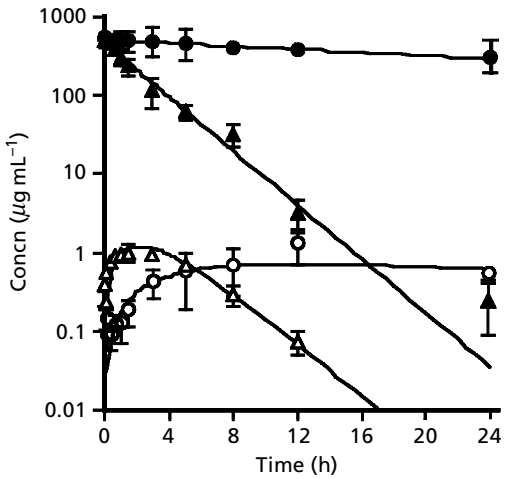

Figure 1 Concentration–time courses of paclitaxel (circles) and docetaxel (triangles) in ascites fluid (closed symbols) and plasma (open symbols) after an intraperitoneal injection of 40 mg kg^{-1} of paclitaxel in 4.2% crEL or 40 mg kg^{-1} of docetaxel in 1.5% PS-80 to rats. Each point and bar represents the mean ± s.d. of measurements from three rats. Each line represents the simulated curve of paclitaxel or docetaxel obtained by using the calculated parameters and the MULTI program.

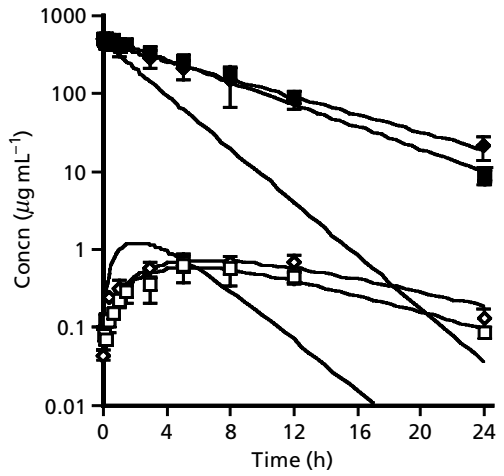

Figure 2 Concentration–time courses of docetaxel in ascites fluid (closed symbols) and plasma (open symbols) after an intraperitoneal injection of 40 mg kg^{-1} of docetaxel in 7.5% PS-80 (diamonds) or 40 mg kg^{-1} of docetaxel in 4.2% crEL (squares) to rats. Each point and bar represents the mean ± s.d. of measurements from three rats. Each line represents the simulated curve of docetaxel after injection of 1.5% PS-80, 7.5% PS-80 or 4.2% crEL obtained by using the calculated parameters and the MULTI program.

concentrations of paclitaxel and docetaxel in ascites fluid and plasma of venous blood were measured (Figure 1). The concentration of paclitaxel in ascites decayed very slowly, whereas that of docetaxel rapidly decreased. Although the plasma concentrations of both taxanes were very low, that of paclitaxel gradually increased until 12 h and that of docetaxel reached a maximum at 1.5 h and then decreased rapidly. On the other hand, the ascites concentration of docetaxel after an intraperitoneal injection of 4.2% crEL or 7.5% PS-80 solution decreased more slowly than after 1.5% PS-80 solution, and the plasma concentrations showed a slower decline (Figure 2).

Table 1 shows the values of $AUC_{a,\ 0\text{–}24\,h}$ and $AUC_{p,\ 0\text{–}24\,h}$ of paclitaxel and docetaxel estimated by using the trapezoidal method. The values of $AUC_{a,\ 0\text{–}24\,h}$ and $AUC_{p,\ 0\text{–}24\,h}$ of paclitaxel were significantly larger, by about 8 and 3 times, than those of docetaxel, respectively. Consequently, the value of the $AUC_{p,\ 0\text{–}24\,h}/AUC_{a,\ 0\text{–}24\,h}$ ratio of paclitaxel was about one-third of that of docetaxel. After intraperitoneal injection of docetaxel in 4.2% crEL or 7.5% PS-80, the value of the $AUC_{p,\ 0\text{–}24\,h}/AUC_{a,\ 0\text{–}24\,h}$ ratio of docetaxel approached that of paclitaxel after injection of 4.2% crEL solution.

Table 2 shows the pharmacokinetic parameters of paclitaxel and docetaxel, obtained by fitting the data to the compartment model. The k_a and k_e values of paclitaxel were extremely small (about one-seventh to one-twentieth and one-third of those of docetaxel, respectively). These parameters in the case of docetaxel were lowered by adding crEL or PS-80 (7.5%) and approached those of paclitaxel. The lines in Figures 2 and 3, which were calculated by using these parameters, agreed well with the observed values.

In-vivo influence of vehicles on permeation of taxanes into red blood cells

Figure 3 shows the time courses of the blood-to-plasma concentration ratio (RBP) after an intravenous or intraperi-

Table 1 Area under ascites or plasma concentration–time curve (AUC) of paclitaxel and docetaxel after intraperitoneal administration (40 mg kg^{-1}) in crEL or PS-80 solution to rats.

	TXL	TXT	TXT + crEL	TXT + PS-80
$AUC_{a,\ 0\text{–}24\,h}$ (μg h mL^{-1})	8870 ± 790*	1170 ± 120	3520 ± 110	3130 ± 320
$AUC_{p,\ 0\text{–}24\,h}$ (μg h mL^{-1})	18.4 ± 3.3*	6.93 ± 1.32	8.59 ± 1.23	11.4 ± 1.1
AUC_p/AUC_a	0.00207 ± 0.00029*	0.00592 ± 0.00153	0.00244 ± 0.00026	0.00364 ± 0.00026

TXL, paclitaxel–4.2% crEL; TXT, docetaxel–1.5% PS-80; TXT+crEL, docetaxel–4.2% crEL; TXT+PS-80, docetaxel–7.5% PS-80; $AUC_{a,\ 0\text{–}24\,h}$ (μg h mL^{-1}), area under ascites concentration–time curve from 0 h to 24 h; $AUC_{p,\ 0\text{–}24\,h}$ (μg h mL^{-1}), area under plasma concentration–time curve from 0 h to 24 h. Each value represents the mean ± s.d. of 3 rats; *$P < 0.05$ vs TXT.

Table 2 Pharmacokinetic parameters of paclitaxel and docetaxel after intraperitoneal administration (40 mg kg^{-1}) in crEL or PS-80 solution to rats.

	Vd_p (mL)	k_a (h^{-1})	Vd_s/F (mL)	k_e (h^{-1})
TXL	20.9 ± 0.3	0.019 ± 0.0018*	1030 ± 230	0.169 ± 0.008
TXT	22.5 ± 2.8	0.394 ± 0.021	2550 ± 480	0.572 ± 0.104
TXT+crEL	19.6 ± 0.7	0.165 ± 0.004	6060 ± 1090	0.194 ± 0.038
TXT+PS-80	23.8 ± 1.0	0.130 ± 0.005	4410 ± 550	0.181 ± 0.033

Vd_p, apparent volume of distribution in the peritoneal cavity; k_a (h^{-1}), apparent first-order absorption rate constant from the peritoneal cavity; Vd_s/F, apparent volume of distribution in the systemic circulation; k_e, apparent first-order elimination rate constant from the systemic circulation; TXL, paclitaxel–4.2% crEL; TXT, docetaxel–1.5% PS-80; TXT+crEL, docetaxel–4.2% crEL; TXT+PS-80, docetaxel–7.5% PS-80. Each value represents the mean ± s.d. of 3 rats; *$P < 0.05$ vs TXT.

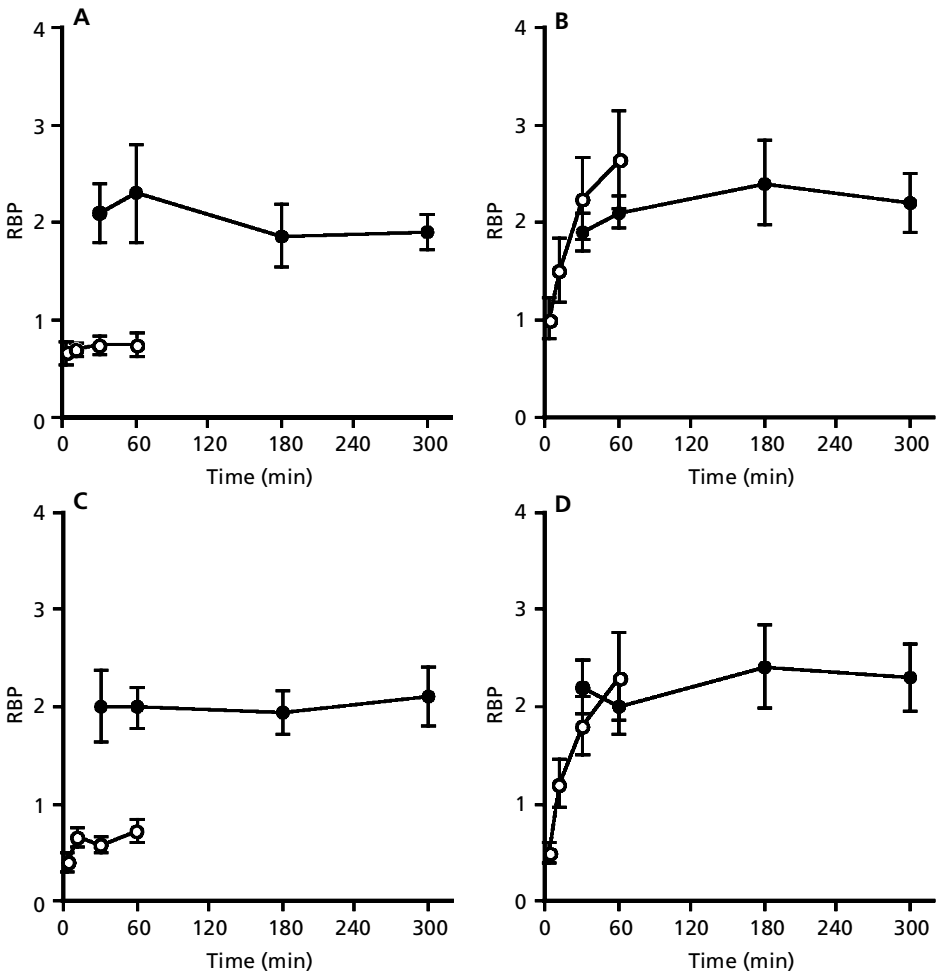

Figure 3 Time courses of blood-to-plasma concentration ratio (RBP) of paclitaxel and docetaxel after intravenous (open circles) or intraperitoneal administration (closed circles) to rats. Rats were intravenously or intraperitoneally administered 0.25 mL or 20 mL of a solution of paclitaxel in 42% or 4.2% crEL (A), docetaxel in 15% or 1.5% PS-80 (B), docetaxel in 42% or 4.2% crEL (C) or docetaxel in 75% or 7.5% PS-80 (D) (each 5 mg kg^{-1} or 40 mg kg^{-1}), respectively. Each point represents the mean ± s.d. of measurements from three rats.

toneal administration of taxanes. Rats were intravenously administered 0.25 mL of paclitaxel 42% crEL solution, docetaxel 15% PS-80 solution, docetaxel 42% crEL solution or docetaxel 75% PS-80 solution to provide a dose of 5 mg kg^{-1} of each anti-cancer drug. Other rats received intraperitoneal administration of 20 mL of paclitaxel 4.2%

crEL solution, docetaxel 1.5% PS-80 solution, docetaxel 4.2% crEL solution or docetaxel 7.5% PS-80 solution to provide a dose of 40 mg kg^{-1} of each anti-cancer drug.

After intravenous administration of 42% crEL solution of paclitaxel and docetaxel, the RBP values for these drugs remained low (about 0.5) for 60 min. However, in the case of intravenous administration of 15% PS-80 solution of docetaxel, the RBP increased gradually from about 1 to 2.5 over 1 h, whereas the RBP of 75% PS-80 solution of docetaxel increased gradually from about 0.5 (lower than that of 15% PS-80 solution). On the other hand, after intraperitoneal administration, the values of RBP for each drug in the four groups were all similar at over 2, independent of time.

In-vitro influence of vehicles on permeation of paclitaxel into red blood cells

Figure 4 shows the effects of PS-80 and crEL on the RBP for paclitaxel at 15 min after incubation of rat blood with 10 μg mL^{-1} of the drug. Both surfactants decreased the RBP with similar potency in a concentration-dependent manner.

Discussion

We found that the ascites and plasma concentration–time courses of paclitaxel and docetaxel in rats after intraperitoneal administration were quite different (Figure 1). In particular, the apparent first-order absorption rate constant from the peritoneal cavity, k_a, of paclitaxel was about one-twentieth of that of docetaxel. We considered that surfactants contained in the injection preparations had probably influenced the disposition kinetics of the drugs, because paclitaxel and docetaxel have similar chemical and physical characteristics. In this study, we diluted Taxol injection to 30 mg of paclitaxel in 5 mL of 50% crEL, and Taxotere injection to 20 mg of docetaxel in 2 mL of 29.5% PS-80. In the clinical study, therefore, paclitaxel solution contained 1% crEL and docetaxel solution contained 0.2% PS-80, whereas in the experiments in rats, paclitaxel solution contained 4.2% crEL and docetaxel solution contained 1.5% PS-80. Consequently, two possibilities could be considered: the tissue permeability of paclitaxel is lower than that of docetaxel, or crEL suppresses drug permeation from the peritoneal cavity to the systemic circulation. An effect of crEL on the pharmacokinetics of paclitaxel has been reported (Sparreboom et al 1996; Bardelmeijer et al 2002; Gelderblom et al 2002). Thus, we examined the two possibilities and obtained the following results. When injection solutions of docetaxel were prepared at 4.2% crEL and 7.5% PS-80 and intraperitoneally administered, in both cases the $AUC_{a,\ 0\text{–}24\,h}$ of docetaxel was increased and the $AUC_{p,\ 0\text{–}24\,h}/AUC_{a,\ 0\text{–}24\,h}$ and the k_a values approached the levels of paclitaxel (Tables 1 and 2). It has been reported that the value of RBP after intravenous administration of paclitaxel is decreased significantly by adding crEL (Sparreboom et al 1999; van Zuylen et al 2001a). In this study, after intravenous injection, the permeation of docetaxel into red blood cells was also decreased to a similar level to that of paclitaxel by adding crEL or increasing the PS-80 concentration (Figure 3). Moreover, in the in-vitro experiment, the uptake of paclitaxel into red blood cells was decreased by both vehicles in a concentration-dependent manner (Figure 4). Thus, the low permeability of paclitaxel into tissues or cells is not specific to the anti-cancer drug, but is due to the vehicle crEL in the injection preparation. Further, the effect is concentration dependent and is not due to the kind of micellization vehicle (i.e., the permeability of docetaxel was also decreased by a higher concentration of PS-80).

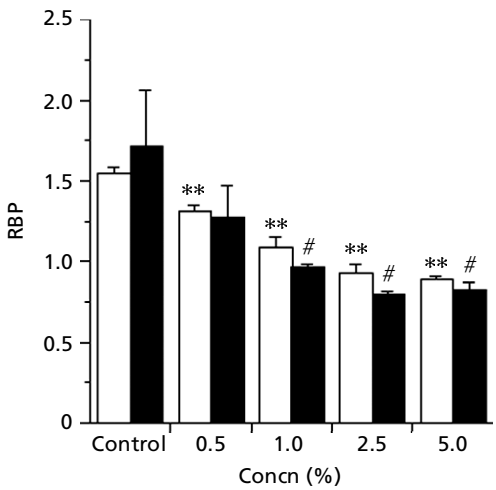

Figure 4 Blood-to-plasma concentration ratio (RBP) of paclitaxel after 15-min incubation with rat blood and paclitaxel in various concentrations of crEL (□) or PS-80 (■). Paclitaxel crEL solution was prepared by diluting Taxol injection with saline, and the minimum concentration of crEL was 0.05%. Paclitaxel PS-80 solution was prepared by adding PS-80 to the 0.05% crEL solution (control). Each column represents the mean ± s.d. of triplicate experiments; $^{**}P < 0.01$ vs 0.05% crEL; $\#P < 0.05$ vs 0% PS-80.

It has been reported that after intravenous administration of crEL or PS-80, the concentration of crEL is maintained for a long period, whereas that of PS-80 declines very rapidly, because PS-80 is readily degraded by serum esterase (Sparreboom et al 1996; Webster et al 1997; van Tellingen et al 1999; van Zuylen et al 2001b). Van Tellingen et al (1999) also noted that PS-80 does not interfere with the disposition of docetaxel. However, after intraperitoneal injection, a high concentration of PS-80 influenced the disposition kinetics of docetaxel in the same manner as crEL. We speculated that this result may occur because of the paucity of esterase in the intraperitoneal cavity.

The RBP value of anti-cancer drugs was lowered by high concentrations of surfactant vehicles in the case of intravenous injection, while the RBP values were all similar after intraperitoneal administration, regardless of the concentration of vehicle (Figure 3). However, the decrease caused by PS-80 rapidly recovered to the level of intraperitoneal administration, while that caused by crEL did

not. When intravenously administered, the drugs are present as micelles with the surfactants, which interfere with the drug contact with red blood cells and permeation into the cells, but when intraperitoneally administered, the drugs appearing in peripheral blood are present in protein-bound form and free form, which readily permeates through the cell membrane. Namely, it appears that the intrinsic membrane permeability values of paclitaxel and docetaxel themselves are similar.

In conclusion, we demonstrated using rats that the disposition kinetics of taxanes after intraperitoneal administration was strongly influenced, in a concentration-dependent manner, by the surfactant vehicles crEL and PS-80. The injection preparation of paclitaxel, Taxol, contains a high concentration of crEL, which suppresses the permeation of the anti-cancer drug into tissues and cells, and this may explain why intraperitoneallly administered Taxol has a lower systemic toxicity than that of Taxotere, which contains a low concentration of PS-80. Nevertheless, it remains to be verified whether Taxol shows the expected anti-cancer activity against intraperitoneal tumours.

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