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Report

Inter-relationships of paclitaxel disposition, infusion duration and Cremophor EL kinetics in cancer patients

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Cremophor EL (CrEL) is a castor oil surfactant used as a vehicle for formulation of a variety of poorly water-soluble agents, including paclitaxel. Recently, we found that CrEL can influence the *in vitro* blood distribution of paclitaxel by reducing the free drug fraction, thereby altering drug accumulation in erythrocytes. The purpose of this study was to investigate the clinical pharmacokinetics of CrEL, and to examine inter-relationships of paclitaxel disposition, infusion duration and CrEL kinetics. The CrEL plasma clearance, studied in 17 patients for a total of 28 courses, was time dependent and increased significantly with prolongation of the infusion duration from 1 to 3 to 24 h ($p<0.03$). An indirect response model, applied based on use of a Hill function for CrEL concentration-dependent alteration of *in vivo* blood distribution of paclitaxel, was used to fit experimental data of the 3 h infusion ($r^2=0.733$; $p=0.00001$). Simulations for 1 and 24 h infusions using predicted parameters and CrEL kinetic data revealed that both short and prolonged administration schedules induce a low relative net change in paclitaxel blood distribution. Our pharmacokinetic/pharmacodynamic model demonstrates that CrEL causes disproportional accumulation of paclitaxel in plasma in a 3 h schedule, but is unlikely to affect drug pharmacokinetics in this manner with alternative infusion durations. [© 2000 Lippincott Williams & Wilkins.]

Key words: Cremophor EL, non-linear pharmacokinetics, paclitaxel.

Introduction

Paclitaxel, a natural product first isolated from the Western yew tree, *Taxus brevifolia*, acts by stabilizing the microtubule cytoskeleton, and possesses antitumor activity against a relatively broad spectrum of malignancies (reviewed by Verweij *et al.*[1]). The variability in clinically tested treatment schedules of this drug is enormous, ranging from short i.v. infusions of less than 1 h to 10 day or even 7 week continuous infusion administrations,[2–4] with large differences in experienced toxicity profiles and with fortuitous implications for the pharmacokinetics of paclitaxel. The latter refers to the experience of non-linear plasma disposition, which appears to be most pronounced with the drug administered as a 3 h infusion, the most frequently used schedule nowadays.[5–7] The mechanisms underlying the non-linearity of paclitaxel disposition are not yet completely understood, although it has been shown that distribution and elimination appear to be linear in the absence of Cremophor EL (CrEL), the non-ionic castor oil vehicle used in the clinical formulation.[8,9] We have shown recently that *in vitro* CrEL causes a profound alteration of paclitaxel accumulation in erythrocytes in a concentration-dependent manner, by reducing the free drug fraction available for cellular partitioning.[10] In this report we (i) evaluated the importance of this *in vitro* observation for cancer patients treated with i.v. administered paclitaxel, (ii) describe the clinical pharmacokinetics of CrEL administered with a 1, 3 and 24 h i.v. paclitaxel infusion, and (iii) propose a pharmacokinetic/pharmacodynamic model to describe the pharmacokinetic profiles of CrEL for these three treatment groups, and the relationship between CrEL plasma concentrations and the paclitaxel blood distribution.

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Materials and methods

Patients and treatment

A total of 17 patients enrolled in Phase I trials performed in Rotterdam (The Netherlands; n=5), Milan (Italy; n=6) or Freiburg im Breisgau (Germany; n=6) was studied during treatment with paclitaxel as a single agent for a variety of malignant solid tumors refractory to standard therapy. They represented either newly recruited patients (Rotterdam) or those for which plasma samples had been previously collected and detailed clinical profiles documented elsewhere.[5,11] Paclitaxel was administered as a 1 h (six courses), 3 h (13 courses) or 24 h (nine courses) i.v. infusion every 3 weeks at doses ranging from 135 to 225 mg/m^2. The drug was formulated in a mixture of CrEL and dehydrated ethanol USP (1:1, v/v) (Taxol; provided by Bristol-Myers Squibb, Woerden, The Netherlands) and diluted further into isotonic sodium chloride or dextrose prior to dosing.

Sample collection and drug analysis

For CrEL, pharmacokinetic evaluation was performed in all patients for a total of 28 courses. Heparinized blood samples of 5 ml were obtained at the following time points: before dosing and at 0.5, 1, 4, and 24 h after infusion (1 h schedule), at 1, 2, 3, 3.08, 3.25, 3.5, 3.75, 4, 5, 7, 9, 11, 15 and 24 h after infusion (3 h schedule) or at 1, 22, 23, 23.92, 24, 24.08, 24.15, 24.5, 25, 26, 27, 30, 36 and 45 h after infusion (24 h schedule). Aliquots of 1 ml of whole blood were snap-frozen at -20°C (3 h schedule only at 1, 2 and 3 h after infusion) and plasma was separated by centrifugation for 5 min at 4000 g (all schedules).

Concentrations of paclitaxel in whole blood and plasma were determined using a validated isocratic reversed-phase high-performance liquid chromatography (HPLC) procedure with UV detection (λ=230 nm), as reported.[12] The analytical method for CrEL was based on binding of the surfactant to Coomassie brilliant blue G-250 in protein-free plasma extracts by measuring the change in ratio of absorbances at 595 nm over 450 nm.[13,14]

Pharmacokinetics

The CrEL plasma concentration–time curves were analyzed using the software package Siphar version 4 (SIMED, Créteil, France) by determination of slopes and intercepts of the plotted curves with a bi-exponential function.[15] Initial parameter estimates were obtained by an automated peeling-algorithm procedure, with an integrated numerical algorithm based on the Powell method and a weighted least-squares operation. The area under the plasma concentration–time curve of CrEL was determined on the basis of the best fitted curves from time 0 up to the last sampling point with detectable levels (AUC_{0-t}) (lower limit of quantitation 0.5 μl/ml). Extrapolation to calculate $AUC_{0-\infty}$ was not performed because based on the limited sampling procedure, half-life estimates of the terminal disposition phase (reported previously to be greater than 80 h with 3 h paclitaxel infusions)[15] and subsequent determinations of total clearance and volume of distribution could not be done with sufficient precision [i.e. the extrapolated part represents a significant amount (greater than 20%) of the $AUC_{0-\infty}$]. Therefore, the apparent plasma clearance of CrEL was estimated by dividing the delivered volume (expressed in ml/m^2 body surface area) by the observed AUC_{0-t}, to allow evaluation of the impact of infusion duration on the pharmacokinetic behavior. Peak plasma concentrations (C_{max}) of CrEL and paclitaxel were determined graphically by visual inspection from scattered plots of concentration–time profiles.

For pharmacodynamic analysis, paclitaxel concentrations were considered as 'total paclitaxel', because an acetonitrile:n-butyl chloride extraction was applied to separate paclitaxel from its binding proteins and CrEL micelles for the assay.[12] Based on our previous *in vitro* partitioning experiments,[10] we assumed that CrEL can decrease the unbound fraction in serum *in vivo* with subsequently decreased erythrocyte binding in a concentration-dependent manner, whereas the elimination rate of paclitaxel from the central compartment remains unchanged.[16] An indirect response model based on the premise that inhibition of paclitaxel uptake by erythrocytes will change the blood to plasma [(B/P)] concentration ratio was applied as follows:

$$\mathrm{d\ (B/P)\ ratio}/\mathrm{d}t = (\mathrm{B/P})_0 + (\mathrm{B/P})_{min} \cdot \{[C_{CrEL}]^{\gamma}/([C_{CrEL}]^{\gamma} + [C_{CrEL}]_{50}{}^{\gamma})\} \quad (1)$$

where $(B/P)_0$ is the paclitaxel blood:plasma concentration ratio in the absence of CrEL, $(B/P)_{min}$ is the minimum paclitaxel blood:plasma ratio that can be achieved, $[C_{CrEL}]$ is the CrEL plasma concentration, which is a forcing function defined by the kinetic analysis, $[C_{CrEL}]_{50}$ is the CrEL plasma concentration producing 50% of maximum decrease of the paclitaxel blood to plasma ratio and γ is the slope coefficient for the Hill function describing the sigmoidity of the fit.

Statistics

All pharmacokinetic parameters are reported as mean values ± SD. Intrapatient differences between the first and second course in dose-normalized parameters were assessed by the coefficient of variation, expressed as the ratio of the SD and the observed mean. Pharmacokinetic variability between the various dose levels and infusion duration was evaluated by the Kruskal–Wallis statistic and Dunn's multiple comparison test, if necessary. Pharmacodynamic parameters [$(B/P)_0$, $(B/P)_{min}$, $[C_{CrEL}]_{50}$ and γ] were estimated by the maximum likelihood method using the Siphar program, and the model evaluated for goodness of fit by minimization of sums of squared residuals and by reduction of the estimated coefficient for fitted parameters. Significance of the relationship was assessed by construction of contingency tables with subsequent χ^2 analysis. Statistical analysis was performed using the NCSS software (version 5.X; Dr Jerry Hintze, Kaysville, UT). All test were two-tailed and the level of significance was set at α=0.05.

Results

CrEL kinetics

Mean pharmacokinetic parameters of CrEL at each of the dose levels tested are listed in Table 1 as a function of the infusion duration. In all cases, CrEL plasma concentrations increased progressively and monoexponentially throughout the infusion in a first-order fashion (Figure 1), most likely because the fractional term associated with the terminal phase is about 0.97,[9] causing spontaneous CrEL distribution in the circulation relative to elimination. Both C_{max}, observed immediately after cessation of the infusion, and AUC_{0-t} were significantly higher at an increased dose with all three schedules ($p<0.04$). The plasma clearance was independent of the dose within each infusion duration ($p>0.44$), although with the 24 h infusion there was a trend toward slower clearance with an increase in dose (Table 1). However, a clear time dependency was noted in CrEL pharmacokinetics with the plasma clearance increasing significantly with an increase in infusion time [e.g. $CL_{1\ h}$=223 ± 11.8 versus $CL_{3\ h}$=322 ± 49.2 ml/h/m^2; p=0.02 (at 225 mg/

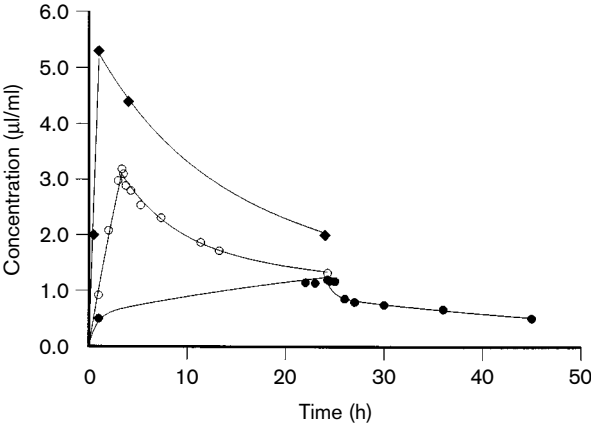

Figure 1. Representative plasma concentration–time curves of CrEL in three patients treated with paclitaxel at a dose level of 175 mg/m^2 given as a 1 (◆), 3 (○) or 24 (●) h i.v. infusion. In all cases, paclitaxel was formulated at 6 mg/ml in a mixture of CrEL-dehydrated ethanol USP (1:1, v/v) and diluted in 5% dextrose or 0.9% sodium chloride solution within 3 h prior to dosing. Pharmacokinetic curves were fitted to a bi-exponential equation assuming a two-compartmental model for distribution and elimination phases using the Siphar version 4 software package.

Table 1. Effect of dose and infusion duration on CrEL pharmacokinetics[a]

T_{inf}[b] (h)	Paclitaxel dose (mg/m^2)	CrEL dose (ml/m^2)	*n*	C_{max} (μl/ml)	AUC_{0-t} (μl·h/ml)	CL (ml/h/m^2)
1	150	12.5	1	4.30	48.4	258
	175	14.6	2	5.30, 5.70	81.6, 89.9	162, 179
	225	18.8	3	5.37 ± 0.96	84.6 ± 4.38	223 ± 11.8
3	135	11.3	3	2.32 ± 0.34	28.9 ± 2.40	392 ± 32.5
	175	14.6	5	3.43 ± 0.47	46.3 ± 7.55	321 ± 55.7
	225	18.8	5	4.46 ± 0.75	59.4 ± 10.0	322 ± 49.2
24	135	11.3	3	0.69 ± 0.14	22.4 ± 4.63	520 ± 121
	175	14.6	6	1.43 ± 0.39	43.1 ± 12.3	364 ± 115

[a]Data were obtained from cancer patients after treatment courses of 1, 3 or 24 h i.v. infusion of paclitaxel at dose levels ranging from 135 to 225 mg/m^2. The parameters were calculated by non-compartmental analysis and data represent mean values ± SD.
[b]T_{inf}, infusion duration of drug administration; *n*, number of treatment courses studied; C_{max}, peak plasma concentrations; AUC_{0-t}, area under the plasma concentration–time curve up to the last time point with detectable levels; CL, apparent plasma clearance.

m^2) or $CL_{3\ h}$=392±32.5 versus $CL_{24\ h}$=520±121 ml/h/m^2; p=0.03 (at 135 mg/m^2)]. Accumulation effects of multiple dosing were not observed in any patient that had blood samples collected on two or three separate consecutive occasions (3-weekly schedules of 3 or 24 h i.v. infusion) and the coefficient of variation in observed AUC values was typically below 10%.

Paclitaxel blood partitioning

The concentration of paclitaxel in plasma and blood after a 3 h i.v. infusion is shown in Figure 2 as a function of the dose administered. At the lowest dose tested (i.e. 135 mg/m^2), the blood:plasma ratio was independent of the concentration (0.99±0.12 to 0.93±0.13; $p>0.15$). Increasing the dose to 175 and 225 mg/m^2, however, resulted in significant decreases in blood:plasma ratios toward the end of infusion to 0.68±0.08, at which about 90% of drug is distributed outside blood cells. To demonstrate the comparative relationship between CrEL concentrations and alterations in the paclitaxel blood:plasma ratio, a simulation based on the proposed pharmacokinetic/pharmacodynamic model (equation. 1) is presented in Figure 3. Using the computer fitting (r^2=0.733; p=0.00001), the paclitaxel blood:plasma ratio in the absence of CrEL was estimated as 1.09, which is in excellent agreement with our previous *in vitro* finding of 1.07±0.004 at a paclitaxel concentration of 1 μg/ml.[10] After increasing CrEL levels, the blood:plasma ratio gradually decreased to a value in which paclitaxel is distributed only in the water phase (corresponding to an erythrocyte:plasma water ratio of about 0.65), with an estimated $[C_{CrEL}]_{50}$ value of 2.297 μl/ml and Hill coefficient γ of 1.35. Simulations for the patients receiving 1 or 24 h i.v. infusions using the predicted parameter values and superposition of the pharmacokinetic data of CrEL are shown in Figure 3. Based on the proposed model, a change in blood:plasma ratio during 24 h infusions is predicted between 0.911 and 1.01 (up to 16.5% decrease of initial value). The 1 h infusions have the lowest relative net change in the ratio (between 0.545 and 0.650), despite having the highest CrEL concentrations. These results show that only with 3 h i.v. infusions substantial disproportional accumulation of paclitaxel in plasma, resulting from CrEL-mediated alteration of blood distribution, is likely to occur.

Discussion

The present study was performed to investigate the clinical pharmacokinetics of CrEL administered over 1, 3 and 24 h i.v. infusions of paclitaxel, and to examine the inter-relationships of paclitaxel disposition, infusion duration and CrEL kinetics. The CrEL plasma clearance was found to be time dependent and increased significantly with prolongation of the infusion duration from 1 to 3 to 24 h. This observation is at odds with most literature concerning CrEL pharmacokinetics following 3 h paclitaxel administration, showing linear increases in both C_{max} and AUC with increasing dose,[15,17] although some other authors have reported slower CrEL clearances at the lower end of

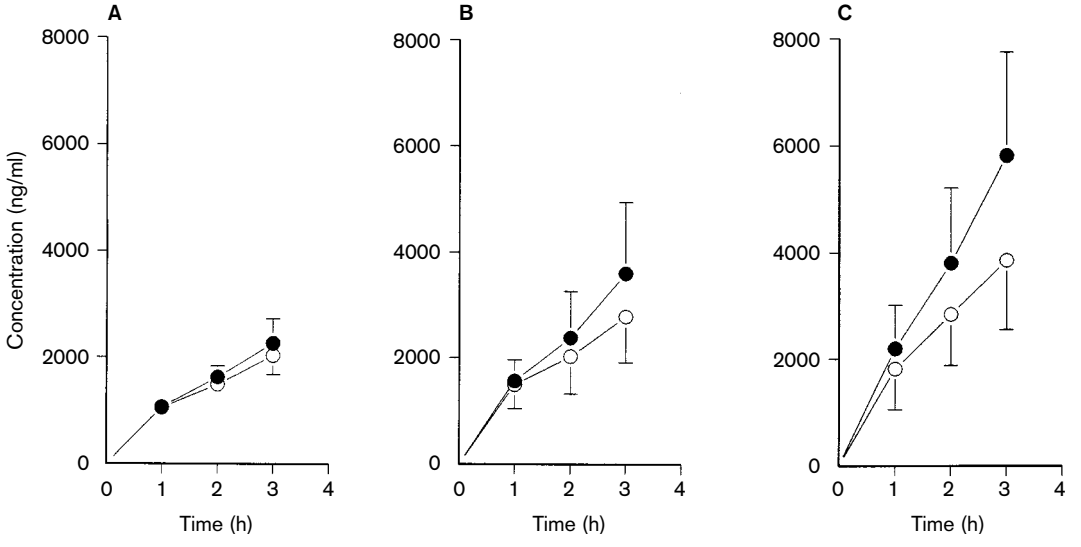

Figure 2. Plasma (●) and blood (○) concentration–time plots of paclitaxel in patients treated with a 3 h i.v. infusion of paclitaxel at dose levels of 135 (A), 175 (B) or 225 (C) mg/m^2. Data represent mean values (symbols)±SD (error bars).

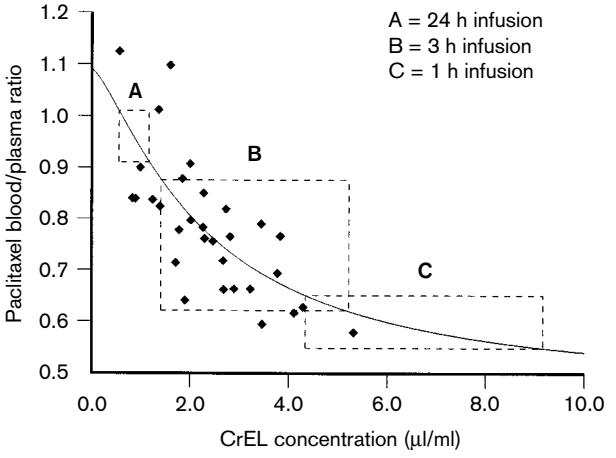

Figure 3. Relationship between the blood:plasma concentration ratio of paclitaxel and the observed plasma concentration of CrEL during 3 h i.v. infusions of paclitaxel. Data were obtained from five patients (13 courses) treated at 135, 175 or 225 mg/m^2. The solid line represents a fit of the data with a sigmoidal minimum-effect model using 1/(CrEL concentration) weighting and an integrated numerical algorithm based on the Powell method. Boxes with dotted lines indicate the range of CrEL peak levels associated with i.v. paclitaxel administration over 1, 3 or 24 h at dose levels ranging between 135 and 225 mg/m^2 (see Table 1), and the predicted paclitaxel blood:plasma concentration ratio obtained by interpolation of the fitted model.

paclitaxel dose ranges when using body surface area-based dose-calculation methods.[18] Our results are in line with those found using an HPLC assay for CrEL described recently.[19] The processes involved in CrEL elimination are not yet fully discerned, although preliminary findings indicate that the cumulative urinary excretion is very low, accounting for less than 0.1% of the administered dose, despite its relatively high hydrophilic nature.[20] Given the limited volume of distribution of CrEL[15] and the prominent role of serum carboxylesterase-mediated metabolic transformation in the elimination of the related surfactant polysorbate 80,[21] it is possible that the underlying time-dependent mechanism is that of capacity-limited CrEL metabolism within the systemic circulation. Regardless of the processes affecting the pharmacokinetic profile of CrEL, our findings indicate that CrEL disposition is highly dependent on infusion duration, with disproportional increases in systemic exposure being associated with shortening of infusion. This finding may be of particular importance in view of the potential role of CrEL in the frequent presence of acute hypersensitivity reactions associated with clinical use of paclitaxel, which are characterized by dyspnea, flushing, rash and generalized urticaria.[22] Despite extensive premedication with high-dose corticosteroids and H_1/H_2-receptor antagonists, the overall frequency of minor reactions is estimated as high as 44%, with major reactions, necessitating discontinuation of paclitaxel therapy, still occurring in approximately 1.5–3% of patients.[23,24] Consistent with the pharmacokinetic selectivity of CrEL for the plasma water phase,[13] Szebeni *et al.* recently postulated a novel concept suggesting that an important contributing mechanism to hypersensitivity reactions from paclitaxel is complement activation due to binding of naturally occurring anti-cholesterol antibodies to the hydroxyl-rich surface of CrEL micelles.[25] Based on an elegant series of *in vitro* experiments, it was shown that CrEL-induced complement activation in human serum was clearly concentration dependent with a minimum activating CrEL level of the order of about 2 μl/ml,[25] concentrations readily achieved clinically in plasma (Figure 1). It should be mentioned in this context that the current trend to pursue shorter schedules of paclitaxel administration in an attempt to simplify complex multidrug regimens can have a much greater impact on complement-activating CrEL levels at the site of infusion and on total CrEL exposure than would be expected in the case of time-independent pharmacokinetics. Indeed, a recent clinical pilot experience in attempting to administer paclitaxel at 175 mg/m^2 by 30 or 45 min i.v. infusion indicated symptoms and signs of significant adverse hypersensitivity reactions in all patients treated within 15 min after start of drug administration, even in the presence of standard antiallergenic premedication.[2]

Consistent with our previous *in vitro* observations,[10] we found in the present study a distinct CrEL concentration dependency of the paclitaxel blood:plasma ratio during 3 h paclitaxel infusions (Figure 2). This finding demonstrates for the first time that CrEL affects the clinical pharmacokinetics of paclitaxel by a disproportional accumulation process in plasma and lends further support to our prior supposition that the ability of CrEL to modulate the murine disposition of various compounds, including paclitaxel and doxorubicin,[9,26,27] may have important clinical ramifications. Mathematical models able to accurately and completely describe paclitaxel concentration–time profiles have shown that the non-linear drug disposition is most likely dictated initially by saturable distribution kinetics,[5,6] and is particularly evident with the 3 h infusion schedule. This is also in keeping with results obtained in mice showing that disproportional plasma levels with an increase in dose did not reflect higher tissue levels[8] and with evidence obtained from trials with prolonged (24 h or longer) i.v. infusions

indicating that the non-linearity of paclitaxel pharmacokinetics was less evident.[5,28,29] Using an indirect response model applied in the pharmacokinetic/pharmacodynamic analysis of CrEL concentrations and corresponding blood distribution of paclitaxel (Figure 3), a change in blood:plasma ratio during 24 h infusions between 0.911 and 1.01 (up to 16.5% decrease of initial value) was predicted, indicating a minor effect of CrEL on paclitaxel distribution. The model also provided additional information on the disposition characteristics of shorter schedules and shed light on some important mechanistic aspect of the paclitaxel–CrEL interaction. Since the estimated Michaelis–Menten constant (K_m) for paclitaxel distribution was previously found to be of the order of paclitaxel peak plasma concentrations following 24 h infusions (135–175 mg/m^2),[6] dose and infusion schedules associated with high drug concentrations relative to K_m (about 70 ng/ml) were expected to display the most distinct signs of non-linearity. In contrast, however, no evidence of non-linear paclitaxel disposition has been described in any trial using 1 h infusion schedules at dose levels associated with distinct deviation of linearity using 3 h schedules (i.e. between about 135 and 225 mg/m^2).[11,30–34] This paradox can be understood in view of the fact that the high CrEL concentrations achieved early into the infusion produce only a low relative net change in the paclitaxel blood:plasma ratio (between 0.545 and 0.650), although the absolute quantitative effect is large already at low-dose input. Measurement of plasma concentrations of CrEL may, therefore, not be the exclusive indicator of the importance of the vehicle–drug interaction, but rather the combination of dose delivered and input rate applied.

Conclusion

Our current study demonstrates that the pharmacokinetic behavior of the paclitaxel vehicle CrEL is subject to considerable variability depending on the duration of i.v. infusion for drug administration. We have identified CrEL-mediated alterations of the paclitaxel blood:plasma ratio as a major contributing mechanism of the non-linear paclitaxel disposition observed in patients with 3 h infusion schedules. In addition, a pharmacokinetic/pharmacodynamic model could accurately describe the biological events for CrEL kinetics and subsequent change in blood:plasma ratio of paclitaxel, and predict the inter-relationships between the parameters under diverse dosing conditions. Since CrEL is increasingly used as a formulation vehicle in pharmaceutical preparations of novel agents, recognition of the complex interplay between kinetic profiles of CrEL and paclitaxel is of particular significance. The present data should therefore be of importance as a guide to better understand the role of this drug vehicle in the future.

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