Performance Verification and Application of a Cancer population for use in Physiologically Based Pharmacokinetic modelling

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Background

Physiologically based pharmacokinetic (PBPK) modelling can be used to predict the pharmacokinetics of drugs. By combining PBPK models with in *vitro-in vivo* extrapolation approaches, it is possible to parameterise human PBPK models as an alternative to animal testing. A further strength of PBPK modelling is that by describing the demographics, physiology, biochemistry and drug metabolising enzyme/transporter levels in different sub-populations, it is possible to explore differences in pharmacokinetics between different groups of individuals. Herein we demonstrate the utility of a PBPK model to predict the pharmacokinetics in cancer patients.

Methods

Literature searches were conducted to find references describing changes in physiological parameters in >3000 patients with cancer compared to healthy subjects, which were incorporated into the generalized Sim-Cancer population in the Simcyp® Simulator V18. The mean AUC and clearance of 6 compounds (Midazolam, Caffeine, Rosiglitazone, S-Warfarin, Tolbutamide and Digoxin) was simulated using the cancer population and compared to observed data in cancer patients. The predicted concentration-time profile of 3 anti-cancer agents (Docetaxel, Methotrexate, and Paclitaxel) using the cancer population were also compared with the results from clinical studies. All the simulated study designs were matched (age, sex and the number of subjects) with the relevant clinical studies. Each simulation was performed, using 10 trials of the number of individuals in each clinical study and the predicted AUC values were calculated for the same duration as the observed studies.

Results

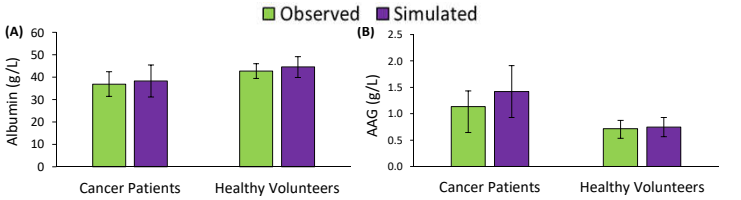

Figure 1: Observed (Independent data) and predicted mean (± SD) of (A) Albumin and (B) AAG plasma levels in cancer patients and healthy volunteers.

Cancer patients have increased Alpha 1-acid glycoprotein (AAG) and decreased albumin plasma levels (Figure 1). These physiological changes result in lower plasma unbound fraction (fup) of Alfentanil in cancer patients compared to healthy subjects, because this compound is highly bound to AAG (Table 1).

Table 1: Plasma unbound fraction (fup) of Alfentanil. Observed data is from colo-rectal cancer patients[1]

Compound	Observed fup%	Simulated fup%	Predicted/ Observed ratio
Alfentanil	Cancer : 5.7 ± 1.75 Healthy: 10.4*	Cancer : 6.9 ± 2.3 Healthy : 11.7 ± 2.3	Cancer : 1.2

*This value is from a meta-analysis of fup of Alfentanil in healthy subjects[2]

Table 2: Observed and predicted mean AUC of 6 compounds

Compounds		AUC (mg/L.h)		
		Predicted	Observed	Predicted/Observed ratio
Midazolam	*Hilli 2017**	0.109	0.096	1.1
	Van Erp 2011	0.125	0.182	0.7
Midazolam (IV)	*Tham 2006**	0.219	0.17	1.3
	*Lepper 2005**	0.083	0.09	0.9
Caffeine (*Goh 2010*) *(Geo mean)*		31.55	24.819	1.3
Rosiglitazone (*Lorusso 2013*)*		1.478	1.3	1.1
Rosiglitazone (*Nguyen 2015*)		1.612	1.713	0.9
S-Warfarin (*Agarwal 2016*)		12.113	8.7	1.4
S-Warfarin (*Camidge 2005*)* *(Geo mean)*		37.048	41.4	0.9
S-Warfarin (*Thsimberidou 2011*)		57.041	73.86	0.8
Tolbutamide (*Shord 2008*)*		715.507	690.8	1.0
Digoxin (*Bjornsson 1986*)		0.023	0.03	0.8

*AUC to infinity

Results

The simulated AUC of Midazolam, Caffeine, Rosiglitazone, S-warfarin, Tolbutamide and Digoxin, and clearance of Midazolam, S-Warfarin, and Tolbutamide in cancer population were within 1.4 fold of the observed values in cancer patients (Table 2 and 3).

Table 3: Observed and predicted mean clearance of 3 compounds

Compounds		Clearance (L/h)		
		Predicted	Observed	Predicted/Observed ratio
Midazolam (IV)	*Tham 2006*	25.1	26.4	1.0
	Lepper 2005	23.6	24.4	1.0
S-Warfarin *(Agarwal 2016)*		0.3	0.587	0.5
S-Warfarin *(Camidge 2005)* *(Geo mean)*		0.3	0.484	0.6
S-Warfarin (*Thsimberidou 2011*)		0.3	0.28	1.1
Tolbutamide *(Shord 2008)*		1.0	1.17	0.9

The predicted pharmacokinetics of the 3 anti-cancer drugs using the Sim-Cancer population could capture the observed values, with the majority of the observed data lying within the 5th and 95th percentiles of the simulated concentration-time profiles of the population (Figure 2).

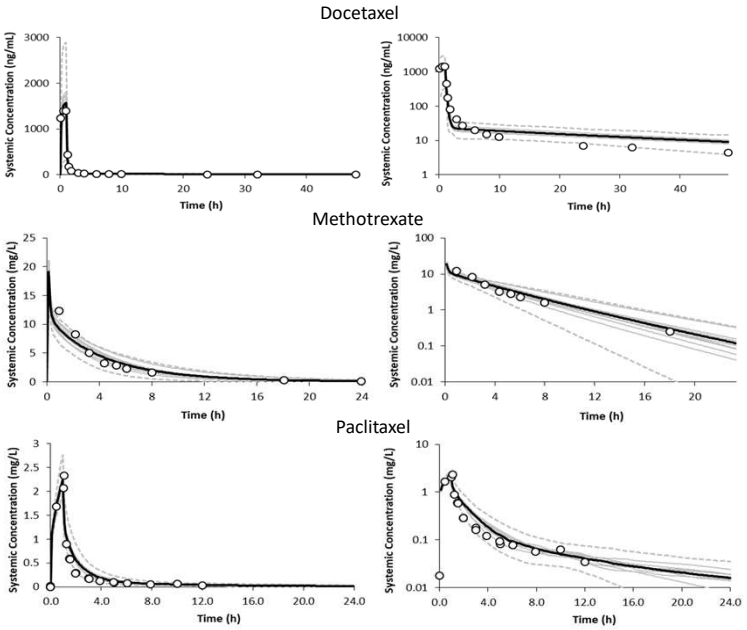

Figure 2: Simulated (black line) and observed (open circles) mean concentration-time profile of 3 anti-cancer drugs (Docetaxel[3], Methotrexate[4], Paclitaxel[5]). The grey lines represent the predictions from individual trials. Dashed lines represent the 5th and 95th percentiles of the simulations.

Conclusions

The utility of the developed PBPK cancer population in predicting the pharmacokinetics of drugs in cancer patients was demonstrated by:

- Accounting for the physiological changes due to cancer in the developed population.
- Verification of the population using 6 different drugs.
- Application of the population in predicting the exposure of 3 anti-cancer drugs.

PBPK models are useful tools to predict the PK of drugs in development, which cannot easily be assessed in a clinical study. Furthermore, it can be used as a practical alternative to animal testing in drug development.

References

1. Meistelman *et al.*, Anesthesiology (1988) 69: A602.
2. Meta-analysis including Bower *et al.*, J Pharm Pharmacol (1989) 41: 654-657.
3. Oostendorp *et al.*, Clin Cancer Res (2009) 15: 4228-4233.
4. Aherne *et al.*, Br Med J. (1978) 1: 1097-1099.
5. Tan *et al.*, Br. J. Cancer (2014) 110: 2647–2654.

We thank Sanofi® for supplying data from cancer patients.

EU Commission's JRC Summer School on Non-Animal Approaches in Science (May 2019, Ispra, Italy)