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ORIGINAL ARTICLE

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A population analysis of the pharmacokinetics of Cremophor EL using nonlinear mixed-effect modelling

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Abstract *Purpose*: The purpose of this study was to develop a population pharmacokinetic model for Cremophor EL used as a formulation vehicle for paclitaxel. *Methods*: Plasma concentration-time data from 70 patients (85 courses) treated with paclitaxel dissolved in Cremophor EL were used. The nonlinear mixed-effect modelling (NONMEM) program was used for the population pharmacokinetic analysis. The influence of patient characteristics on the pharmacokinetics of Cremophor EL was determined. The stability of the final model was evaluated using bootstrapping. *Results*: The data were optimally fitted to a three-compartment model with Michaelis-Menten elimination from the central compartment. The following pharmacokinetic parameters were estimated: volume of the central compartment (V1 = 2.59 l), volumes of two peripheral compartments (V2 = 1.81 l, V3 = 1.61 l), intercompartmental clearance between central and peripheral compartments (Q12 = 1.44 l/h, Q13 = 0.155 l/h), maximal elimination rate (Vmax = 0.193 ml/h), and concentration at half Vmax (Km = 0.122 ml/l). Interindividual variability of the pharmacokinetic parameters was quantified for V1 (25%), V2 (36%) and Vmax (31%). Residual variability consisted of a combined additional (0.095 ml/l) and proportional error (7%). Gender, body surface area and performance status according to the World Health Organization were significantly correlated with V1, V2 and Vmax, respectively ($P < 0.0001$). The median parameter estimates of 1000 bootstrap samples were in accordance with those obtained with the original data set, indicating the validity of the population model. *Conclusions*: The population model was able to adequately describe the pharmacokinetic parameters and influence of covariates on the pharmacokinetics of Cremophor EL. This model can be used when studying the relationship between the pharmacokinetics and toxicity of Cremophor EL, and the drug's influence on the pharmacokinetics of paclitaxel.

Keywords Cremophor EL · Population pharmacokinetic model · Validation

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Introduction

Cremophor EL is a polyethoxylated castor oil that is used for the formulation of vitamin preparations and a variety of poorly water-soluble drugs including teniposide, cyclosporin A and paclitaxel [19, 32, 34]. Taxol is the pharmaceutical product in which paclitaxel is dissolved (6 mg/ml) in a mixture of Cremophor EL and ethanol (1:1 v/v) [32]. Cremophor EL can cause hypersensitivity reactions by complement activation [2, 16, 31]. Cremophor EL can also cause neurotoxicity probably caused by the ethoxylated derivatives of castor oil [31]. Despite the extensive use of Cremophor EL as a solubilizing agent in clinical formulations and its reported toxicity, its pharmacokinetics in humans have not been extensively studied [15, 17, 19, 23, 27]. There is, however, substantial evidence that Cremophor EL can alter the pharmacokinetics of certain cytotoxic drugs with clinical implications, e.g. paclitaxel [20, 24, 27, 30, 31].

In several studies the pharmacokinetics of Cremophor EL in mice and cancer patients have been studied in relation to its use as a pharmaceutical solubilizer of paclitaxel [20, 24, 27, 30]. Dose increments of paclitaxel dissolved in Cremophor EL result in disproportionate increases in systemic exposure to paclitaxel, as represented by the area under the concentration versus time curve (AUC). In the absence of Cremophor EL a linear pharmacokinetic behaviour of paclitaxel has been observed [20]. Several mechanisms of the nonlinear pharmacokinetics of paclitaxel induced by Cremophor EL have been reported [4, 12, 13, 24, 25, 27, 29, 30, 33]. Cremophor EL might inhibit the elimination of paclitaxel by preventing access of the drug to the elimination sites [4]. Furthermore, it has been suggested that Cremophor EL induces a serum lipoprotein dissociation product with a high affinity for paclitaxel [25, 33]. More recently, it has been demonstrated that Cremophor EL can form micelles in blood in vitro, acting as a high-affinity drug-transporting site for paclitaxel resulting in a decreased free paclitaxel fraction in plasma [12, 13, 24, 29, 30]. Cremophor EL can decrease the blood/plasma ratio of paclitaxel at higher dose levels by reducing the uptake in red blood cells [29].

The pharmacokinetic behaviour of paclitaxel can thus be influenced by the pharmacokinetics of Cremophor EL. Consequently, Cremophor EL can modify the toxicity profile of paclitaxel [7]. Assessment of the clinical pharmacokinetics of Cremophor EL during paclitaxel administration may be of major importance. The purpose of this study was to develop a population pharmacokinetic model of Cremophor EL when administered in combination with paclitaxel. In this population analysis, the pharmacokinetic parameters and the patient characteristics that correlate with the pharmacokinetics of Cremophor EL were determined.

Material and Methods

Patient population

Plasma concentration-time data (85 courses) of Cremophor EL concentrations were collected during safety and pharmacokinetic multicentre studies of paclitaxel performed in 70 cancer patients (21 patients with hepatic dysfunction). The results of these studies have been published recently [3, 8, 9, 18]. In these studies paclitaxel was infused intravenously (i.v.) with or without coinfusion of carboplatin in patients with primarily metastatic breast, ovarian and non-small-cell lung cancer. The patient characteristics are summarized in Table 1. Every course was included separately in the data set, resulting in 85 identification numbers in this population pharmacokinetic analysis. Paclitaxel (Taxol; Bristol Myers Squibb, Syracuse, N.Y.) was provided as a sterile 6 mg/ml solution dissolved in Cremophor EL/ethanol 1:1 v/v. Prior to administration this solution was diluted with 500–1000 ml 0.9% sodium chloride solution to a final paclitaxel concentration between 0.3 and 1.2 mg/ml. As Cremophor EL may leach plasticizer from infusion lines, adapted PVC-free administration equipment was used.

Paclitaxel was infused i.v. in 3-, 24- and 96-h infusions at doses ranging from 100 to 250 mg/m^2. The corresponding Cremophor EL doses ranged from 8.3 to 20.8 ml/m^2 in the 3-h infusion schedule (78 courses), from 11.2 to 14.5 ml/m^2 in the 24-h infusion schedule (3 courses), and from 8.7 to 11.6 ml/m^2 in the 96-h infusion schedule (4 courses). Written informed consent was obtained from all patients. Standard premedication with dexamethasone (20 mg orally at 12 and 6 h prior to paclitaxel administration), clemastine (2 mg i.v. 30 min prior to paclitaxel administration) and cimetidine (300 mg i.v. shortly before paclitaxel administration) was administered to prevent hypersensitivity reactions. If indicated, 5-HT$_3$-receptor antagonists were administered i.v. as standard antiemetic agents. The Medical Ethics Committees of the participating hospitals approved the studies.

Table 1. Patient characteristics ($n=70$) and serum parameter values during 85 courses (*BSA* body surface area, *AST* aspartate aminotransferase, *ALT* alanine-aminotransferase, *GGT* gamma-glutamyl transpeptidase, *LDH* lactate dehydrogenase)

	Number	Median	Range
Patients			
Female	44		
Male	26		
Number of courses with pharmacokinetic data			
First course	70		
Second course	15		
Paclitaxel dose range (mg/m^2)			
3-h infusion	78		100–250
24-h infusion	3		135–175
96-h infusion	4		105–135
Cremophor EL dose range (ml/m^2)			
3-h infusion	78		8.3–20.8
24-h infusion	3		11.2–14.5
96-h infusion	4		8.7–11.6
Carboplatin dose range (mg/m^2)			
3-h infusion	32		300–400
Age (years)		52	24–75
Primary site of disease			
Lung	32		
Ovary	17		
Breast	16		
Colon	1		
Pancreas	1		
Sarcoma	1		
Endometrium	1		
Granulosa theca cell	1		
WHO performance status			
0	21		
1	48		
2	16		
BSA (m^2)		1.82	1.50–2.30
Creatinine (μmol/l)		78	37–120
AST (U/l)		19	7–260
ALT (U/l)		21	3–343
Alkaline phosphatase (U/l)		112	52–1269
GGT (U/l)		116	7–1527
Albumin (g/l)		36	23–52
Total bilirubin (μmol/l)		7	3–50
LDH (U/l)		306	190–5942

Pharmacokinetic sampling and bioanalysis

Plasma concentration-time data were obtained by pharmacokinetic sampling during the first course ($n=70$) and the second course ($n=15$). The samples for Cremophor EL analysis were collected into heparinized tubes prior to the start of the infusion, at 1 and 2 h

after the start, at the end of the infusion, and at 5, 30 and 60 min, and 1.5, 2, 4, 8, 10, 12, 30 and 48 h after the end of the infusion in the 3-h infusion schedules. In the 24-h infusion schedules, blood samples were taken prior to the start of the infusion, at 3, 10 and 20 h after the start of the infusion, at the end of the infusion, and at 5, 15, 30 and 60 min, and 2, 4, 8, 12, 24 and 30 h after the end of the infusion. In the 96-h infusion schedule, blood samples were taken prior to the start of the infusion, at 8, 48 and 72 h after the start of the infusion, at the end of the infusion, and at 4, 9 and 19 h after the end of the infusion. Whole blood was centrifuged immediately after withdrawal for 5 min at 3000 rpm, and the plasma fraction was stored at –20ºC until analysis. The Cremophor EL concentrations in plasma were determined by a validated reversed-phase high-performance liquid chromatographic method based on the determination of ricinoleic acid after saponification of Cremophor EL, followed by precolumn derivatization and reversed-phase high-performance liquid chromatography as has been described in detail elsewhere [21, 27].

Population pharmacokinetic analysis

The program NONMEM (nonlinear mixed-effect modelling, version V 1.1, double precision) and the PREDPP package were used throughout the analysis [1]. Since the patients were sampled extensively, first-order conditional estimation was applied with interaction. The NONMEM analysis consisted of the following three-step approach [14].

Basic population pharmacokinetic model

The first step consisted of the development of a basic population pharmacokinetic model. The data were fitted to a three-compartment model with Michaelis-Menten elimination (Fig. 1). The following pharmacokinetic parameters were estimated: volume of the central compartment (V1 in litres), volume of the first peripheral compartment (V2, in litres), volume of the second peripheral compartment (V3, in litres), intercompartmental clearance from the central compartment to the first peripheral compartment (Q12, in litres per hour), and to the second peripheral compartment (Q13, in litres per hour), maximal elimination rate (Vmax, in millilitres per hour), and the concentration at half of the Vmax (Km, in millilitres per litre). Standard errors for all parameters were calculated using the COVARIANCE option in the NONMEM program. Interindividual variabilities in V1, V2 and Vmax were estimated using a lognormal error model. For V1 the interindividual variability was as defined in Eq. 1:

$$\ln V1_j = \ln V1_{pop} + \eta_j^{V1} \quad (1)$$

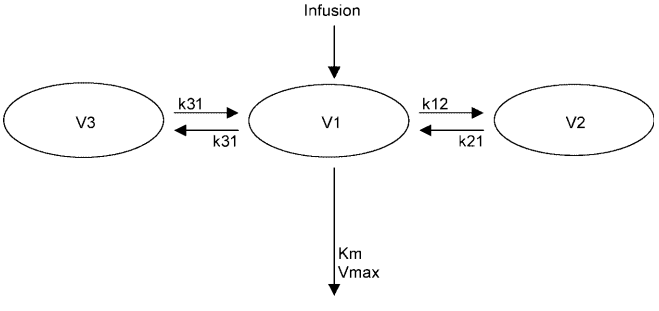

Fig. 1. Schematic overview of the basic population pharmacokinetic model: a three-compartment model with Michaelis-Menten elimination from the central compartment (*V1*). *V2* and *V3* indicate the two peripheral compartments. *k12*, *k21*, *k13* and *k31* indicate the intercompartmental rate constants. *Vmax* is the maximal elimination rate, and *Km* is the plasma-concentration of Cremophor EL at half Vmax

where $V1_j$ represents the V1 of the *j*th individual and $V1_{pop}$ is the population value, and η_j^{V1} is the interindividual random effect that is normally distributed with mean zero and variance ω^2.

The residual variability was estimated using a combined additive and proportional model:

$$C_{obsj} = C_{predj}(1 + \varepsilon_2) + \varepsilon_1 \quad (2)$$

where C_{obsj} is the observed concentration in the *j*th patient (C_{obsj}) and its respective prediction (C_{predj}), and ϵ is an independent random variable with mean zero and standard deviation σ that was assumed to be constant in this population analysis.

The stability of the basic pharmacokinetic model was evaluated by the bootstrap resampling technique as implemented in the program Wings for NONMEM (WFN version 3) designed by Dr. N.H. Holford and available via the internet (http://wfn.sourceforge.net) [5]. The median parameter estimates obtained from the 1000 bootstrap replications were compared with those obtained from the original data set.

Intermediate model

The second step consisted of an individual Bayesian regression analysis. For each subject, individual pharmacokinetic parameters were calculated using the individual Cremophor EL plasma concentration-time data and the population pharmacokinetic parameter estimates obtained in the first step. The individual Bayesian estimates were plotted against the demographic factors and blood chemistry parameters (as covariates). The relationships between the covariates and the Bayesian parameter estimates of each individual patient were investigated graphically in the program Xpose (Xpose, version 2.0; Uppsala University, Sweden) as implemented in the S-PLUS statistical software package (version 2000; Mathsoft, Cambridge, Mass.) [11]. The following 13 covariates were investigated for their correlation with the pharmacokinetics of Cremophor EL: age, gender, weight, body surface area (BSA), performance status according to the World Health Organization (PS), serum creatinine, serum alanine-aminotransferase (ALT), serum aspartate-aminotransferase (AST), serum alkaline phosphatase, serum gamma-glutamyl-transpeptidase (GGT), serum albumin, serum bilirubin and serum lactate dehydrogenase (LDH). The selected covariates that showed a graphical relationship with a pharmacokinetic parameter were tested by univariate analysis. These covariates were entered individually into the basic population pharmacokinetic model by forward inclusion. Continuous covariates, e.g. BSA, were centred to their median values [10]. For instance, the relationship between V2 and BSA was as described in Eq. 3:

$$V2 = \theta3 * (1 + \theta4 * (BSA - 1.82)) \quad (3)$$

where V2 represents the value of V2 in litres, $\theta3$ the V2 value of a (median) patient with a BSA of 1.82 m^2, and $\theta4$ is the increase or decrease in V2 per metre squared difference in BSA.

Dichotomous covariates were modelled as described in Eq. 4:

$$V1(\in 1) = \theta1 * \theta2^{FLAG1} \quad (4)$$

where V1 represents the value of V1 in litres, $\theta1$ the V1 value in females (FLAG1 = 0), and $\theta2$ the change in V1 in males (FLAG1 = 1).

Several criteria were taken into account when comparing the models. The difference in the NONMEM objective function value that is equal to minus twice the log likelihood of the data, after the introduction of a covariate in the model, approximates to a chi-squared distribution with one degree of freedom. During the forward inclusion of the covariates in the basic model, the significance level was set at $P < 0.005$ that is associated with a decrease in the NONMEM objective function value of > 7.8. All significant covariates were incorporated into an intermediate multivariate model.

Final population pharmacokinetic model

The development of the intermediate model was followed by multivariate analysis that consisted of a stepwise backward elimination procedure. Covariates retained in the intermediate model when elimination of the covariate caused an increase in the NONMEM objective function value of >10.8 that is associated with a significance level of $P < 0.001$. The stability and performance of the final model was evaluated using the bootstrap method by fitting the final model to 1000 bootstrap samples. The parameter estimates and the 95% confidence intervals obtained from the original data set were compared with the median parameter estimates including the 2.5–97.5% percentile range obtained from the 1000 bootstrap replicates.

Results

The plasma concentrations versus time curves of Cremophor EL after the start of the infusion were analysed. Individual plots of plasma concentration versus time curves after a 3-, 24- and 96-h i.v. infusion are shown in Fig. 2.

Population pharmacokinetic analysis

Basic population pharmacokinetic model

Two- and three-compartment models with first-order elimination and Michaelis-Menten elimination, and with linear distribution and saturable distribution were fitted to the Cremophor EL concentration-time data. According to the objective function values (OFV), the standard error values, and the goodness of fit plots, it appeared that the data were best fitted by a three-compartment model with Michaelis-Menten elimination (Fig. 1). The population pharmacokinetic parameters (without taking covariates into account) including the standard errors, the interindividual variability and the residual errors are summarized in Table 2. All pharmacokinetic parameters were estimated accurately, except for the Km. The relative standard error of this parameter was 71%. Interindividual variability was determined for V1, V2 and Vmax. Inclusion of interindividual variability for V3, Q12, Q13 and Km did not improve the fit. This should not be interpreted as an absence of interindividual variability in these pharmacokinetic parameters. It indicates that the data did not contain sufficient information to estimate the interindividual variability of these parameters. The residual variability consisted of an additional error of 0.099 ml/l and a proportional error of 6.8%.

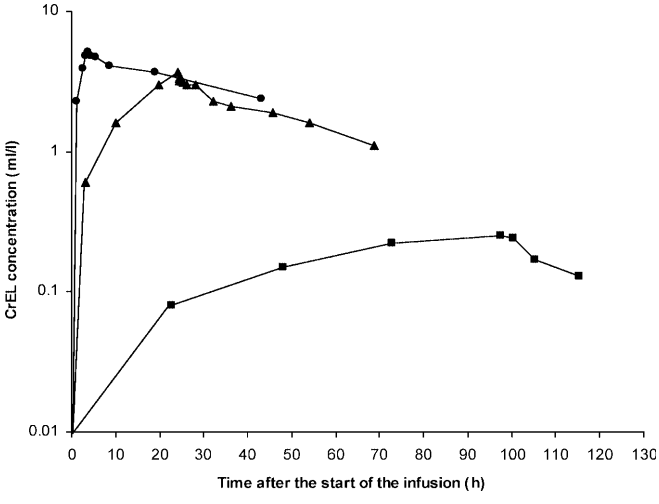

Fig. 2. Plasma concentration versus time curves of Cremophor EL in three representative patients treated with a 3-h (*circles*), a 24-h (triangles) and a 96-h (*squares*) i.v. infusion of paclitaxel dissolved in Cremophor EL at doses of 30, 24.6, and 19.4 ml, respectively (corresponding paclitaxel doses 360, 295 and 235 mg, respectively)

The stability of the basic pharmacokinetic model was tested by the bootstrap method. From the original concentration-time data, 1000 bootstrap resamples were generated. The median values of the parameter estimates obtained by 1000 bootstrap resamples were in accordance with the parameters of the model (data not shown). Parameter estimates of the basic model were all within 5.6% of the median bootstrap value. We concluded that the stability of the basic population pharmacokinetic model was adequate. The basic model was used in the development of the final population pharmacokinetic model.

Intermediate model

The graphical analysis of the plots of covariates versus individual pharmacokinetic parameters indicated a possible relationship between BSA, age, weight, gender, PS, bilirubin, AST, ALT and V1, between BSA, age, weight, gender, PS, creatinine, alkaline phosphatase, GGT, AST, ALT and V2 and between BSA, creatinine, age, weight, gender, PS, creatinine, AST, ALT and Vmax. Forward inclusion ($P < 0.005$) of these covariates in the basic model resulted in an intermediate multivariate model with the following significant covariates: V1: gender, weight, PS, BSA; V2: gender, BSA, weight; and Vmax: PS, BSA, weight.

Final population pharmacokinetic model

Stepwise backward elimination ($P < 0.001$) was used to obtain the final population pharmacokinetic model. Gender was significantly correlated with V1, BSA with V2, and a PS of 2 with Vmax. Figure 3 shows the relationships between the Bayesian estimates of V1, V2 and Vmax, and gender, BSA and PS calculated from the final model. Inclusion of these three covariates in the final population pharmacokinetic model resulted in a decrease in the objective function value of 51.6 when compared to the value of the basic model (Table 3). The final population pharmacokinetic model of Cremophor EL is defined in the Eqs. 5 to 7:

Table 2. Population parameters of the basic and final population pharmacokinetic model of Cremophor EL and the corresponding parameter estimates obtained by 1000 bootstrap resamplings (*BSA* body surface area, *IIV* interindividual variability, *Km* plasma concentration at half Vmax, *PS* performance status according to the World Health Organization, *Q12* intercompartmental clearance from the central to the first peripheral compartment, *Q13* intercompartmental clearance from the central to the second peripheral compartment, *RSE* relative standard error, *V1* volume of the central compartment, *V2* volume of the first peripheral compartment, *V3* volume of the second peripheral compartment, *Vmax* maximal elimination rate)

Parameter	Basic population PK model		Final population PK model		Parameter estimates (after 1000 bootstrap replicates)	
	Estimate	RSE (%)	Estimate	RSE (%)	Median	2.5–97.5 percentiles
V1 (l)	2.86	7	2.59	7	2.59	2.16–2.92
Gender			1.30	7	1.31	1.13–1.51
Q12 (l/h)	1.42	28	1.44	24	1.42	0.925–2.46
V2 (l)	1.75	9	1.81	9	1.81	1.49–2.13
BSA (m^2)			1.13	18	1.13	0.67–1.51
Q13 (l/h)	0.154	25	0.155	22	0.155	0.099–0.239
V3 (l)	1.60	8	1.61	7	1.61	1.36–1.97
Km (ml/l)	0.197	71	0.122	61	0.124	0.026–0.870
Vmax (ml/h)	0.214	11	0.193	9	0.196	0.151–0.265
PS 2			1.48	10	1.48	1.22–1.88
IIV on V1 (%)	30.8	20	24.7	22	24.2	19.8–30.5
IIV on V2 (%)	41.5	27	36.5	28	35.5	26.7–47.0
IIV on Vmax (%)	33.9	27	30.7	24	30.4	23.6–39.4
Residual error						
Additional (ml/l)	0.0985	32	0.0951	34	0.0943	0.0512–0.190
Proportional (%)	6.83	8	6.94	8	6.78	5.30–7.77

$$V1 = \left(2.59 * \left(1.30^{\mathrm{FLAG1}}\right)\right) \quad (5)$$

where FLAG1 = 1 in males, FLAG1 = 0 in females.

$$V2 = 1.81 - (1 + 1.13 * (BSA - 1.82)) \quad (6)$$

$$V\max = \left(0.193 * \left(1.48^{\mathrm{FLAG2}}\right)\right) \quad (7)$$

where FLAG2 = 1 when PS = 2, FLAG2 = 0 when PS = 0 or 1.

In the final model V1 was 30% higher in males, Vmax was 48% higher in patients with a PS of 2 compared to patients with a PS of 0 or 1, and V2 was higher in patients with a higher BSA.

The correlation between the interindividual variability of V1, V2 and Vmax was evaluated. The matrix plots showed no correlation between η_j^{V1}, η_j^{V2} and η_j^{Vmax} (plots not shown). The inclusion of the covariance between interindividual variability of V1 and V2, V2 and Vmax, V1 and Vmax (ΔOFV = –4.7) produced no significant decrease in the objective function in NONMEM. We concluded that there was no significant correlation, and therefore it was not included in the final model. The population pharmacokinetic parameters of the final model including the standard errors, interindividual variability, and the residual errors are summarized in Table 2. The interindividual variabilities decreased to 24.7% (V1), 36.5% (V2) and 30.7% (Vmax). The residual error was almost unchanged (additional error 0.095 ml/l, proportional error 6.94%). The relative standard error of the Km was decreased to 61% in the final model compared to 71% in the basic model.

The Cremophor EL concentrations obtained after the 3- or 24-h infusions were higher than the Km value during the whole observation period, whereas the concentrations obtained after the 96-h infusion were in the Km range. In order to explore the impact of the four patients receiving 96-h infusion on the Km value, we repeated the final analysis with these four patients excluded. This resulted in an increase of the Km value to 1.15 ml/l with a relative standard error of 71%. Consequently, the concentration-time data of the 96-h infusions substantially influenced the estimation of the Km value.

Plots indicating the goodness of fit of the final model are depicted in Fig. 4. Model- and Bayesian-predicted concentrations were symmetrically distributed around the line of unity (Fig. 4A, B). No trend was seen in the plot of individual weighted residuals (i.e. the weighted difference between the observed and the individually predicted concentrations) versus individually predicted concentrations (Fig. 4C). Moreover, no time-dependent trend was observed in the plot of the weighted residuals (the weighted difference between the observed and the predicted concentrations based on the parameter estimates for the typical individual) versus time (Fig. 4D).

The final model was fitted to the 1000 bootstrapped samples to evaluate its stability and performance. The values of all parameter estimates obtained by bootstrapping are summarized in Table 2. The median parameter estimates were all within 2.7% of the parameter estimates of the final model, indicating that the performance and stability of the final population pharmacokinetic model of Cremophor EL was adequate. However, the 97.5% percentile of the Km value (0.87) produced by the bootstrap procedure was considerably higher than the boundary of the 95% confidence interval produced by the final model (0.27). This difference was

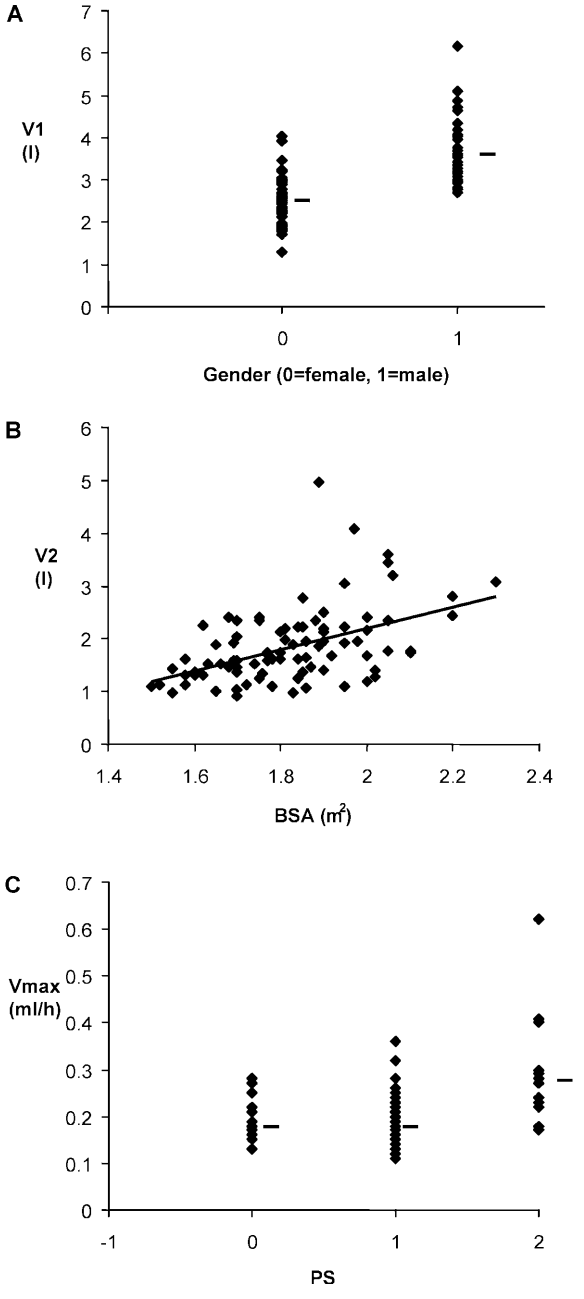

Fig. 3A–C. Significant relationships between individual pharmacokinetic parameters (Bayesian estimates) and covariates ($P < 0.0001$): between V1 and gender (**A**), between V2 and BSA (**B**), and between Vmax and PS (**C**)

probably caused by bootstrap datasets that did not contain patients receiving the 96-h infusions resulting in higher estimated Km values.

Discussion

Despite the extensive clinical use of Cremophor EL as a formulation vehicle for various hydrophobic drugs, reports of its pharmacokinetics are sparse [15, 17, 19, 23, 27]. It has recently been reported that Cremophor EL can influence the pharmacokinetic and toxicity profile of the drugs dissolved in it, e.g. paclitaxel [20, 24, 27, 30, 31]. The amount of Cremophor EL used in the formulation of hydrophobic drug varies from 5.5 ml/m^2 (propofol, diazepam and aplidine) to 12 ml/m^2 (paclitaxel) [31]. The purpose of this study was to develop a population pharmacokinetic model of Cremophor EL, as the solvent for paclitaxel, and to elucidate relationships between the pharmacokinetic parameters and patient characteristics, i.e. demographic factors and blood chemical variables.

Table 3. Differences in the objective function values between the final population pharmacokinetic model and the final model with one significant covariate eliminated (*BSA* body surface area, *PS* performance status according to the World Health Organization, *V1* volume of the central compartment, *V2* volume of the first peripheral compartment, *V3* volume of the second peripheral compartment, *Vmax* maximal elimination rate)

	Objective function	Difference in objective function	*P* value
Basic population model	–857.9		
Final population model	–909.5		
Eliminated covariate			
Gender on V1	–891.7	17.7	< 0.0001
BSA on V2	–894.0	15.4	< 0.0001
PS 2 on Vmax	–893.9	15.6	< 0.0001

Previous reports with respect to the pharmacokinetics of Cremophor EL are conflicting. Noncompartmental pharmacokinetic analyses have shown that the elimination of Cremophor EL can be linear as well as nonlinear with a disproportionate increase in the exposure at higher Cremophor EL doses [15, 19, 23, 27]. In these studies various assays for the determination of Cremophor EL in plasma were used that could have contributed to the differences in Cremophor EL concentrations. In one study the bioassay was based on the determination of the modulation of multidrug resistance (mdr) in vitro by inhibition of P-glycoprotein inhibition [19]. In this study, the Cremophor EL concentrations in plasma were lower than the plasma concentrations determined by two other assays based on the measurement of ricinoleic acid and the binding of Cremophor EL to Coomassie brilliant blue G-250 [19, 21, 22, 32]. Moreover, the bioassay based on mdr modulation has some disadvantages including the relatively large sample volume and its relatively poor sensitivity and precision [21].

Our final population pharmacokinetic model revealed that the plasma concentration-time data of Cremophor EL could be best fitted to a three-compartment model with Michaelis-Menten elimination after i.v. infusion as a solvent of paclitaxel in cancer patients. The saturated elimination could be due to capacity-limited Cremophor EL metabolism of the carboxylesterases within the systemic circulation [17, 31]. The estimated population value of the total volume of distribution (= V1 + V2 + V3) was low (6.0 l) implying that the volume of distribution in humans is not much larger than the volume of the central

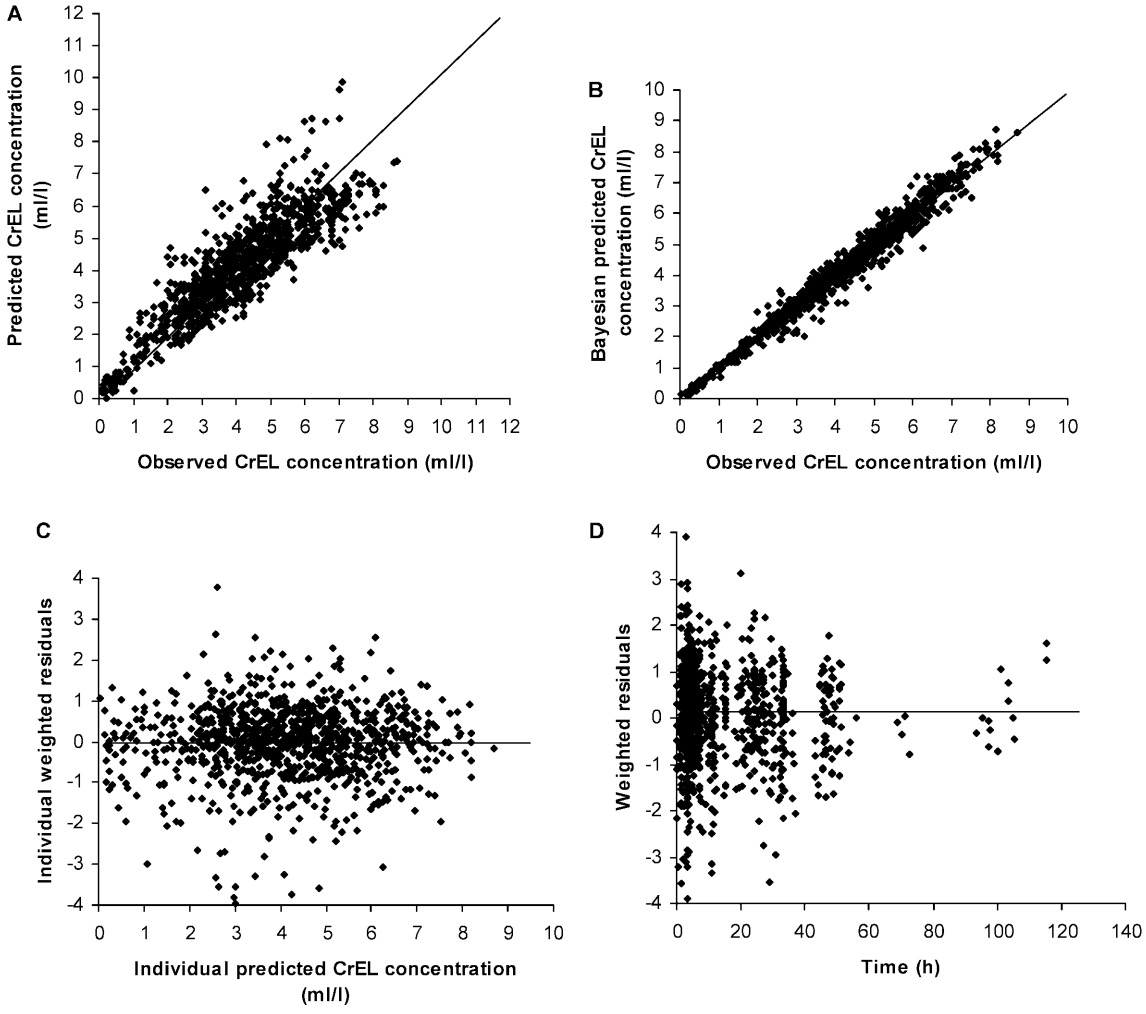

Fig. 4A, B. Goodness of fit plots of the observed concentrations versus the model-predicted concentrations (**A**) and Bayesian-predicted concentrations (**B**) as estimated by the final population pharmacokinetic model. **C** Plot of the individual weighted residuals (i.e. the weighted difference between the observed and the Bayesian predicted concentrations) versus the Bayesian predicted concentrations. **D** Plot of the weighted residuals (i.e. the weighted difference between observed and model-predicted concentrations) versus time. *Solid line* (**A**, **B**) line of identity

blood compartment. This is in accordance with the low volume of distribution found in studies in which a non-compartmental pharmacokinetic analysis of Cremophor EL was performed [15, 23]. This also implies that the distribution of Cremophor EL is limited to the peripheral tissues. Moreover, it can be hypothesized that V1 refers to the plasma compartment, and that V2 and V3 refer to the blood cells and micelles, respectively.

In our final population model, the interindividual variability in V1, V2 and Vmax could partially be explained by gender, BSA and PS, respectively. The volume of the central compartment was 31% higher in males than in females. The volume of the first peripheral compartment increased with BSA, and the Vmax was 48% higher in patients with a PS of 2 compared to patients with a PS of 0 or 1. The renal and hepatic elimination of Cremophor EL has been reported to be very low. In one patient 0.08% of the administered dose was excreted in urine after a 3-h i.v. infusion [6]. It has been reported that Cremophor EL is eliminated by serum carboxylesterases as ricinoleic acid [28, 31]. In a study of 27 patients performed at our institution, a higher Cremophor EL clearance was observed in patients with hepatic dysfunction than in patients with normal hepatic function after noncompartmental pharmacokinetic analysis [17]. In this population analysis, 21 of these patients were included. The relationships between the biochemical parameters, that indicate hepatic dysfunction, and the Vmax were not significant. We hypothesize that the higher Vmax in patients with a PS of 2 in our population analysis could be attributable to a higher serum esterase concentration in these patients. Higher serum esterase levels may be caused by hepatic dysfunction that results from liver metastasis that is more often present in patients with a PS of 2 compared to patients with a PS of 0 or 1.

The bootstrapping resampling method, that is considered to be a powerful internal validation technique, showed that the final population pharmacokinetic model was stable [26]. The median values of the parameter

estimates obtained by bootstrapping were in accordance with the parameter estimates of the final model. The distribution of all parameter estimates showed a narrow range (Table 2) except for the Km. This observation is in accordance with the high relative standard error (61%) of the Km value in the final population pharmacokinetic model implying that the population parameter estimate was not very accurate.

The 95% confidence interval of Km obtained by the bootstrap resampling was large compared to the confidence interval obtained with the final model. As indicated before, this may have resulted from the small number of patients receiving Cremophor EL in the 96-h infusion. This indicates that bootstrapping is of limited use when a small subset of patients has a large impact on the estimation of a pharmacokinetic parameter.

It is known that the pharmacokinetic behaviour of Cremophor EL can influence the pharmacokinetic and toxicity profile of paclitaxel and other dissolved drugs [20, 24, 27, 30]. Several suggested mechanisms for the nonlinear pharmacokinetics of paclitaxel have been rejected by van Zuylen et al. [30]. They reported that the observed decrease in hepatobiliary elimination of paclitaxel in the presence of Cremophor EL in rats is not caused by alterations in paclitaxel elimination by Cremophor EL but by micelle formation in plasma. Consequently, paclitaxel cannot reach the elimination sites [30]. They also excluded altered protein binding due to the formation of high-density lipoproteins induced by Cremophor EL because an in vitro study showed that paclitaxel accumulation in erythrocytes induced by Cremophor EL is also observed in the absence of any plasma proteins [24]. It has been reported that the micelle formation of Cremophor EL most likely affects the paclitaxel pharmacokinetics in plasma [13, 24, 27, 29, 30]. Consequently, the free paclitaxel fractions in plasma are lower at higher Cremophor EL concentrations in plasma [13, 24, 27, 29, 30].

In conclusion, we showed that the nonlinear pharmacokinetics of Cremophor EL after i.v. infusion can accurately be described by the developed population pharmacokinetic model. This population model of Cremophor EL could be used in the development of a pharmacokinetic/pharmacodynamic population model to further explore the relationships between the pharmacokinetics of Cremophor EL and its toxicity. Moreover, this population pharmacokinetic model could be used to further develop a detailed population pharmacokinetic model of paclitaxel after i.v. administration when it is dissolved in Cremophor EL.

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