Cancer Chemother Pharmacol (2002) 49: 119–125
DOI 10.1007/s00280-001-0394-2

ORIGINAL ARTICLE

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Entrapment by Cremophor EL decreases the absorption of paclitaxel from the gut

Received: 8 March 2001 / Accepted: 12 October 2001 / Published online: 20 November 2001

Abstract *Background:* Recent studies in mice and patients have shown that the low oral bioavailability of paclitaxel can be increased by coadministration of P-glycoprotein blockers. However, in patients an increase in the oral paclitaxel dose from 60 to 300 mg/m^2 does not result in proportionally higher plasma levels. We hypothesized that the surfactant Cremophor EL, present in the formulation of paclitaxel, may be responsible for this nonlinear absorption by entrapping paclitaxel within the intestinal lumen, probably by inclusion in micelles. *Methods:* Paclitaxel was administered to mdr1ab P-glycoprotein knockout mice with either the conventional (controls) or a seven-fold higher amount of Cremophor EL (test group). Plasma, gastrointestinal tissues with their contents and faeces were collected and analysed by high-performance liquid chromatography to determine the levels of paclitaxel and Cremophor EL. The critical micellar concentrations of Cremophor EL in the contents of the small intestine were also established by an in vitro assay. *Results:* Paclitaxel recoveries in the faeces of the control and test groups were 7.6% and 35.8%, respectively. The peak plasma level and plasma AUC were reduced in the test group by about 75% and 40%, respectively. Only in mice from the test group did substantial quantities of paclitaxel together with Cremophor EL reach the caecum, thus passing through the small intestine. The concentration of Cremophor EL in the distal part of the small intestine and the caecum was 15 times higher in the test group and well above the critical micellar concentration of Cremophor EL. *Conclusions:* These results show that Cremophor EL prevents efficient uptake of paclitaxel from the gut, probably by entrapment within micelles. Other formulations should be developed for oral therapy with paclitaxel.

Keywords Oral administration · Paclitaxel · Cremophor EL

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Introduction

Paclitaxel is an important anticancer agent in the treatment of various human malignancies and is routinely administered by intravenous infusion [6, 12]. Based on our finding that P-glycoprotein (P-gp) in the intestinal epithelium limits the absorption of orally administered paclitaxel [16], we are currently exploring the feasibility of the oral route for administration of this drug. We have shown that the oral bioavailability of this drug can be increased significantly by coadministration of inhibitors of P-gp such as cyclosporin A and SDZ PSC 833 in mice [1, 2] as well as in patients [10, 11]. However, two dose-escalation studies in patients, one by our own group (paclitaxel dose 60–300 mg/m^2 [8]) and the other by Britten et al. (paclitaxel dose 180–540 mg/m^2 [3]), have shown that an increase in the oral dose of paclitaxel does not result in proportionally higher plasma levels.

In a mass balance study in patients receiving 300 mg/m^2 of oral paclitaxel together with 15 mg/kg of oral cyclosporin A, 60.9 ± 13.6% (mean ± SD) of the dose of paclitaxel was recovered in the faeces as unchanged drug [9], suggesting poor uptake at this high dose level.

Moreover, we also recovered 31.9 ± 6.9% of the dose of the major vehicle constituent Cremophor EL (CrEL) in the faeces. For reasons of availability, all clinical and preclinical studies with oral paclitaxel performed thus far have utilized the commercially available formulations of paclitaxel for intravenous administration (Taxol, Paxene). These formulations consist of 6 mg/ml of paclitaxel dissolved in a mixture of CrEL and ethanol (1:1 v/v). CrEL is used to solubilize drugs with a low aqueous solubility such as paclitaxel by the formation of micelles.

We hypothesized that the large quantities of CrEL present in the gastrointestinal lumen may be associated with the poor absorption of paclitaxel. To test this hypothesis we administered a dose of 10 mg/kg of paclitaxel with either the same amount of CrEL as used in our previous studies (0.89 g/kg) or with extra CrEL (6.24 g/kg) orally to mdr1ab P-gp knockout mice. Because drug-transporting P-gps are absent in these mice, efficient absorption of paclitaxel from the intestinal lumen can be expected [16]. Plasma and gastrointestinal tissues with their contents were collected from mice killed between 0.25 and 8 h after treatment, and faeces fractions were collected during the periods 0–8 and 8–24 h after treatment. Paclitaxel and CrEL were quantified by high-performance liquid chromatography. Since entrapment of paclitaxel within micelles is a likely explanation for the interaction between paclitaxel and CrEL, we investigated micelle formation of CrEL in the contents of the small intestine using an in vitro assay [4, 7]. We report here the results of these experiments, which show that the amount of CrEL in the formulation is an important factor in the absorption of paclitaxel from the intestinal lumen.

Material and methods

Animals

Female FVB mdr1ab knockout mice [13] were used throughout the experiments. All mice were 9–14 weeks old and had a body weight between 18.2 and 31.6 g, which was evenly distributed between the test groups. Mice were allowed access to water and food ad libitum and were maintained and handled according to institutional guidelines which are based on Dutch law.

Drugs and chemicals

Paclitaxel (6 mg/ml) formulated in CrEL/ethanol (1:1 v/v) (Taxol) and 2′-methylpaclitaxel were obtained from Bristol-Myers Squibb (Princeton, N.J.). Pure paclitaxel compound was obtained from Sankyo (Tokyo, Japan). CrEL (polyoxyethyleneglycerol triricinoleate 35) and the hemimagnesium salt of 8-anilino-1-naphthalene sulphonic acid (ANSA) were from Sigma Chemical Co. (St. Louis, Mo.). Lyophilized bovine serum albumin (fraction V) was obtained from Rôche/Boehringer Mannheim (Almere, The Netherlands). Saline was purchased from Braun (Emmer-Compascuum, The Netherlands) and HEPES buffer (1 *M*) from GibcoBRL (Paisley, UK). The anaesthetic methoxyflurane (Metofane) was obtained from Mallinckrodt Veterinary (Mundelein, Ill.). All other chemicals were purchased from E. Merck (Darmstadt, Germany) and were of analytical or Lichrosolv gradient grade. Water purified by a Milli-Q Plus system (Millipore, Milford, Mass.) was used in all aqueous solutions. Blank human plasma was obtained from the Blood Bank (Amsterdam, The Netherlands).

Drug solutions

Two paclitaxel drug formulations for oral administration were prepared for the pharmacokinetic experiments. Drug solution 1 was a sixfold dilution of the clinical paclitaxel formulation (Taxol) with saline. This solution contained 1 mg/ml of paclitaxel, 89 mg/ml of CrEL and 67 mg/ml of ethanol. Drug solution 2 contained 0.5 mg/ml of paclitaxel, 312 mg/ml of CrEL and 33 mg/ml of ethanol and was prepared by mixing 1 ml clinical paclitaxel solution, 2.5 ml pure CrEL and 8.5 ml saline. The amount of CrEL in this drug solution was close to the maximum able to be administered conveniently to the mice. Higher amounts were problematic due to the high viscosity of the surfactant.

Pharmacokinetic experiment

Two groups of P-gp knockout mice were included in this study. The control group received 10 ml/kg of drug solution 1 resulting in dose levels of 10 mg/kg of paclitaxel, 0.89 g/kg of CrEL and 0.67 mg/kg of ethanol. The test group received 20 ml/kg of drug solution 2 resulting in dose levels of 10 mg/kg of paclitaxel, 6.24 g/kg of CrEL and 0.67 mg/kg of ethanol. All drug solutions were administered orally by gavage. No anaesthetic was used for drug administration.

To study the effect of CrEL on the plasma pharmacokinetics of paclitaxel, blood was obtained from two to four animals of the control and the test group per time-point at 15 and 30 min and 1, 2, 4, 6 and 8 h after drug administration. Blood was obtained by cardiac puncture under methoxyflurane anaesthesia and collected in tubes containing potassium EDTA as anticoagulant. The plasma fraction was separated by centrifugation at 4°C for 5 min at 3000 *g*. To study the passage of paclitaxel and CrEL through the intestinal tract we also dissected the stomach, the small intestine (which was divided into three segments of equal length), the caecum and the colon. To avoid loss of intestinal contents during the sampling procedures, we did not separate the contents from the tissue, but homogenized the whole sample in 2 ml 40 g/l bovine serum albumin at 4°C using a Polytron PT1200 homogenizer (Kinematika, Switzerland). The contribution of the paclitaxel levels in the tissue was negligible relative to the total amount of drug in the samples.

To study the excretion profiles of paclitaxel and CrEL over time, five animals from each group were housed in Ruco Type M/1 metabolic cages (Valkenswaard, The Netherlands). After an acclimatization period of 2 days, the oral drug solutions were administered to the mice. Faeces fractions were collected during the periods 0–8 and 8–24 h after drug administration. The faeces samples were homogenized at 4°C in ten volumes of 40 g/l bovine serum albumin in water as described above. All samples were stored at –20°C until analysis.

Analytical methods

Paclitaxel and its metabolites 3′ *p*-hydroxypaclitaxel and 6α-hydroxypaclitaxel in all samples were determined using high-performance liquid chromatography with UV detection [15]. The lower limit of quantitation of paclitaxel and metabolites was 25 ng/ml using 200 µl plasma and 250 ng/ml using 200 µl of a homogenized faeces sample. The levels of CrEL in faeces and tissue homogenate samples were quantified by a previously described high-performance liquid chromatography method [17]. This method is based on quantification of *N*-ricinoleoyl-1-naphthylamine after saponification of CrEL in alcoholic potassium hydroxide, followed by extraction of the released fatty acid ricinoleic acid by chloroform and derivatization with 1-naphthylamine. The lower limit of

quantitation was 0.01% w/v using 50 µl homogenized sample corresponding to 0.5–2 mg/g faeces or tissue specimen. Each sample was also processed without saponification to correct for the presence of free ricinoleic acid. This product is formed by in vivo degradation of CrEL. The levels of free ricinoleic acid in faeces resulted in a chromatographic signal that was 5–10% of the response observed after saponification of the sample. For gastrointestinal samples this contribution ranged up to 30%.

Pharmacokinetic data analysis

The area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule without extrapolation to infinity. The peak plasma concentration (C_{max}) and the time at which the maximal plasma level was reached (t_{max}) were determined graphically. The unpaired Student's *t*-test (two-tailed) was used to compare the pharmacokinetic parameters. *P*-values < 0.05 were considered statistically significant.

Determination of the critical micelle concentration of CrEL in HEPES buffer and in the small intestine contents

The method of De Vendittis et al. [4] was used to determine the critical micelle concentration (CMC) of CrEL. This method is based on an increase in the fluorescence intensity after inclusion of the fluorescent probe ANSA into the hydrophobic core of micelles. The CMC is represented by the CrEL concentration at which the fluorescence intensity abruptly increases as indicated by an abrupt change in the slope of the fluorescence intensity versus the CrEL concentration.

First, the method was tested by determination of the CMC of CrEL in HEPES buffer as was done by Knemeyer et al. [7]. To 500 µl CrEL stock solution (0.001 to 1% w/v in 50 m*M* HEPES) were added 500 µl ANSA stock solution (10 m*M* in 50 m*M* HEPES) and 500 µl 50 m*M* HEPES buffer. After incubation for 1 h at 37°C, 150-µl aliquots of each test solution were added to the wells of a Costar 96-well plate (Corning, Corning, N.Y.). The fluorescence intensity was measured using a PerSeptive Biosystems CytoFluor multiwell plate reader Series 4000 (Framingham, Mass.) with excitation and emission wavelengths of 360 and 460 nm, respectively. The bandwidth of both channels was 40 nm.

To study micelle formation in the lumen of the small intestine, 30 untreated mice were killed and the contents of the small intestine were collected (the total amount of intestinal contents recovered was about 10 ml). Prior to the experiment the intestinal contents were homogenized using a Polytron PT1200 homogenizer. To 825 µl of intestinal contents were added 100 µl CrEL stock solution (0.01 to 33% w/v in saline) and 75 µl ANSA stock solution (40 m*M* in saline). After incubation for 1 h at 37°C, 100-µl aliquots of each test solution were added to the wells of a 96-well plate and the fluorescence intensity was measured as described above.

Results

Consistent with our hypothesis, the animals in the test group, receiving a sevenfold higher dose of CrEL, excreted a significantly higher fraction of the paclitaxel dose in the faeces ($P = 0.002$). In the faeces of the animals in the test group, $35.8 \pm 6.0\%$ of unchanged paclitaxel was excreted within 24 h, while this was only $7.6 \pm 1.9\%$ in the control group (Table 1). Most of the paclitaxel was recovered in the faeces specimen collected during the period 0–8 h after oral drug administration. The total excreted fraction of the paclitaxel metabolites 3′ *p*-hydroxypaclitaxel and 6α-hydroxypaclitaxel was $38.6 \pm 2.1\%$ of the administered paclitaxel dose in the control group and $25.9 \pm 1.8\%$ in the test group. The test group also excreted more CrEL in the faeces than the control group (46.1 ± 5.3 vs 2.4 ± 1.3 mg/g, corresponding to 13.2 ± 1.2 and $3.5 \pm 1.1\%$ of the dose, respectively). As was observed for paclitaxel, most of the CrEL was recovered in the specimens collected during the period 0–8 h after administration. There was no significant difference in the total amount of faeces produced between the two groups (1.3 ± 0.1 vs 1.5 ± 0.1 g/24 h, $P = 0.284$).

The addition of extra CrEL had a marked effect on the plasma pharmacokinetics of paclitaxel (Fig. 1). The C_{max} of the animals of the test group was reduced by 75% when compared to the value found in the animals of the control group (257 ± 41 vs 1018 ± 92 ng/ml, $P = 0.003$). The t_{max} was delayed from 1 h to between 2 and 4 h. The AUC decreased by 40% from 2044 ± 128 ng/ml·h in the control group to 1314 ± 108 ng/ml·h in the test group ($P < 0.001$).

To study the profiles of the passage of paclitaxel and CrEL through the gastrointestinal tract, we collected the gastrointestinal tissues (stomach, small intestine, caecum and colon) with their contents from the same mice used in the plasma pharmacokinetic experiment and determined the fractions of paclitaxel and CrEL (Fig. 2). The small intestine, where most of the drug absorption supposedly takes place, was divided into three segments of about equal length to monitor the passage of

Table 1 Faecal excretion of paclitaxel, paclitaxel metabolites and CrEL. The control group received 10 mg/kg paclitaxel and 0.89 g/kg CrEL, and the test group received 10 mg/kg paclitaxel and 6.24 g/kg CrEL by oral administration. Data are means ± SEM ($n = 4$–5) (*n.d.* not detectable)

Group	Fraction	Paclitaxel (% of dose)	Total metabolites (% of dose)[a]	CrEL	
				% of dose	mg/g faeces
Control	0–8 h	6.6 ± 1.5	32.5 ± 2.6	3.5 ± 1.1	2.4 ± 1.3
	8–24 h	1.0 ± 0.4	6.1 ± 0.6	n.d.	n.d.
	Total	7.6 ± 1.9	38.6 ± 2.1	3.5 ± 1.1	2.4 ± 1.3
Test	0–8	31.2 ± 5.7	12.2 ± 1.5	11.4 ± 1.0	42.9 ± 5.3
	8–24	4.6 ± 0.6	13.7 ± 1.8	1.8 ± 0.5	3.2 ± 0.9
	Total	35.8 ± 6.0*	25.9 ± 1.8*	13.2 ± 1.2*	46.1 ± 5.3*

*$P \leq 0.002$ relative to controls
[a]Cumulative excretion of 3′ *p*-hydroxypaclitaxel and 6α-hydroxypaclitaxel

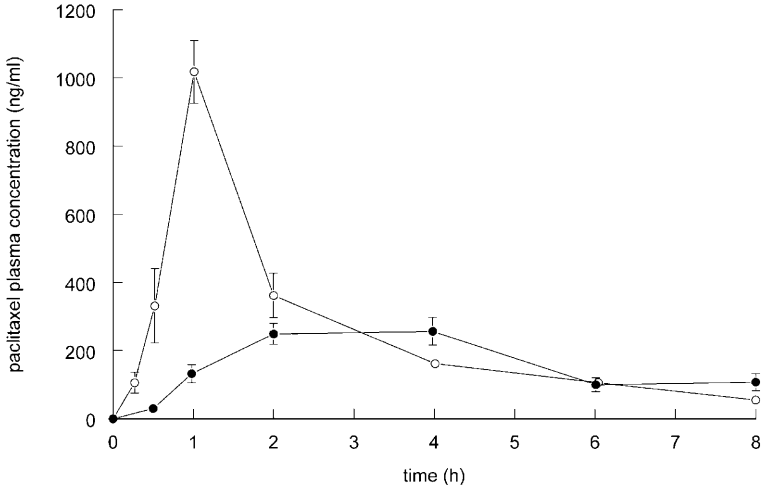

Fig. 1 The plasma concentration-time curves of paclitaxel in mice of the control group (*open circles*) and the test group (*filled circles*). Data are means ± SEM ($n = 2$–4 animals per time-point)

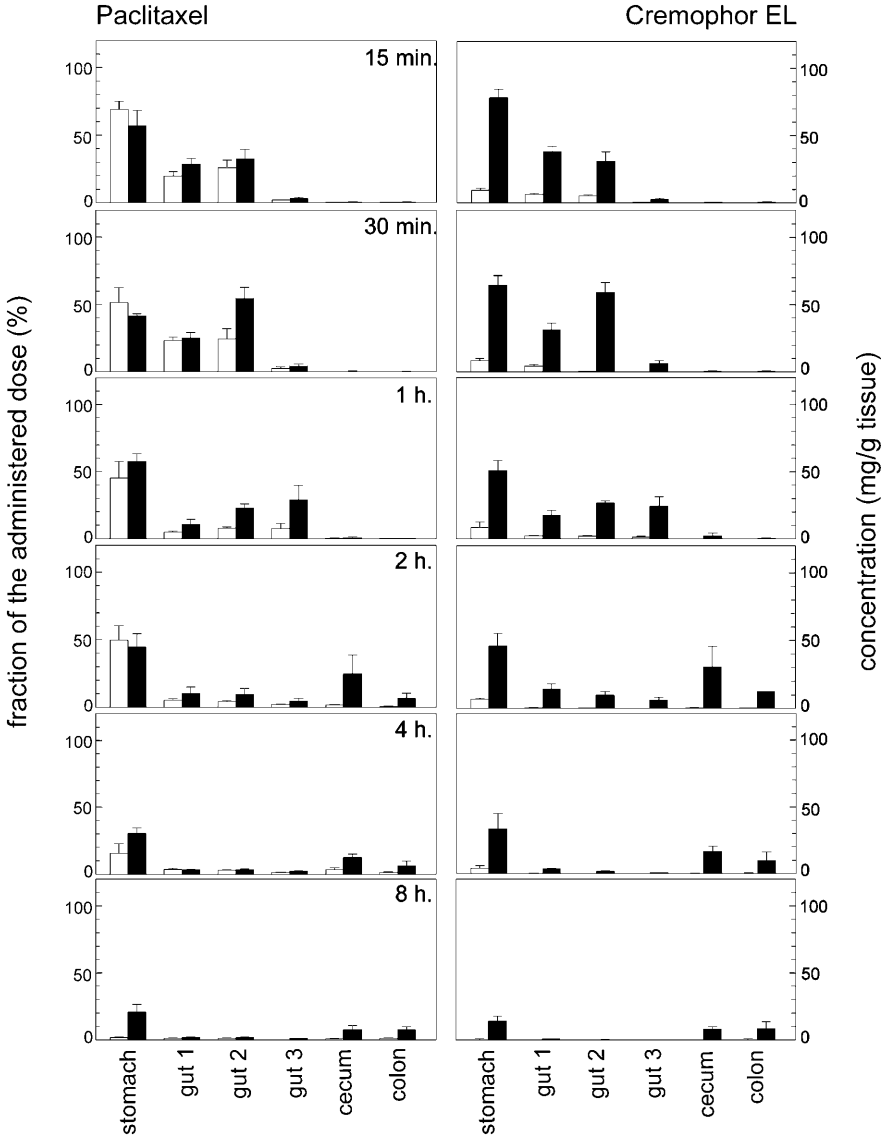

Fig. 2 The fraction of paclitaxel (as percent of dose, *left*) and the concentrations of CrEL (as milligrams per gram tissue, *right*) in gastrointestinal specimens obtained at 15 and 30 min and 1, 2, 4 and 8 h after oral administration. The *open bars* represent the control group, the *filled bars* the test group. Data are means ± SEM ($n = 2$–4)

paclitaxel and CrEL in more detail. The results indicated no major differences in the rates of drug release from the stomach into the gut and subsequent passage through the gut between the control and the test group. At 15 min after oral administration the distribution of paclitaxel throughout the gastrointestinal lumen was comparable between the two groups and the differences in the concentration of CrEL reflected the sevenfold difference in the administered dose.

However, between 30 min and 1 h after administration, the total fraction of paclitaxel present in the distal parts of the small intestine (gut 2 and gut 3, Fig. 2) was higher in the test group than in the control group. Only in animals of the test group had a substantial fraction of the drug reached the caecum within 2 h of drug administration, thus passing through the small intestine without being absorbed. Apparently, in the test group the rate of absorption of paclitaxel was lower than the rate of passage through the small intestine. Overall, there appeared to be a close relationship between the concentration of paclitaxel and CrEL in the intestine. In the test group those specimens containing high levels of paclitaxel also contained high levels of CrEL ranging between 20 and 50 mg/g of sample (2–5% w/w). In the control group the maximum concentration of CrEL present in the distal part of the small intestine was only 2 mg/g (0.2% w/w), while the concentration in the caecum of these animals was at all time-points lower than 0.5 mg/g (0.05% w/w). Accordingly, the maximal fraction of paclitaxel that passed through the small intestine unabsorbed was small (about 3% of the dose).

We determined the CMC of CrEL in 50 m*M* HEPES buffer (Fig. 3A). As can be seen in the insert, the CMC was 0.008% w/v. This result is in line with those reported by Knemeyer et al. [7]. Next, we determined the CMC of CrEL in small intestinal contents (Fig. 3B). The fluorescence signal of ANSA in the biological matrix was already relatively high. Although this resulted in

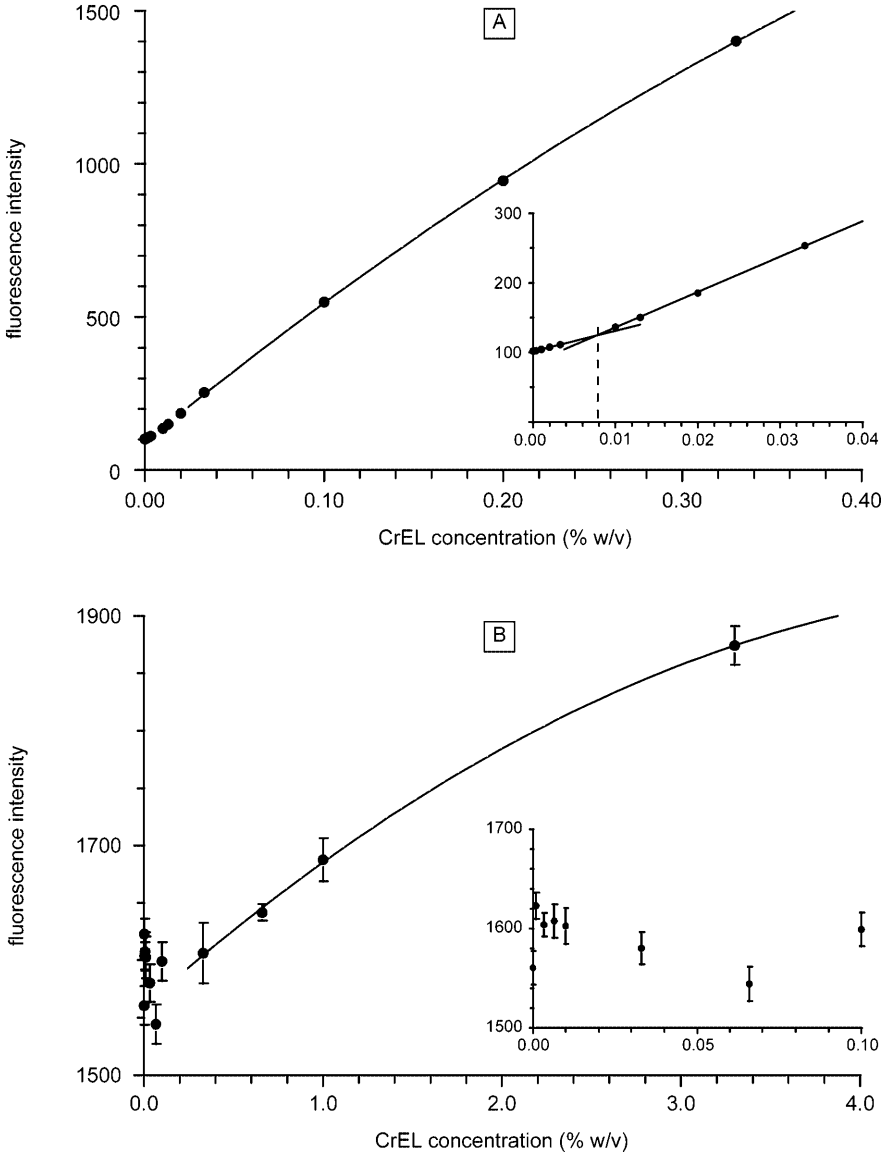

Fig. 3 **A** Typical example of the determination of the critical micelle concentration of CrEL in 50 m*M* HEPES buffer, pH 7.0. The *insert* shows the fluorescence intensity of the test solutions with CrEL concentrations up to 0.04%, the intersection between the extrapolated lines corresponding to the critical micelle concentration of 0.008% w/v. **B** Determination of the critical micelle concentration of CrEL in the contents of the small intestine. The insert shows the variability of fluorescence intensity of the test solutions with CrEL concentrations up to 0.1% w/v. All data are means ± SEM ($n = 5$–8). The absence of error bars indicates that the SEM is smaller than the size of the symbols

somewhat larger variations in fluorescence readings, in particular in samples containing low quantities of CrEL, it is clear that a CrEL concentration-dependent increase in the fluorescence signal occurred starting from concentrations of 0.33% w/v, indicating that micelles were being formed above this concentration. The decreasing slope observed at the highest concentrations (3.3% w/v) was also observed in the aqueous matrix (not shown).

Discussion

The results of this study support the hypothesis that CrEL restricts the uptake of paclitaxel in the intestinal lumen after oral administration. The addition of extra CrEL to the oral formulation of paclitaxel resulted in a fivefold higher excretion of unchanged paclitaxel in the faeces of mdr1ab P-gp knockout mice ($P = 0.002$). At the same time the excretion of the metabolites of paclitaxel was decreased, which is also indicative of reduced absorption of the drug. These results were further confirmed by the data obtained from the plasma pharmacokinetic experiment. The AUC of paclitaxel decreased significantly ($P < 0.001$), which was mainly the result of a 75% reduction in the peak plasma level. A relationship between the reduction in absorption of paclitaxel and the amount of CrEL available in the gastrointestinal lumen was evident. The absolute amount of CrEL recovered unchanged in the faeces of the test group was about 20-fold higher than that recovered from the control group (46.1 ± 5.3 vs 2.4 ± 1.3 mg/g, $P < 0.002$). Moreover, there appeared to be a close relationship between the fraction of paclitaxel and the concentration of CrEL in the contents of the gastrointestinal lumen (Fig. 2).

The observed effects of CrEL on the pharmacokinetics of paclitaxel were probably not related to changes in the rate of passage of drug through the gastrointestinal tract because we observed no differences between the two groups in the rate of drug release from the stomach into the gut and the total amount of faeces excreted within 24 h. It is also unlikely that interference with or injury to the intestinal mucosa could have resulted in decreased uptake of paclitaxel from the gut. A histological examination performed in an earlier study did not reveal changes in the intestinal mucosa of mice given oral paclitaxel with the P-gp blocker cyclosporin A [2]. Moreover, interactions with the barrier function of the intestines would result in an increase rather than a decrease in absorption [18].

The most likely mechanism behind the interaction between paclitaxel and CrEL rests on the property of CrEL to form micelles in aqueous solution, which include the drug within their hydrophobic core. The results of our in vitro experiments indicated that micelles were being formed in the small intestinal contents at CrEL concentrations of 0.33% w/v and higher. This is considerably higher than in buffer solutions, probably because of the presence of compounds that interfere with micelle formation (e.g. bile salts). However, this value was about tenfold lower than the CrEL levels found in the intestines of animals in the test group. When paclitaxel reached the distal part of the small intestine of the animals in the test group (1 h after administration, Fig. 2), the concentration of CrEL in that segment was 30 mg/g (3% w/w). In the control group, however, the maximal concentration of CrEL present in the distal part of the small intestine was only 0.2% w/w, which appears to be insufficient for micelle formation.

It should be noted that the analytical assay for CrEL is based on quantification of the fatty acid ricinoleic acid, which is released after hydrolysis of CrEL. Each molecule of CrEL may contain up to three ricinoleate side chains attached to the polyoxyethylated glycerol backbone. However, due to in vivo degradation, glycerol molecules with only one or two side chains may have been present in the faecal and intestinal samples. The analytical assay cannot distinguish between these different forms of CrEL, and, given the surfactant properties of these mono- and diricinoleic acid products, it seems reasonable to assume that these molecules could also have contributed to micelle formation.

Our studies confirm that the pharmaceutical formulation can play a crucial role in the bioavailability of drugs used for oral administration. A phenomenon comparable to that shown here has also been described for other drugs. For example, vitamin K1 formulated in CrEL has been shown to possess less-favourable absorption characteristics when compared to alternative lipid-bile salt mixed-micellar formulations [14].

The results of our study may help to explain the apparent nonlinear absorption of orally administered paclitaxel in patients, which has been observed during dose-escalation studies [3, 8]. In humans, the effect of CrEL on the absorption of paclitaxel might be even more pronounced than in mice. The dose of CrEL administered to mice in the test group was about 30% lower than that administered to patients receiving 300 mg/m^2 of paclitaxel. Based on dose conversion from body weight to body surface according to the method described by Freireich et al. [5], mice received 18.7 g/m^2 of CrEL, while patients received 26.8 g/m^2 [9]. Moreover, the rate of degradation of CrEL appears to be lower in humans. Patients excrete 31.9% of the dose in the faeces within 4 days of administration [9], whereas only 13.2% of the dose was recovered in the faeces of the mice in the test group (Table 1).

In conclusion, our results show that CrEL entraps paclitaxel in the gastrointestinal lumen, probably by inclusion into micelles, decreasing the absorption of the drug. This finding would imply that the bioavailability of orally administered paclitaxel in patients could be improved by administration in a CrEL-free formulation. Based on these findings a clinical study investigating the role of CrEL in the oral bioavailability of paclitaxel in patients has been initiated.

Acknowledgements This research was supported by grant NKI98-1799 of the Dutch Cancer Society. The authors gratefully acknowledge the excellent biotechnical assistance of Ton Schrauwers.

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