Population Pharmacokinetic Model for Cremophor EL

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BACKGROUND:

The pharmacologically active micelle-forming vehicle Cremophor EL (CrEL) has been shown to affect the pharmacokinetics of paclitaxel after Taxol® administrations. CrEL micelle entrapment of paclitaxel within the plasma has been suggested as the primary underlying mechanism. The pharmacokinetics of CrEL has been shown to be schedule dependent and capacity limited elimination within the plasma has been suggested (Model I Table I)[1]. The aim of this study was to develop a population pharmacokinetic model that could describe and predict CrEL plasma concentrations after Taxol® administration and to investigate the critical aggregation concentration (CAC) in human plasma *in vitro*.

PATIENTS AND METHODS:

The learning data set included 147 CrEL concentration time profiles obtained from 116 patients participating in pharmacokinetic studies of paclitaxel after 1, 3 or 24 hour infusions of Taxol®. CrEL concentrations were measured with a Coomassie Brilliant Blue G-250 colorimetric dye bidning assay as previously described[2]. The population pharmacokinetic analysis was performed using NONMEM[3]. A validation data set with 45 individuals receiving 3-hour infusions of Taxol® was used to investigate the predictive performance of the model. The apparent CAC was estimated by observing changes in plasma surface tension determined with a droplet weight method[4], 1, 3 and 24 hour after addition of CrEL/EtOH/NaCl or Taxol® (infusion preparation).

Table I Parameter estimates

Parameter	*MODEL I*[1]	*MODEL II*	*RSE (%)*	*MODEL III*	*RSE (%)*
V1 (L)	2.86	4.54	4.2	4.56[a]	4.3
BSA on V1				0.748[a]	16
Q12 (L/h)	1.42	1.17	13	1.13	13
$V2_{1\ \&\ 3\ hour\ infusion}$ (L)	1.75	1.32	13	1.39[b]	12
BSA on $V2_{1\ \&\ 3\ hour\ infusion}$				1.64[b]	10
$V2_{24\ hour\ infusion}$	1.75	16.3	38	16.7	33
Q13 (L/h)	0.154	0.479	5.9	0.487	6.1
V3 (L)	1.60	3.53	7.7	3.55	6.5
Km (mL/L)	0.197	2.57	43	2.73	26
Vmax (mL/h)	0.214	0.64	29	0.682[c]	17
BSA on Vmax				0.921[c]	27
$CL_{24\text{-}hour\ infusion}$		0.12	24	0.109	19
IIV_{V1} (%)	30.8	39	28[d]	33	37[d]
IIV_{V2} (%)	41.5	110	20[d]	97	22[d]
IIV_{Vmax} (%)	33.9	42	21[d]	37	24[d]
Residual error:					
Additive (mL/L)	0.0985	0.148	26	0.151	28
Proportional (%)	6.83	8.67	19	8.64	22

V1, V2 and V3, volumes of distribution of the central and peripheral compartments; Q12 and Q13, intercompartmental clearances; Km, plasma concentration at half maximal elimination rate; Vmax, maximal elimination rate; CL, clearance; BSA, body surface area; IIV, interindividual variability; [a] V1 = 4.56* (1+0.748*(BSA-1.73)); [b] V2 = 1.39*(1+1.64*(BSA-1.73)); [c] Vmax = 0.682*(1+0.921*(BSA-1.73)); [d] RSE is related to the corresponding variance term [1] van den Bongaard et al. 2002

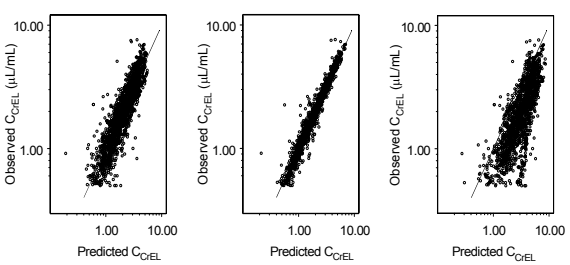

Figure 1. Observed Cremophor EL concentrations versus predictions based on; population parameter estimates, MODEL III, individual covariate and dose information (left panel) and individual predictions from Empirical Bayes estimates based on (MODEL III), individual covariates and measured concentrations (middle panel), population parameter estimates, (MODEL I) and individual dose information (right panel).

REFERENCES:

[1] van den Bongard, H. J., R. A. Mathot, O. van Tellingen, J. H. Schellens & J. H. Beijnen: A population analysis of the pharmacokinetics of Cremophor EL using nonlinear mixed-effect modelling. *Cancer Chemother Pharmacol* 2002, **50,** 16-24

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[3]Beal, S. L. & L. B. Sheiner: NONMEM users guides. GloboMax, Inc., Hanover Maryland, 1989-1998.

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RESULTS:

A three-compartment model with capacity limited elimination with an additional linear elimination pathway as well as a separate volume of distribution for the 24-hour infusion schedule were required to describe all data (Figure 1). Body surface area was statistically significant P<0.001 as covariate on maximal elimination rate, volume of distribution of the central compartment and one of the peripheral compartments. Parameter estimates with relative standard error are presented in Table I. The population model could adequately describe the concentrations of the validation data set where the prediction errors were similar as for the learning data set (Figure 2). The previously published population pharmacokinetic model for CrEL based on a different assay and different dosing schedules (3, 24 and 96 hour infusion)[1] could not describe our data (Figure 1(right panel) and Figure 2). The apparent CAC in plasma was 0.04 % (Figure 3), which corresponds to 0.39 µL/mL.

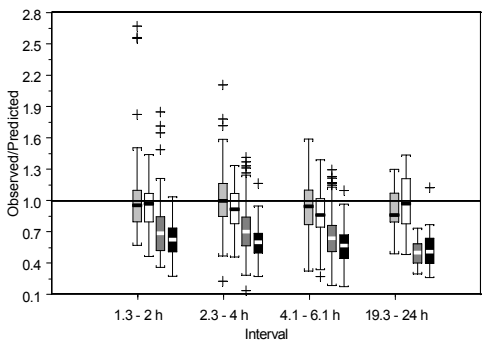

Figure 2. Prediction errors (observed/predicted concentrations of Cremophor EL) for the 3-hour infusion data within the four time intervals around the scheduled sparse sampling points (1.5, 3, 5 and 21 h) of the validation data set are shown. The boxes represent 25th and 75th percentiles, the median (line within the box), whiskers 1.5*(inter-quartile range) and outliers (+) of prediction errors from MODEL III, learning data set (grey box, black line), MODEL III, validation data set (white box, black line), MODEL I, learning data set (grey box, white line) and for reference the prediction error from MODEL I, validation data set (black box, white line) is included.

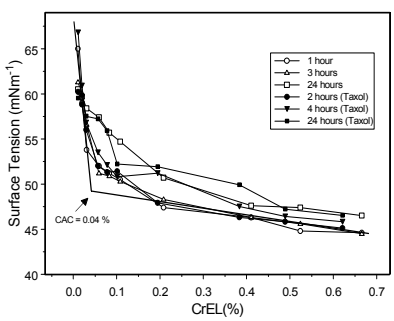

Figure 3. Surface tension measurements in spiked human plasma, 1-24 hours after adding CrEL/EtOH/NaCl (empty symbols) and Taxol® infusion preparation (filled symbols). CrEL concentrations are shown in % (w/w). Critical aggregation concentration (CAC) is based on series ≤ 3 hours after administration.

CONCLUSIONS:

The developed population model for CrEL could be used to predict and describe CrEL concentrations after Taxol® administration, which could be most useful when no CrEL concentration data is available and the population pharmacokinetic models for paclitaxel including CrEL concentrations are needed. The apparent CAC of CrEL in plasma *in vitro* is within the range of concentrations obtained after Taxol® infusions *in vivo*. This supports the theory of CrEL being the major cause of the non-linear pharmacokinetics of paclitaxel in plasma, either by micelle entrapment or by providing a preferable environment in larger lipophilic aggregates.