Pharmacokinetics of Paclitaxel and its Metabolites using a Mechanism-Based Model

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− Significant correlation of mdr-1 SNP to clearance of a paclitaxel metabolite *in vivo* when using Hill-equation-like kinetics to describe Cremophor EL binding

Objectives: The influence of the genotypes of the metabolizing enzymes, CYP2C8 and CYP3A4, and the transporter protein mdr-1/ABCB1 on the clearance of paclitaxel are still not fully established. To further investigate the impact of these enzymes on the metabolic pattern of paclitaxel in vivo this study aimed to expand a previously developed mechanism-based model for population pharmacokinetics of paclitaxel (Taxol), where the solvent Cremophor EL explains the non-linear disposition [1], to also include the kinetics of its primary metabolites; 6α-hydroxypaclitaxel (6α) and p-3'-hydroxypaclitaxel (p3), and its secondary metabolite; 6α-, p-3'-dihydroxypaclitaxel (6α-p3), which is formed by further oxidization of the primary metabolites (Figure 1).

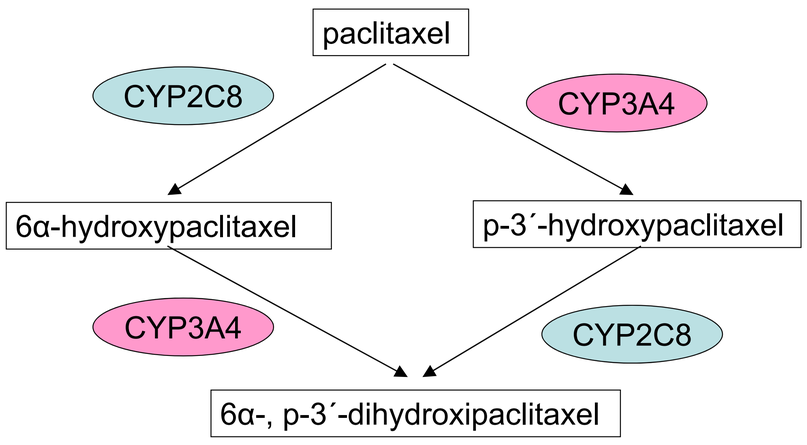

Figure 1. Metabolism of paclitaxel

Methods: 33 women diagnosed with gynaecological cancer were treated with paclitaxel in combination with carboplatin during a 3-h infusion at a dose of 175 mg/m^2 (n=30) or 135 mg/m^2 (n=3). Genotypes were determined for CYP2C8, CYP3A4 and mdr-1 variants along with CYP3A4 activity. Population pharmacokinetic analysis of plasma samples was performed using NONMEM VI. The PRIOR subroutine with prior information from literature was used to support lack of data for unbound concentrations of paclitaxel [1] and concentrations of Cremophor EL. Fixed parameter estimates were used for the Cremophor EL model [2]. For parameter estimates not supported by priors, the standard errors provided by NONMEM were complemented by log-likelihood profiling.The predictive performance of the final model was evaluated using visual predictive checks based on 1000 simulations (Figure 2).

Table 1. Parameter estimates of the paclitaxel metabolite base model

Parameter	Estimate	RSE (%)	LLP 95% CI	
			Lower	Upper
$CL_{6\alpha}/fm_{pac}$ (L/h)	2830	26	1850	4750
$V_{6\alpha}/fm_{pac}$ (L)	1390	24	945	2230
$B_{CrEL,6\alpha}$	43.0	40	24.4	99
$B_{add,6\alpha}$ (µmol/L)	0.000754	12	0.000588	0.000947
$\varepsilon_{1,\,6\alpha}$ (%)	0.254	5.6	0.229	0.284
$\varepsilon_{2,\,6\alpha,\,i=1}$ (µmol/L)	0.00447	30	0.00250	0.00772
$IIV_{CL6\alpha/fmpac}$ (CV%)	0.366	36[a]	0.251	0.538
CL_{p3}/fm_{pac} (L/h)	1470	16	1090	2020
V_{p3}/fm_{pac} (L/h)	1140	13	883	1490
$B_{CrEL,p3}$	8.60	32	5.24	16.1
$B_{add,p3}$ (µmol/L)	0.00124	10	0.00103	0.00149
$\varepsilon_{1,\,p3}$ (%)	0.377	4.8	0.345	0.416
$IIV_{fp3/fmpac}$ (CV%)	0.728	29[a]	0.527	1.08
$CrEL_{50}$ (mL/L)	4.48	18	3.55	6.21
$Hill_{CrEL}$	2.71	13	2.20	3.39
$IIV_{HillCrEL}$ (CV%)	0.401	38[a]	0.268	0.589
$CL_{6\alpha\text{-}p3}/fm_{met}$ (L/h)	831	15	606	1140
$V_{6\alpha\text{-}p3}/fm_{met}$ (L)	167	23	97.1	246
$\varepsilon_{1,\,6\alpha\text{-}p3}$ (%)	0.498	8.4	0.426	0.593
$\varepsilon_{2,\,6\alpha\text{-}p3}$ (µmol/L)	0.00197	22	0.00134	0.00315
$IIV_{CL6\alpha\text{-}p3/fmmet}$ (CV%)	0.607	39[a]	0.408	1.04

[a] RSE is related to the corresponding variance term

$$[6\alpha]_t = [6\alpha]_u + \frac{B_{CrEL,6\alpha} * [CrEL]^{Hill_{CrEL}}}{(CrEL_{50})^{Hill_{CrEL}} + [CrEL]^{Hill_{CrEL}}} * [6\alpha]_u + B_{add,6\alpha} * [CrEL]$$

Equation 1.

Results: Model building was based on 1156 samples; 345 from paclitaxel, 332 from 6α, 336 from p3 and 143 from 6α-p3. Parameters for paclitaxel were close to prior values (73-129%). Estimated unbound metabolite concentrations were best fitted using a one compartment model. Total 6α and p3 concentrations were both found to be dependent on Cremophor EL concentrations, and were best fitted using a Hill equation with an additive Cremophor EL component (Equation 1). No association between total 6α-p3 and Cremophor EL was found. $CL_{6\alpha}/fm_{pac}$ was significantly bidirectional correlated with the mdr-1 tri allele G2677T/A . Individuals with SNP variant G/A (n = 3) or G/G (n= 5) (lumped) showed a 30% increase while individuals with variant T/T (n = 8) showed a 27% decrease in $CL_{6\alpha}/fm_{pac}$ relative the reference group G/T (n = 17) ($p < 0.05$). However, the 95% and 90% CIs (but not the 80% CI) of the estimated differences included 0.

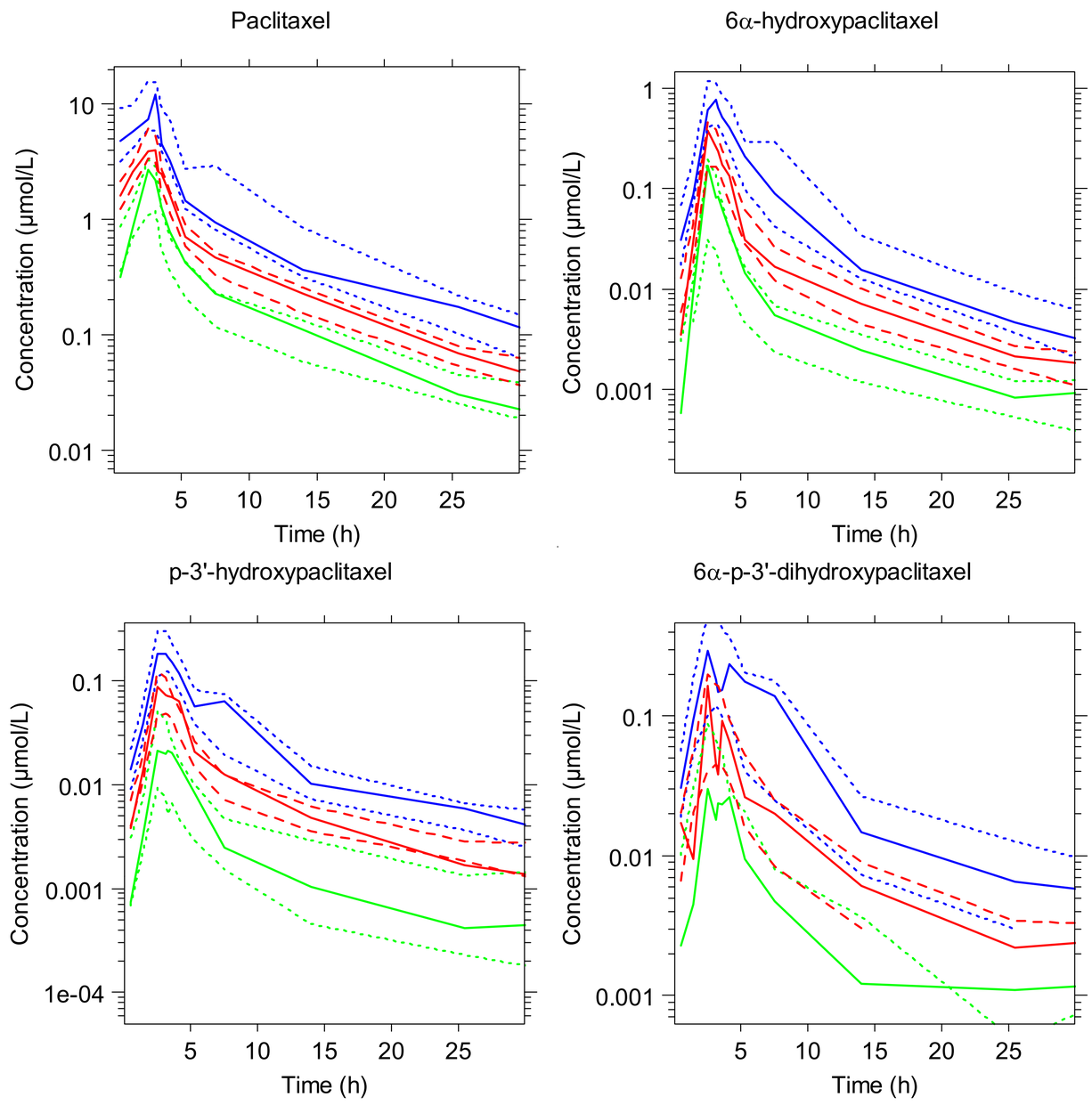

Figure 2. Visual predictive checks based on 1000 simulations. 95%CI of 5th green), 50th (red) and 95th (blue) percentiles of simulated data. Solid lines = observations, dashed and dotted lines = simulations.

Conclusions: The mdr-1 tri allele G2677T/A may affect clearance of the paclitaxel metabolite 6α-hydroxypaclitaxel. Paclitaxel primary metabolite kinetics seems to be highly influenced by Cremophor EL concentrations.

[1] Henningsson, A., Karlsson, M.O., Gianni, L., Vigano, L., Sparrebom, A., 2001. Mechanism-based pharmacokinetic model for paclitaxel. J. Clin. Oncol. 19, 4065–4073.
[2] Henningsson, A., Sparrebom, A., Loos, W.J., Verweij, J., Silvander, M., Karlsson, M.O., 2005. Population pharmacokinetic model for Cremophor EL. PAGE 14, 770, Abstract.

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