Development of a PBPK model for docetaxel as a CYP3A substrate and accounting for binding to multiple plasma proteins

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Background

Docetaxel is an anticancer agent commonly used in the treatment of solid tumors. There is high interindividual variability in the pharmacokinetics of docetaxel that is related to both toxicity and efficacy. Plasma protein levels, most notably of α_1-acid glycoprotein (AAG) which shows high variability in cancer patients, affect docetaxel clearance and contribute to the pharmacokinetic variability [1]. In addition docetaxel is cleared through CYP3A4, biliary and renal elimination pathways, thus has interaction potential as a victim when used in combination with CYP3A4 inhibitors.

We aimed to develop a PBPK model for docetaxel as a CYP3A substrate and incorporating fraction unbound in plasma (fu) predicted from binding to multiple plasma proteins.

Methods

A PBPK model for docetaxel in cancer patients was developed in Simcyp V17 Release 1 using the built in Cancer population model.

Elimination of docetaxel was characterized using a reverse translation approach whereby CL_{int} per mg protein was derived from IV clearance and the relative contributions of CYP3A4, renal and biliary clearance pathways to systemic clearance were apportioned using *in vitro* and *in vivo* data (Table 1) [1-3].

The fu was predicted from *in vitro* binding to AAG, albumin and lipoprotein [4] (Table1) and plasma AAG and albumin concentrations.

In vitro studies have suggested docetaxel is a substrate for OATP1B3, OATP1B1 and P-gp, but clinical studies have not indicated a significant impact of activity on these transporters on the clinical PK of docetaxel administered by IV infusion. Thus, they were not incorporated into the model.

Simulations were performed to predict the interaction with ketoconazole. The simulated study design, age of subjects and proportion of females were matched to the clinical study design.

Table 1. Table of input values for docetaxel.

Parameter	Value	Method/Reference
Molecular weight (g/mol)	807.89	
log P	2.8	
Compound type	Neutral	
B/P	0.69	
HSA K_D (µM)	137	[4]
AAG K_D (µM)	6.9	[4]
% Bound to lipoprotein (CV)	40 (15%)	[4]
Distribution Model	Minimal PBPK Model	
V_{SS} (L/kg)	1.84	Predicted - Method 2 [5]
k_{in} (1/h) / k_{out} (1/h)	2.71/0.04	Estimated from [6]
V_{SAC} (L/kg)	1.35	
CL_{IV} (L/h)	36.7	[1]
CYP3A4 CL_{int} (µL/min/pmol)	3.05	[2]
CYP3A5 CL_{int} (µL/min/pmol)	0.35	[2]
CL_{int} (HLM) (µL/min/mg protein)	46.8	[2]
CL_{int} (Bile) (µL/min/10^6 cells)	15.6	[3]
CL_R (L/h)	2.45	[7]

Results

The plasma concentration profile of docetaxel following a single IV dose was adequately captured by the PBPK model (Figure 1).

The median predicted contribution of CYP3A to the clearance of docetaxel in cancer patients was 77.6%. Biliary clearance (8.1%), renal clearance (5.4%) and additional HLM clearance (8.4%) also contributing to the systemic clearance of docetaxel. Simulated and observed docetaxel C_{max} and AUC ratios are in reasonable agreement for a range of ketoconazole doses (Table 2).

The predicted fu for cancer patients was 0.063 ± 0.012 (mean ± SD) compared to the reported mean fu of 0.058-0.066 measured for cancer patients [8,9] (Figure 2).

Results (Cont'd)

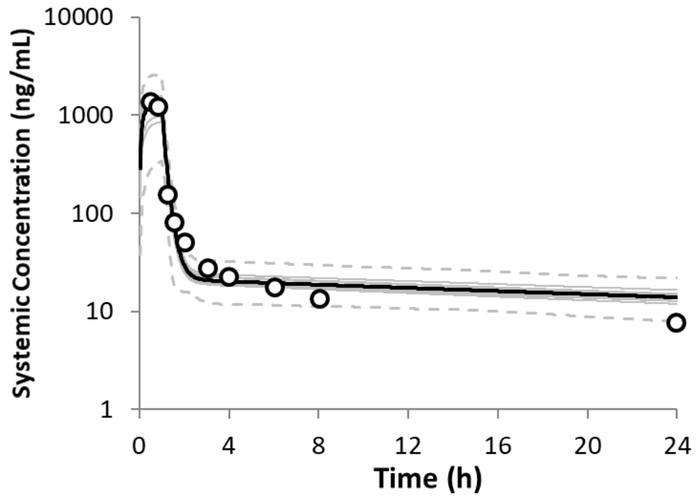


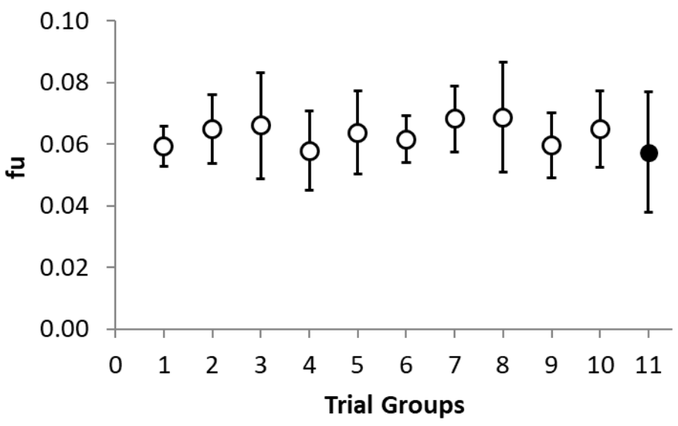
Figure 1. Mean plasma concentration-time profile of docetaxel after an IV dose of 50 mg/m² administered by 1 hour infusion.
Grey lines represent the predictions from individual trials (10 trials 15 individuals). Dashed lines represent the 5th and 95th percentile of the total virtual population. Observed values (○) are from [10].

Table 2. Observed and predicted C_{max} and AUC ratios for docetaxel in the presence of ketoconazole.

Observed values show reported #population mean or $population geometric mean (90% confidence interval). Predicted values show #population mean (trial range for 10 simulated trials) or $population geometric mean (trial range for 10 simulated trials).

	Observed		Predicted			
Ketoconazole dose	Dose normalized C_{max} ratio	Dose normalized AUC ratio	C_{max} ratio	Predicted/ observed	AUC ratio	Predicted/ observed
200 mg od for 3 days [9]	1.27#	2.19#	1.40 (1.22-1.54)#	1.10	1.57 (1.32-1.73)#	0.72
400 mg tid; 7 doses [11]	1.02#	2.08#	1.46 (1.24-1.65)#	1.43	1.79 (1.47-2.06)#	0.86
200 mg tid [12]	-	1.68 (1.34-2.10)$	1.39 (1.32-1.44)$	-	1.90 (1.82-1.95)$	1.13
200 mg am, 200 mg pm, 400 mg evening [12]	-	1.60 (1.26-2.04)$	1.41 (1.26-1.58)$	-	2.07 (1.84-2.34)$	1.29
400 mg tid [12]	-	2.62 (1.92-3.52)$	1.36 (1.22-1.54)$	-	2.00 (1.78-2.28)$	0.76

Figure 2. Simulated (○) and observed (●) mean values of docetaxel fu (± SD).
Observed data were obtained from [9]. Virtual individuals (n=7 individuals per trial; 36-59 years old, 43% females) received an IV infusion of 100 mg/m² docetaxel.



Conclusions

A PBPK model for docetaxel was developed and verified for use in the prediction of interaction with CYP3A4 inhibitors *a priori*. Mechanistically accounting for variability in fu related to multiple plasma protein concentrations should improve prediction of variability in clearance for cancer patients.

References

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