Anti-Cancer Drugs 2000, **11,** pp. 687–694

Clinical report

Cremophor EL pharmacokinetics in a phase I study of paclitaxel (Taxol®) and carboplatin in non-small cell lung cancer patients

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The purpose of our study was to investigate the pharmacokinetics of Cremophor EL following administration of escalating doses of Taxol® (paclitaxel dissolved in Cremophor EL/ethanol) to non-small cell lung cancer (NSCLC) patients. Patients with NSCLC stage IIIb or IV without prior chemotherapy treatment were eligible for treatment with paclitaxel and carboplatin in a dose-finding phase I study. The starting dose of paclitaxel was 100 mg/m^2 and doses were escalated with steps of 25 mg/m^2, which is equal to a starting dose of Cremophor EL of 8.3 ml/m^2 with dose increments of 2.1 ml/m^2. Carboplatin dosages were 300, 350 or 400 mg/m^2. Pharmacokinetic sampling was performed during the first and the second course, and the samples were analyzed using a validated high-performance liquid chromatographic assay. A total of 39 patients were included in this pharmacokinetic part of the study. The doses of paclitaxel were escalated up to 250 mg/m^2 (20.8 ml/m^2 Cremophor EL). Pharmacokinetic analyses revealed a low elimination-rate of Cremophor EL (Cl=37.8–134 ml/h/m^2; $t_{½}$=34.4–61.5 h) and a volume of distribution similar to the volume of the central blood compartment (V_{SS}=4.96–7.85 l). In addition, a dose-independent clearance of Cremophor EL was found indicating linear kinetics. Dose adjustment using the body surface area, however, resulted in a non-linear increase in systemic exposure. The use of body surface area in calculations of Cremophor EL should therefore be re-evaluated. [© 2000 Lippincott Williams & Wilkins.]

Key words: Clinical pharmacokinetics, Cremophor EL, paclitaxel, phase I study.

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Introduction

Paclitaxel is a taxane derivative with significant activity in various cancers, including breast, ovarian, non-small cell lung, and head and neck cancer.[1,2] Its i.v. administration, however, is complicated due to the poor water solubility of the drug.[3] The current clinical i.v. formulation of paclitaxel (Taxol®) contains ethanol and Cremophor EL (polyoxyethyleneglycerol triricinoleate 35), a polyoxyethylated castor oil (1:1 v/v).[4] The latter vehicle is an effective histamine releaser and has been associated with hypersensitivity reactions in paclitaxel-treated patients.[5–7] Other findings of clinical importance are the effects of Cremophor EL on the pharmacokinetics and biodistribution of paclitaxel.[8,9] Dose increments of paclitaxel dissolved in ethanol/Cremophor EL result in non-linear increases in the systemic exposure to paclitaxel, as represented by the area under the concentration–time curve (AUC), and, therefore, side effects are poorly predictable.[10,11] In addition, combination chemotherapy with paclitaxel preceded or followed by cisplatin is associated with important schedule-dependent toxicities, such as leukocytopenia. Recent *in vitro* studies showed that Cremophor EL might contribute to this effect by reducing the intracellular accumulation of cisplatin.[12] Finally, several studies suggest that Cremophor EL may enhance cytotoxicity of paclitaxel,[13,14] whereas in other studies investigators observed that high levels of Cremophor EL antagonized the *in vitro* cytotoxicity of paclitaxel at certain concentrations.[15] The ability of Cremophor EL to increase drug sensitivity through reversal of P-glycoprotein-mediated multidrug resistance (MDR) has been extensively investigated and it

was demonstrated that the plasma concentrations of Cremophor EL after administration of Taxol® are sufficiently high to reverse MDR.[16–19] However, more recent *in vivo* data contradict this finding.[20,21] In summary, the various implications associated with the clinical use of Cremophor EL warrant a more extended pharmacologic examination of this pharmaceutical vehicle. So far, little is known about the human pharmacokinetics of Cremophor EL in dose-escalation studies with paclitaxel or in combination schemes of paclitaxel and platinum compounds. We investigated, therefore, the pharmacokinetics of Cremophor EL as part of a dose-escalating and sequencing study of paclitaxel and carboplatin, performed by Huizing *et al.*,[22,23] in patients with non-small cell lung cancer.

Patients and methods

Patients

The pharmacokinetics of Cremophor EL were determined in addition to a pharmacologic evaluation of paclitaxel and carboplatin kinetics, in a study previously reported.[23] This study was performed at three institutes in Amsterdam; the Academic Medical Center, the Free University Hospital and the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital. Briefly, patients with NSCLC stage IIIb or IV were included and eligibility criteria were the following: (i) age <75 years and >18 years; (ii) an Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant 2$; (iii) life expectancy >12 weeks; (iv) acceptable functions of bone marrow [absolute neutrophil count (ANC) $\geqslant 2.5 \times 10^9$/l and platelet count $\geqslant 100 \times 10^9$/l), liver (serum bilirubin $\leqslant 30$ μmol/l, alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) $\leqslant 2.5\times$ the upper normal limit] and kidneys (serum creatinine $\leqslant 140$ μmol/l); and (v) written informed consent.

Study plan

At each dose level six patients were entered who were randomized for either paclitaxel followed by carboplatin or carboplatin followed by paclitaxel at the first course. At the second and subsequent courses the alternate sequence was administered. The starting dose of paclitaxel was 100 mg/m^2 and doses were escalated with dose steps of 25 mg/m^2 paclitaxel. Initially, the dose of carboplatin was fixed at 300 mg/m^2. Paclitaxel (Taxol®; Bristol-Myers Squibb, Syracuse, NY) was administered in a 3-h infusion and carboplatin (Paraplatin®; Bristol-Myers Squibb) was administered in a 30-min infusion immediately after paclitaxel (or in the alternate sequence). Courses were repeated every 4 weeks. Carboplatin was supplied as a lyophilized product containing 150 mg carboplatin and 150 mg mannitol as bulking agent. The content of each vial was reconstituted with 15 ml water for injection and subsequently diluted in 250 ml dextrose 5% prior to infusion.

Paclitaxel was provided as a sterile 6 mg/ml solution in a mixture of Cremophor EL and ethanol (1:1 v/v; Taxol®) and prior to administration this concentrated solution was diluted with 500–1000 ml 0.9% sodium chloride solution to a final paclitaxel concentration not exceeding 0.6 mg/ml. As Cremophor EL may leach plasticizer from the infusion lines, an adapted PVC-free administration equipment was used. Patients were premedicated with dexamethasone, clemastine and cimetidine, according to a standard scheme.[23] Antiemetics were given according to the institutional guidelines.

Pharmacokinetics

Pharmacokinetic sampling was performed during the first and second course. Samples for Cremophor EL analysis were collected in heparinized tubes at 21 time points up to 48 h after paclitaxel administration: prior to the start of the infusion, 1 and 2 h after the start, at the end of the infusion (about 3 h after start), at 5, 10, 15, 30, 45 and 60 min after the end of the infusion, and at 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 30 and 48 h after the end of the infusion. Whole blood was centrifuged immediately after withdrawal (5 min; 1500 *g*) and the plasma fraction was stored at -20°C until analysis. Cremophor EL concentrations in plasma were quantified using a validated high-performance liquid chromatographic assay, with a lower limit of quantification of 0.5 ml/l.[24,25] Non-compartmental methods were applied to calculate the pharmacokinetic parameters of Cremophor EL.[26] The AUC was calculated, using the linear trapezoidal rule with extrapolation of the terminal phase to infinity (C_{last}/k, in which C_{last} is the last measured concentration). The slope of the terminal phase and the elimination rate constant (k) were calculated by linear regression analysis of the logarithmic plasma concentration–time curve. A minimum of three concentration–time points were used. The C_{max} is the highest measured concentration and the T_{max} represents the point in time at which this concentration was reached. The clearance (Cl) was estimated as dose/AUC and the volume of distribution at steady state (V_{SS}) was calculated using the following equation:

$$V_{SS} = \frac{\text{dose} \times \text{AUMC}}{\text{AUC}^2} - \frac{\text{dose} \times \text{infusion time}}{2 \times \text{AUC}}$$

AUMC in this equation represents the area under the moment–time curve and was also calculated using the linear trapezoidal rule with extrapolation to infinity [$(C_{last} \times T_{last})/k+C_{last}/k^2$), with T_{last} as the time point at which C_{last} was measured). The elimination half-life ($t_{½}$) was determined as ln 2/k. Statistical analysis of the results was performed using SPSS/PC+ (SPSS/PC+ Advanced Statistics™, version 6.1, 1994; Chicago, IL).

Results

Patients and study course

Cremophor EL samples were analyzed in 39 courses from 39 patients; 27 females and 12 males. Their median age was 57 years (range 38–74) and their median performance status was 1 (range 0–2). During all analyzed courses the sequence of administration was paclitaxel followed by carboplatin. Dose escalation of paclitaxel was performed as follows: 100–125–150–175–200–225–250 mg/m^2, which is equivalent to dose escalation steps of Cremophor EL of 8.33–10.4–12.5–14.6–16.7–18.8–20.8 ml/m^2. One patient at the dose level of 250 mg/m^2 paclitaxel received 350 mg/m^2 carboplatin and one patient received 400 mg/m^2 carboplatin, also in combination with 250 mg/m^2 paclitaxel. All other patients received 300 mg/m^2 carboplatin.

Pharmacokinetics

Pharmacokinetic parameters of Cremophor EL for all dose levels are summarized in Table 1. In Figure 1 the mean plasma concentration–time curves for each dose level are depicted. In Figure 2 the AUCs of Cremophor EL are plotted against the dose of Cremophor EL in ml/m^2 and in Figure 3 the AUC values are plotted against the total dose in ml. Plots of the C_{max} versus the dose are shown in Figures 4 and 5. Figure 6 presents a plot of the AUC values of Cremophor EL versus the AUC values of paclitaxel, as reported by Huizing *et al.*[23] Regression analysis resulted in a significant correlation ($p<0.001$) between the plotted values. The mean T_{max} was not significantly different at increasing doses and coincided with the end of the infusion. The mean Cl of Cremophor EL at a paclitaxel dose of 100 mg/m^2 was not significantly different from the mean Cl at a dose of 250 mg/m^2. A large, although not statistically significant (p=0.061) difference, in Cl was found between the two cohorts when Cl/m^2 was considered. Differences between the mean $t_{½}$ and mean V_{SS} values were not statistically significant.

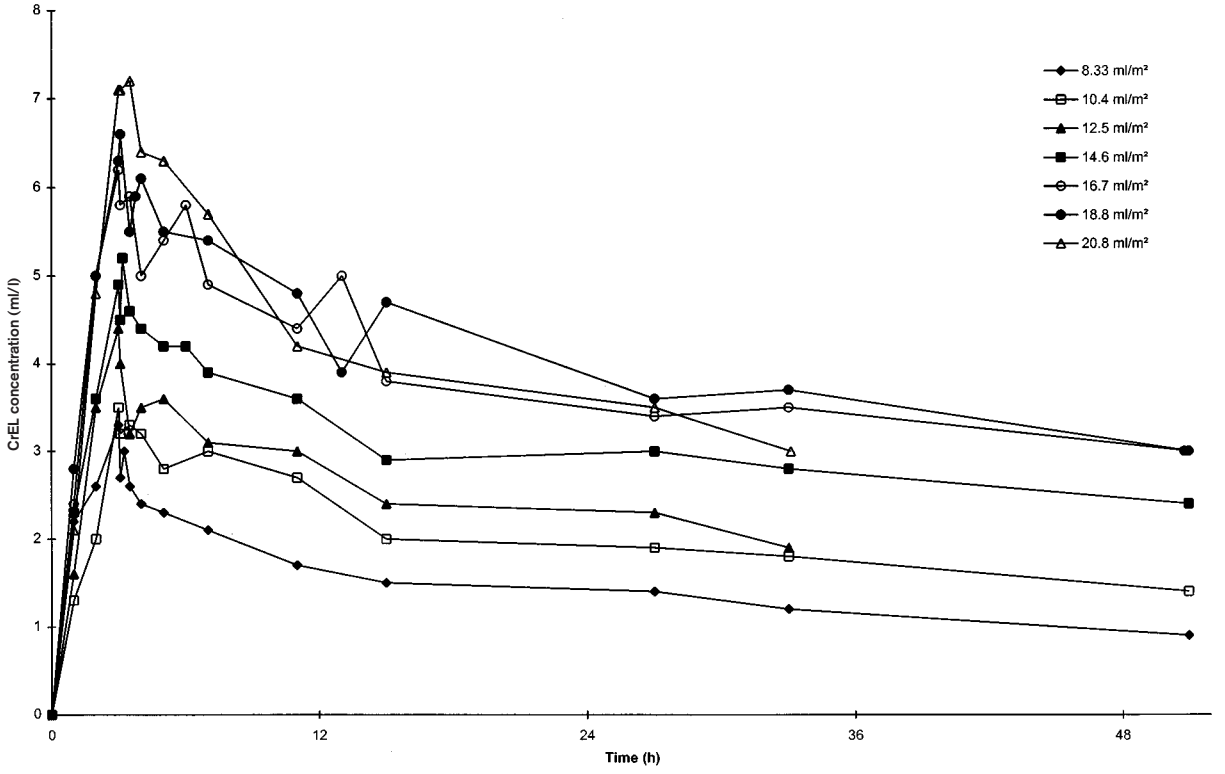

Figure 1. Mean plasma concentration–time curves of Cremophor EL after administration of escalating doses of paclitaxel.

Table 1. Pharmocokinetics of Cremophor EL after paclitaxel infusion

Dose of paclitaxel (mg/m^2)	Dose of Cremophor EL (ml/m^2)	*n*	AUC (hml/l)	C_{max} (ml/l)	T_{max} (h)	Cl (ml/h)	Cl (ml/h/m^2)	$t_{½}$ (h)	V_{SS} (l)
100	8.33	5	108±74.4	3.3±0.6	2.2±1.2	258±273	134±121	35.9±34.4	4.96±3.13
125	10.4	7	162±81.8	3.7±0.9	3.5±0.5	138±51.4	75.6±28.6	34.4±13.4	5.65±1.77
150	12.5	5	247±80.1	4.4±0.7	3.1±0.1	102±47.5	52.4±25.8	51.3±14.6	6.94±4.56
175	14.6	7	373±129	5.1±1.0	3.7±0.8	84.6±28.0	43.2±13.8	61.5±22.1	6.37±1.86
200	16.7	7	435±89.5	6.0±1.2	3.1±0.3	72.1±18.0	39.6±8.28	58.5±14.8	5.98±1.21
225	18.8	5	438±68.8	6.8±1.4	3.0±0.3	84.4±12.7	37.8±15.7	53.3±16.3	6.10±2.72
250	20.8	3	377±116	7.1±0.6	3.5±0.5	108±33.6	44.2±21.7	54.9±33.3	7.85±3.87

Area under the concentration–time curve (AUC), maximal concentration (C_{max}), time of C_{max} (T_{max}), clearance (Cl), elimination half-life ($t_{½}$) and volume of distribution (V_{SS}) of Cremophor EL after paclitaxel infusion. Data are presented as means±SD.

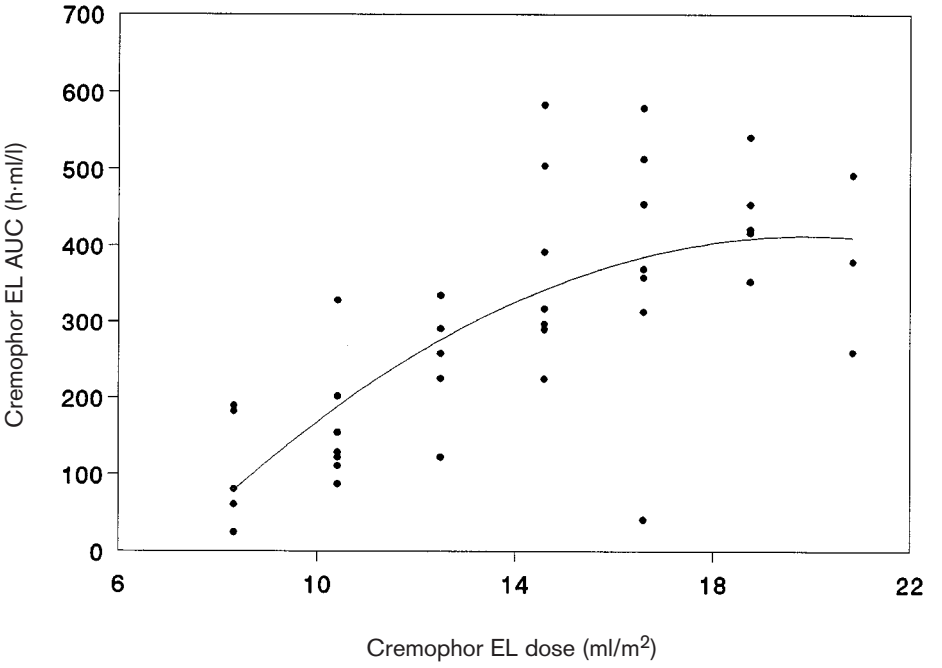

Figure 2. AUC of Cremophor EL plotted against the administered dose of Cremophor EL in ml/m^2.

Discussion

It is widely assumed that Cremophor EL is involved in the hypersensitivity reactions associated with the i.v. administration of paclitaxel and that Cremophor EL is responsible for the non-linear pharmacokinetic behavior of paclitaxel.[3–11] For these and other reasons, it is important to investigate the plasma pharmacokinetics of Cremophor EL after administration of escalating doses of paclitaxel. Complete plasma concentration–time curves of Cremophor EL were measured in 39 patients.

A plot of the AUC of Cremophor EL versus the dose/m^2, revealed a clear non-linearity (Figure 2). A disproportional increase in AUC with dose was observed in the paclitaxel dose range 100–175 mg/m^2 (Cremophor EL 8.3–14.6 ml/m^2), whereas no further increase in AUC occurs at the higher dose levels (175–250 mg/m^2; Cremophor EL doses 14.6–20.8 ml/m^2) (Figure 2). Apparently, at paclitaxel doses exceeding 175 mg/m^2, a further increase in administered dose does not result in any further increase in the AUC of Cremophor EL. An increase in clearance is not a likely explanation for this phenomenon, as the elimination system appeared to become saturated already at lower dose levels. A more likely explanation is an increase in the volume of distribution at doses exceeding 14.6 ml/m^2 with a longer half-life. Considering the relatively small volume of distribution (V_{SS}) of Cremophor EL, small differences will have

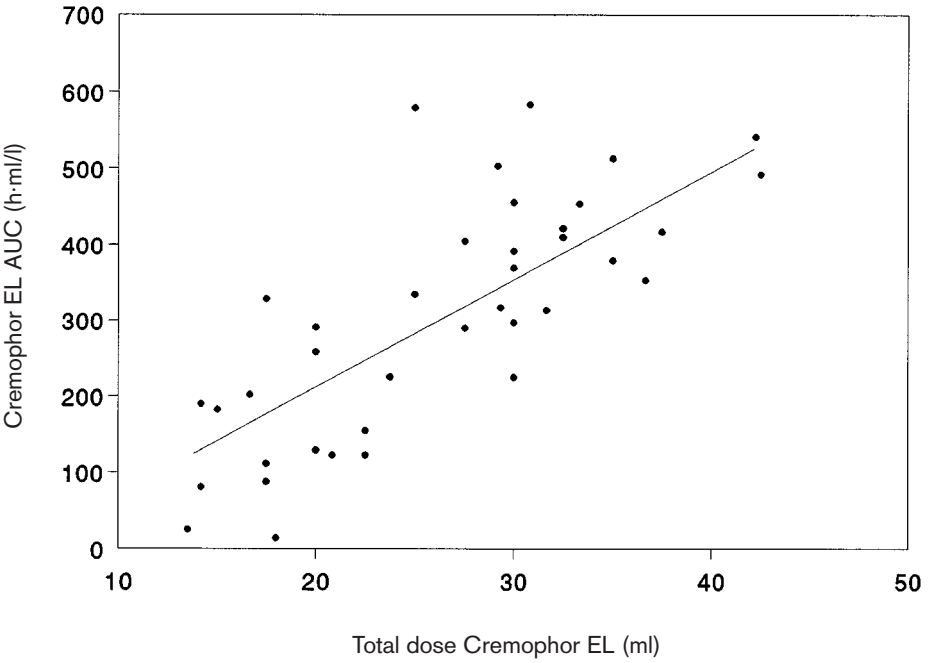

Figure 3. AUC of Cremophor EL plotted against the administered dose of Cremophor EL in ml.

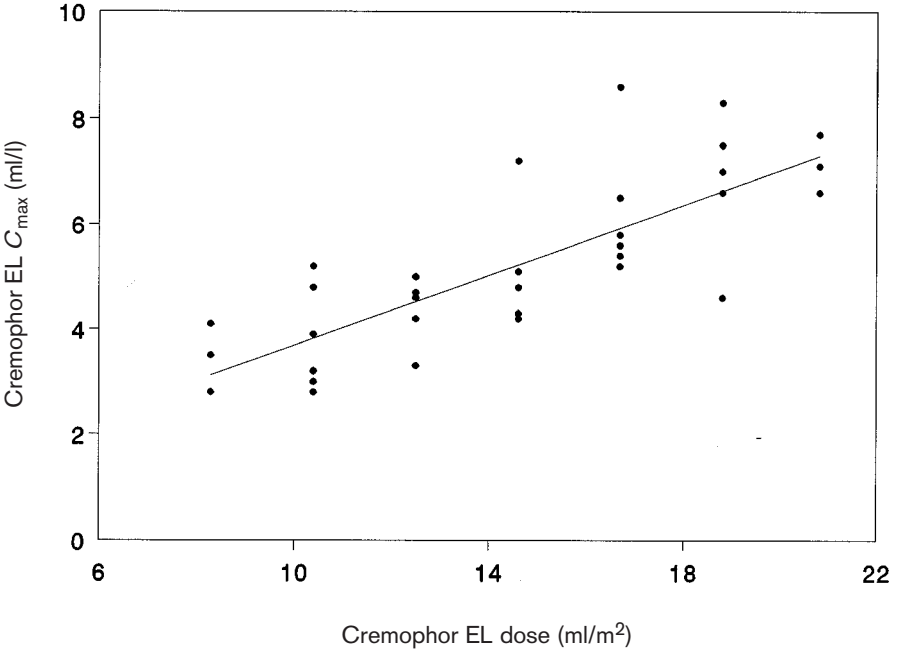

Figure 4. C_{max} values of Cremophor EL plotted against the dose of Cremophor EL in ml/m^2.

considerable impact. We did not observe statistically significant differences in V_{SS} and terminal half-lives at exceeding doses of Cremophor EL; however, this could be due to the large interpatient variability and the relatively small number of patients per cohort.

When the AUC of Cremophor EL was plotted against the total dose administered, the results indicated a linear behavior (Figure 3). Plots of the C_{max} of Cremophor EL against the dose, either in ml/m^2 or in ml, also revealed linearity (Figures 4 and 5). This inconsistency implies that the use of the body surface area (BSA) for dose adjustment in this case should be

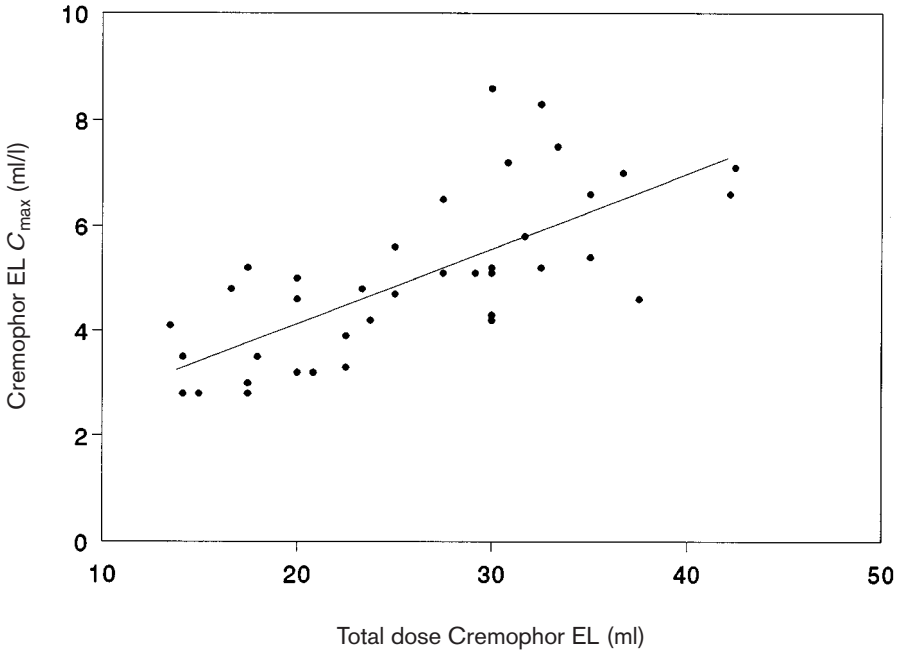

Figure 5. C_{max} values of Cremophor EL plotted against the dose of Cremophor EL in ml.

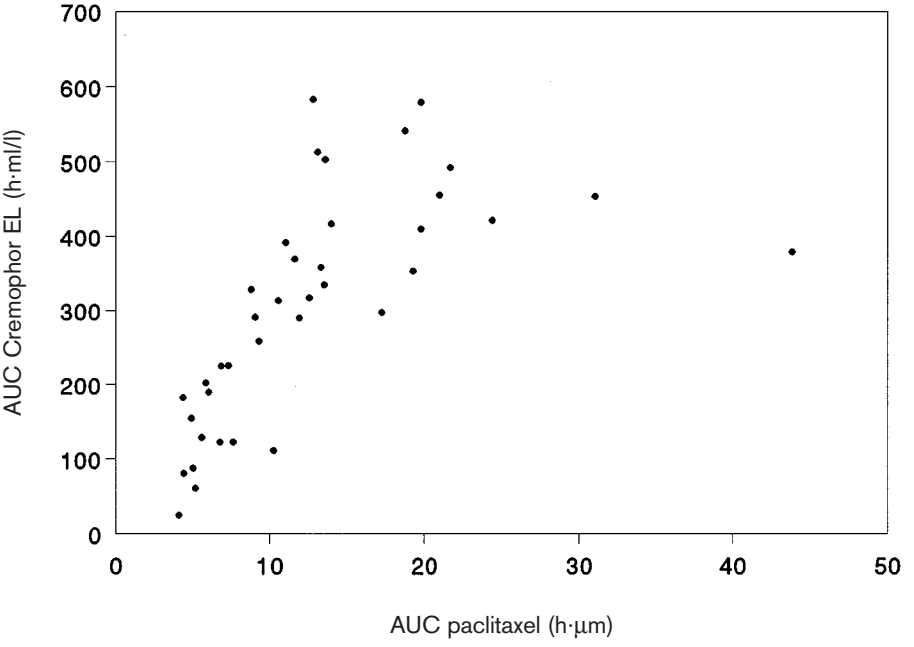

Figure 6. Plot of the AUC values of Cremophor EL versus the corresponding AUC values of paclitaxel, as reported by Huizing *et al.*[23]

re-evaluated. BSA is equivalent to the two-dimensional surface area of an individual's skin and it has been known for almost a century that BSA correlates with basal metabolic rate. However, for a number of drugs, among which paclitaxel, no correlation was found between BSA and pharmacokinetic parameters as Cl and V_{SS}.[27,28] It is therefore not unlikely that the use of BSA in this study was inappropriate and results in an

incorrect prediction of the exposure to paclitaxel, or in this case, to Cremophor EL. When considering the total dose administered, the exposure to Cremophor EL tends to increase in a linear way with increasing doses.

Sparreboom *et al.* reported linear kinetics of Cremophor EL,[29,30] and their pharmacokinetic data are in well agreement with our data. However, they also observed substantial interpatient variability. Earlier observations in mice and preliminary data from humans[25,29–32] also indicated a V_{SS} of Cremophor EL roughly equivalent to the volume of the intravascular compartment, implying that the tissue distribution of Cremophor EL is insignificant. The elimination half-life was relatively long and consequently, 24 h after administration of paclitaxel substantial levels of Cremophor EL are still present for sustained periods of time. In addition, our Cremophor EL kinetic data are in agreement with published data of paclitaxel administered as a single agent.[31,33] Thus, the combination with carboplatin apparently did not influence the pharmacokinetics of Cremophor EL.

Various processes may be involved in the elimination of Cremophor EL, including degradation in the blood stream by serum lipases, hepatic metabolism and biliary clearance. As indicated by the long elimination half-life, any metabolic conversion in the blood occurs at a low rate and the involved enzymes may be easily saturated. In addition, binding of Cremophor EL to plasma lipoproteins may be concentration-dependent, which may in turn produce significant changes in biodistribution and clearance.[8,34] Therefore, the overall effects on the pharmacokinetic profile can be quite complex and more data are warranted to elucidate the various mechanisms involved and their relative influences.

Several speculations exist regarding the pharmacokinetic interactions of Cremophor EL and paclitaxel. It has been suggested that inhibition of P-glycoprotein (P-gp) by Cremophor EL results in a diminished clearance of paclitaxel.[32] It is possible that Cremophor EL inhibits P-gp-mediated biliary excretion of paclitaxel, as was also demonstrated for doxorubicin.[35] Secondly, Cremophor EL is capable of forming micelles which can entrap paclitaxel.[31] Micellar entrapment of the drug by Cremophor EL may result in a decreased or delayed liver uptake and, consequently, a decreased clearance of paclitaxel. It is, however, unlikely that the non-linear pharmacokinetics of paclitaxel are caused mainly by saturation of drug elimination pathways.[20] Therefore, the non-linearity is more likely to be due to an alteration in distribution. It was previously mentioned that Cremophor EL alters the biodistribution of paclitaxel through its effects on plasma protein binding.[8] Other *in vitro* experiments indicate that Cremophor EL, at clinical relevant concentrations, increases the affinity of paclitaxel for plasma, thereby causing the free fraction of paclitaxel to be dependent on the Cremophor EL concentration.[31] Cremophor EL plasma AUC values were significantly correlated to the corresponding plasma AUC values of paclitaxel in our study ($p < 0.001$, Figure 6), which favors the hypothesis that Cremophor EL entraps paclitaxel in the plasma compartment. Thus far, none of the above-mentioned mechanisms has been fully elucidated and based on the few available data in humans, any firm conclusions regarding their pharmacokinetic interaction cannot be drawn yet.

In summary, we investigated the pharmacokinetics of Cremophor EL after administration of paclitaxel in order to clarify its pharmacologic effects. The most important findings were a low rate of elimination, resulting in sustained high levels of Cremophor EL and a linear increase in the systemic exposure (AUC) with increasing doses. Adjustment of dose for BSA resulted in a different non-linear profile. Recognition of the pharmacokinetic behaviour of Cremophor EL is important in particular with respect to the clinical use of paclitaxel formulated in Cremophor EL, as non-linear pharmacokinetics potentially result in an unpredictable toxicity profile. The presented results may therefore be a valuable addition to the current knowledge of Cremophor EL pharmacology.

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(Received 28 June 2000; revised form accepted 18 July 2000)