Population pharmacokinetics of orally administered paclitaxel formulated in Cremophor EL

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Aim

The vehicle Cremophor EL (CrEL) has been shown to impair the absorption of paclitaxel by micellar entrapment of the drug in the gastrointestinal tract. The goal of this study was to develop a semimechanistic population pharmacokinetic model to study the influence of CrEL on the oral absorption of paclitaxel.

Method

Paclitaxel plasma-concentration time profiles were available from 55 patients (M:F, 17 : 38; total 67 courses; 797 samples), receiving paclitaxel orally once or twice daily (dose range 60–360 mg m⁻²) together with 12–15 mg kg⁻¹ cyclosporin A. A population pharmacokinetic model was developed using the nonlinear mixed effect modelling program NONMEM.

Results

After absorption, paclitaxel pharmacokinetics were best described using a two-compartment model with linear distribution from the central compartment into a peripheral compartment and first-order elimination. Paclitaxel in the gastrointestinal tract was modelled as free fraction or bound to CrEL, with only the free fraction available for absorption into the central compartment. The equilibrium between free and bound paclitaxel was influenced by the concentration of CrEL present in the gastrointestinal tract. The concentration of CrEL in the gastrointestinal tract decreased with time with a first order rate constant of 1.73 h⁻¹. The bioavailability of paclitaxel was independent of the dose and of CrEL. Estimated apparent paclitaxel clearance and volume of distribution were 127 l h⁻¹ and 409 l, respectively. Large interpatient variability was observed. Covariate analysis did not reveal significant relationships with any of the pharmacokinetic parameters.

Conclusion

A pharmacokinetic model was developed that described the pharmacokinetics of orally administered paclitaxel. CrEL strongly influenced paclitaxel absorption from the gastrointestinal tract resulting in time-dependent but no significant dose-dependent absorption over the examined dose range studied.

Introduction

Paclitaxel (Taxol) is a potent anticancer agent used in the treatment of various human malignancies [1, 2], and is regularly administered intravenously (i.v.).

Paclitaxel is poorly soluble in water and therefore its i.v. formulation contains the solubilizing agent Cremophor EL[®] (CrEL). This vehicle is responsible for causing severe hypersensitivity reactions [3] and for

the nonlinear pharmacokinetics of i.v. administered paclitaxel [4–7].

Administering paclitaxel orally is more convenient and acceptable for the patient. However, oral treatment with paclitaxel is not feasible because of its low bioavailability, for which there are several mechanisms. First, paclitaxel is a substrate with high affinity for the efflux protein P-glycoprotein (P-gp), which is highly expressed in the mucosa of the gastrointestinal tract, oriented towards the intestinal lumen [8]. Second, paclitaxel undergoes metabolism mediated by cytochrome P450 (CYP) enzymes to form 6 α -hydroxypaclitaxel, 3' ρ -hydroxypaclitaxel and 6 α ,3' ρ -dihydroxypaclitaxel, all of which are substantially less active than paclitaxel itself [9–12]. Two major CYP enzymes, namely CYP2C8 and CYP3A4, are involved in the hydroxylation of paclitaxel [13–15].

Cyclosporin A (CsA) is a potent inhibitor of both P-gp and CYP3A4 [16]. Co-administration of CsA with orally administered paclitaxel increases the bioavailability of the latter significantly [17–19]. To improve the systemic absorption of oral paclitaxel, CsA can therefore be administered before oral dosing of the drug. When paclitaxel is given by this route, the i.v. formulation containing CrEL is often diluted with water. No systemic uptake of CrEL takes place after oral administration [17, 18], thus it is unlikely that CrEL modifies the pharmacokinetics of systemically absorbed paclitaxel. However, CrEL appears to decrease the absorption of paclitaxel from the intestine, probably by encapsulating it in micelles in the gastrointestinal tract [20, 21].

Moreover, studies have shown that the area under the plasma concentration-time curve (AUC) of orally administered paclitaxel does not increase proportionally with increasing dose [22–24], which may be explained by the increasing amount of CrEL in the oral formulation.

To gain more detailed insight into the influence of CrEL on the oral absorption of paclitaxel, we developed a mechanism-based pharmacokinetic model for oral paclitaxel formulated in CrEL and administered in combination with CsA.

Patients and methods

Patient population

Plasma concentration-time data for oral paclitaxel were obtained during safety and pharmacokinetic studies using different treatment schedules (i.e. one or two oral administrations per day) and different doses of paclitaxel. Except for one, these studies have been published elsewhere [21, 23, 24]. In Table 1, the different treatment protocols are described. Data from patients who vomited within 1 h after paclitaxel administration have been excluded. Data from a total of 55 patients were available. Patient characteristics are summarized in Table 2. More details of the patients and the eligibility criteria for the studies have been described previously [21, 23, 24]. The six patients not studied previously, had advanced breast cancer and received high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin with peripheral blood progenitor cell transplantation. After

Table 1

Treatment protocols

Treatment schedule [reference]	Total patients (n)	Pharmacokinetic sampling scheme
Weekly 200 mg [not published]	6	Full curves of two administrations: $t = 0, 1/2, 1, 1 1/2, 2, 3, 4, 7, 10, 24$ h.*
One administration of 60 (13 $\times$), 120 (2 $\times$), 180 (6 $\times$), 210 (3 $\times$), 250 (3 $\times$), 300 (5 $\times$) or 360 (1 $\times$) mg/m ² [23]	33	Full curve of one administration: $t = 0, 1/4, 1/2, 3/4, 1, 1 1/4, 1 1/2, 2, 3, 4, 7, 10, 24, 30, 48$ h.*
Two administrations of 60 (1 $\times$), 90 (3 $\times$), 120 (3 $\times$) or 160 (3 $\times$) mg/m ² with an interval of 7 h [24]	10	Full curve of both administrations: $t = 0, 1/2, 1, 2, 3, 4, 6, 7, 7 1/2, 8, 9, 10, 11, 13, 24, 48$ h†
Two administrations of 60 mg m ⁻² with 1 week interval, one administration with and one without CrEL.	6	Full curves of two administrations: $t = 0, 1/4, 1/2, 3/4, 1, 1 1/4, 1 1/2, 2, 3, 4, 7, 10, 24, 30$ h.*
Three patients received 5 ml m ⁻² CrEL and three 15 ml m ⁻² [21]		

* $T = 0$ is time-point of ingestion of paclitaxel.

† $T = 0$ and 7 are time-points of ingestion of paclitaxel.

Table 2

Patient characteristics ($n = 55$, M:F 17 : 38) recorded before the start of treatment

Characteristic	Median	Range
Age (years)	53	26–69
Body weight (kg)	71	50–103
Body surface area (m^2)	1.81	1.52–2.22
Serum creatinine (μM)	82	61–127
Aspartate amino transferase ($U\ l^{-1}$)	20	6–57
Alanine amino transferase ($U\ l^{-1}$)	23	4–86
Alkaline phosphatase ($U\ l^{-1}$)	134	36–439
γ -glutamyl transferase ($U\ l^{-1}$)	98	10–873
Serum albumin ($g\ l^{-1}$)	44	29–54
Serum total bilirubin (μM)	7	4–21
Lactate dehydrogenase ($U\ l^{-1}$)	344	116–1129

recovery, these patients continued on oral paclitaxel treatment with CsA coadministration. All patients studied had normal cardiac, renal, hepatic, haematopoietic and pulmonary function.

All study protocols were approved by the Medical Ethics Committee of the Institute, and all patients gave written informed consent.

Drug administration

The i.v. formulation of paclitaxel (Paxene®; 6 mg ml^{-1} paclitaxel dissolved in CrEL and ethanol 1 : 1 w/v, Baker Norton Pharmaceuticals, Miami, FL, USA) was swallowed with 100 ml of tap water after an overnight fast. A standard breakfast was served 2 h after paclitaxel administration. A total of six patients received paclitaxel formulated in CrEL (5 ml m^{-2} or 15 ml m^{-2}), but also as a formulation in polysorbate [21]. Prior to the oral administration of paclitaxel, patients ingested CsA (Neoral®, Novartis, Basel, Switzerland) as a solution (also formulated in CrEL) or capsules. Paclitaxel was given 10 min after the oral solution of CsA or 30 min after the CsA capsules, at dose between 12–15 mg kg^{-1} . Since 10 mg kg^{-1} CsA has been defined as the minimal required dose in this regimen [23, 25], it was assumed that the extent of P-gp and CYP3A4 inhibition was the same at all doses. Pre-medication of the patients was comparable in all protocols [21, 23, 24].

Sampling and analysis

The times of blood sampling in the different protocols are given in Table 1. Whole blood (5 ml) was collected in heparinized tubes and centrifuged immediately for

5 min at 3000 g. Plasma was separated and stored at $-20\ ^\circ C$ until analysis. Paclitaxel concentrations in plasma were determined using a validated HPLC assay with solid-phase extraction [26]. The concentration range of the assay was 10–10 000 ng ml^{-1} . The accuracy and within-day precision were 96–100% and 1.2–7.4%, respectively.

Population pharmacokinetic analysis

Plasma concentration-time data for paclitaxel were analysed using the nonlinear mixed effect modelling software program NONMEM (version V, level 1.1, double precision) [27]. The first-order conditional estimate (FOCE) procedure with INTERACTION was used throughout.

Because of the large number of samples taken during the absorption process, our dataset was rich enough for accurate characterization of this process. A precise description of the absorption process may also be important because it largely influences the subsequent population pharmacokinetic parameters clearance (Cl) and volume of distribution (V) [28]. Since it is not possible to simultaneously estimate both bioavailability (F) and Cl, and F and V, values for Cl/F and V/F were determined.

Interindividual variability and interoccasion variability for different pharmacokinetic parameters were estimated using an exponential error model. Residual variability was estimated with a proportional error model.

Model development was guided by both graphical and statistical methods. The objective function value (OFV) as calculated by NONMEM, was used to assess the goodness-of-fit. The significance of any increase in the goodness-of-fit was tested using the likelihood ratio test. A difference in OFV of more than 10.83, corresponding to a significance level $P < 0.001$ was used for discriminating between two hierarchical models differing in one parameter. Standard errors for all parameters were calculated using the covariance option in the NONMEM program. The goodness-of-fit plots were examined using the program Xpose (Xpose, Version 2.0, Uppsala University, Sweden) as implemented in the S-Plus statistical package (version 2000, Mathsoft, Cambridge, MA) [29].

Covariate analysis

A covariate analysis was performed with the base model to establish possible relationships between patient characteristics and the pharmacokinetics of paclitaxel. The covariates tested are depicted in Table 2. Variables were

centered to their median values. For example, the relationship between Cl and body weight (WGT) was modelled as:

$$Cl_{pop} = \theta_1 * (WGT/71)^{\theta_2}$$

where Cl_{pop} is the population value for clearance, θ_1 is the value for Cl of a patient with the median WGT (71 kg), and θ_2 is the exponential decrease or increase in Cl. A covariate was considered potentially significant when the decrease in OFV was >6.6 ($P < 0.01$) compared with that in the model without the covariate. All potentially significant covariates were introduced into an intermediate model, and significant covariates were selected using a stepwise backward elimination procedure. A covariate was considered significant when elimination of this covariate resulted in an increase in OFV of > 7.8 ($P < 0.005$).

Results

After oral administration of a single paclitaxel dose, the time of peak concentration, T_{max} , was between 1 and 4 h. A typical concentration-time profile is shown in Figure 1.

Model development started using a simple linear pharmacokinetic model. Oral administration was considered as a bolus injection into compartment 1, from which paclitaxel was absorbed into the central compartment (compartment 2). After absorption, paclitaxel kinetics were described by a two-compartment model with linear distribution to a peripheral compartment (compartment 3) and linear elimination (Figure 2). One- or three-compartment models did not describe the data better.

Analysing the absorption process during the first 5 h, it was observed that the simple model over-estimated the rate of paclitaxel absorption in the first 2 h, but underestimated it from then on (Figure 3A). It was hypothesized that CrEL prevented paclitaxel absorption due to encapsulation in CrEL micelles in the first hours after administration. Owing to the breakdown, elimination and distribution of CrEL micelles in the gastrointestinal tract, the concentration of CrEL will decrease and the amount of paclitaxel available for absorption will increase with time. This was subsequently modelled mechanistically by the introduction of a CrEL compartment and a second paclitaxel depot compartment, the latter representing the fraction of drug in the gastrointestinal tract encapsulated in CrEL micelles (Figure 2). In this model, the paclitaxel dose is administered into compartment 1 and the amount of CrEL to compartment 4. The amount of CrEL in the latter compartment influences the equilibrium (k_{eq}) between unbound and bound paclitaxel in compartments 1 and 5, respectively, which is modelled as an extremely rapid process. The amount of CrEL decreases with time with an estimated first-order rate constant k_{crem} . Therefore, more unbound paclitaxel becomes available for absorption in the central compartment with time. Modelling the absorption process in this manner significantly improved description of the data (Figure 3(B)). Moreover, a decrease in the objective function of 533 points was observed.

It was indeed observed that a higher paclitaxel dose did not result in a proportionally higher AUC (Figure 4). However, if there was dose-dependent absorption from the gastrointestinal tract, estimated

Figure 1

A typical individual plasma concentration-time curve for paclitaxel after once daily oral dosing of 60 mg m⁻² (absolute dose 103 mg) in combination with cyclosporin A (experimental data are presented)

clearance (or volume of distribution) would increase with increasing paclitaxel dose, if this process was not accounted for. However, this was not observed (Figure 5). Nevertheless, several attempts were undertaken to model the dose-dependent bioavailability of paclitaxel. Since it was suggested that the bioavailability of paclitaxel decreases with increasing amounts of administered CrEL due to encapsulation of paclitaxel in CrEL, we also attempted to model decreasing paclitaxel bioavailability with increasing CrEL dose using the equation:

$$F = 1 - \text{DoseCrEL} * \theta_1$$

$$\text{or } F = 1 - (\text{DoseCrEL}/(\text{DoseCrEL} + \theta_1))$$

where F is the bioavailability and θ_1 is an estimate constant.

Since paclitaxel was administered as a solution containing 6 mg drug per ml CrEL/ethanol (1 : 1 w/v), increasing doses of paclitaxel are accompanied by a proportional increase in the amount of CrEL in the formulation, with concomitant lower bioavailability. However, these models did not result in a better description of the data, and θ_1 could not be estimated. Since micelles incorporating paclitaxel are only formed when the concentrations of CrEL are higher than the critical micellar concentration, similar models with a threshold

CrEL concentration were tested, but did not improve the fit.

Several other attempts were made to model the dose-dependent bioavailability of paclitaxel, incorporating: (1) elimination of bound paclitaxel from the gastrointestinal tract and (2) no drug absorption into the central compartment ($k_{\text{abs}} = 0$) after a certain (estimated) threshold period. However, no improvement of fit to the data was obtained, and it was concluded that dose-dependent bioavailability could not adequately describe our data.

The final model as depicted in Figure 2 best fitted the data. A model incorporating non-linear distribution and elimination from the central compartment was tested, but did not describe the data better. Covariant analysis did not result in significant relationships with any pharmacokinetic parameter, final estimates of which are summarized in Table 3. Large interpatient variability in paclitaxel pharmacokinetics was observed. Goodness-of-fit plots for the final population pharmacokinetic model are shown in Figure 6.

Discussion

There is increasing interest in the oral administration of cytotoxic agents, which is convenient for the patient and can improve patients' quality of life. Moreover, for paclitaxel, the oral route circumvents systemic exposure

Figure 2

Final population pharmacokinetic model for orally administered paclitaxel formulated in Cremophor EL and coadministered with cyclosporin A

Figure 3

Measured concentrations minus individual predicted paclitaxel concentrations (IWRES) in the absorption phase vs. time, (A) not accounting for; (B) accounting for the influence of Cremophor EL on the absorption rate using the final model

Figure 4

The relationship between dose and AUC after orally administered paclitaxel

Figure 5

The relationship between dose and oral clearance after orally administered paclitaxel

Table 3

Population pharmacokinetic parameters for paclitaxel

Parameter	Estimate (RSE percentage)	% IIV (RSE percentage)	% IOV (RSE percentage)
Clearance (l h^{-1})	127 (9.61)		31.8 (38.3)
Volume of distribution (l)	409 (16.8)		
Absorption rate constant k_{abs} (h^{-1})	0.62 (37.7)	61.1 (33.5)	
Distribution rate constant k_{23} (h^{-1})	0.241 (17.5)	31.3 (66.5)	
Distribution rate constant k_{32} (h^{-1})	0.0946 (12.9)		
Elimination rate constant Cremophor	1.73 (12.4)		
EL k_{crem} (h^{-1})			
Equilibrium rate constant free and bound paclitaxel $k_{\text{eq}} = k_{15}/k_{51}$ (h^{-1})	0.334 (43.4)		
Bioavailability	1 FIX	55.0 (22.5)	
Residual proportional error (%)	45.1 (10.2)

Figure 6

Goodness of fit plots for the final population pharmacokinetic model for paclitaxel. (A) Observed concentrations vs. model predictions; (B) Observed concentrations vs. the individual Bayesian predictions

to CrEL, which can induce hypersensitivity reactions [3]. However, a complicating factor in oral treatment with paclitaxel is its formulation in CrEL, which appears to influence the absorption of paclitaxel from the gastrointestinal tract. We developed a semimechanistic population pharmacokinetic model that accurately describes the influence of CrEL on the absorption of orally administered paclitaxel.

We described a time-dependent influence of CrEL on the absorption of paclitaxel. This observation may be explained by micellar entrapment of paclitaxel by CrEL in the gastrointestinal tract, thereby preventing its absorption [20, 21]. Owing to the distribution of CrEL micelles over the gastrointestinal tract wall, and the degradation and elimination of micelles with time, paclitaxel may be liberated and then absorbed in the circulation. This may be explained by (1) dilution of micelles in the gastrointestinal tract by increasing the contact surface area and to concentrations lower than the critical micellar concentration (which appeared to be 0.33% w/v in the small intestine of mice [20]) or (2) degradation of CrEL, since it has been shown that only 32% of administered CrEL is recovered in faeces [30]. The amount of CrEL in the hypothetical compartment in our semimechanistic model approached zero within approximately 5 h after administration.

Several authors have suggested that encapsulation of paclitaxel in CrEL micelles may also be responsible for the limited availability of paclitaxel for absorption [20, 21]. In a preclinical study with P-gp knock-out mice receiving 10 mg kg^{-1} paclitaxel, a 7-fold increase in CrEL resulted in an increase in faecal unchanged drug excretion from 7 to 36% and a decrease in the plasma AUC of paclitaxel of 40% [20]. From this study it was

concluded that CrEL prevents efficient uptake of paclitaxel from the gut. Results obtained comparing the relative bioavailability of paclitaxel with and without CrEL in six patients, showed a significant difference in the AUC of the drug between the two formulations [21]. However, increasing the amount of CrEL by 3-fold did not result in a significantly different AUC [21]. Three studies of oral paclitaxel formulated in CrEL have shown that the AUC of the drug did not increase proportionally with increasing dose [22–24]. Since a higher dose of paclitaxel contains more CrEL and therefore increased micelle formation occurs, a larger fraction of the drug may remain encapsulated, and will be eliminated unchanged by the faeces. Another hypothesis for the possible nonlinear absorption of paclitaxel is the poor aqueous solubility of the drug and its limited dissolution in the gastrointestinal tract [23, 24].

In our study we did not observe dose-dependent bioavailability of paclitaxel, for which there may be two explanations. First, it is possible that the positive results from previous studies [22–24] may not be significant due to the small number of patients ($n = 3$) studied at each dose level or to the accuracy with which the AUCs were calculated (which is illustrated by the large differences in pharmacokinetic parameters obtained using both noncompartmental and compartmental methods [22]). Second, dose-dependency was not detected due to the high interpatient variability observed in our concentration-time data (about 6-fold). High interindividual variation in paclitaxel pharmacokinetics has also been found by others [22–24].

In the absorption of paclitaxel from the intestine, two processes contribute significantly to this pronounced interindividual variability. These are (1) the activity of intestinal and liver cytochrome P450 enzymes, which varies between individuals due to induction, inhibition, genetic polymorphism or disease state, and (2) the activity of the multidrug efflux pump P-gp and its inhibition. Interactions with food or other substrates for CYP3A and P-gp, may also play a role in the absorption of orally administered paclitaxel. Moreover, vomiting and diarrhoea can cause unpredictable changes in absorption. Substantial pharmacokinetic variability may cause differing efficacy and toxicity in patients since paclitaxel, like most other cytotoxic drugs, has a narrow therapeutic window.

Population pharmacokinetic models for i.v. administered paclitaxel have been developed by different groups [31–34]. The observed nonlinear distribution of i.v. paclitaxel has been ascribed to the presence of CrEL in the circulation. Circulating CrEL micelles entrap paclitaxel resulting in a non-linear increase in

plasma paclitaxel concentrations and amounts of CrEL, since distribution to peripheral tissues is limited [4–7]. This nonlinear pharmacokinetics has been described by two-compartment models with saturable distribution and saturable elimination from the central compartment [31–33]. A more mechanistic model was developed using total and unbound plasma concentrations as well as blood concentrations [34]. Studies in mice have demonstrated that in the absence of CrEL in the circulation, both the distribution and elimination of paclitaxel are linear processes [6, 35]. However, saturable binding of paclitaxel to platelets has been described *in vitro* [36]. Moreover, the pharmacokinetics of orally administered paclitaxel in study medication not containing CrEL have also been described with saturable distribution to the peripheral compartment [37, 38]. In our study, saturation of the transfer of drug to distribution to the peripheral compartment could not be modelled. Apparent Cl and V obtained in our study were both higher than those obtained in the two studies in which oral paclitaxel was administered without CrEL [37, 38] (Cl 127 vs. 85 and 89 l h⁻¹; V 409 vs. 170 and 190 l). Owing to the influence of CrEL on the pharmacokinetics of i.v. paclitaxel, these data cannot be validly compared with those obtained after oral administration. Therefore, the therapeutic target exposures proposed for i.v. paclitaxel [33, 39–41] are not applicable to oral dosing, since only the fraction of free paclitaxel is available for distribution to the tumour.

In conclusion, the present pharmacokinetic model describes the nonlinear absorption of orally administered paclitaxel in the presence of CrEL. To increase the usefulness of the oral route for paclitaxel, the development of a non-CrEL based formulation is necessary, since CrEL significantly influences the absorption of paclitaxel from the intestine.

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