Predicting Concentration vs Time Profiles in Man From In Vitro and Pre-clinical Data - An Evaluation of PBPK

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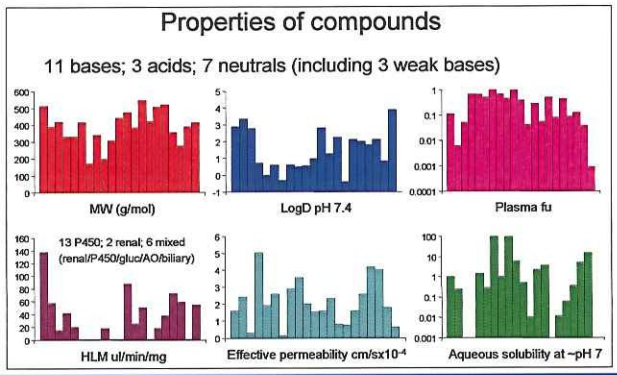
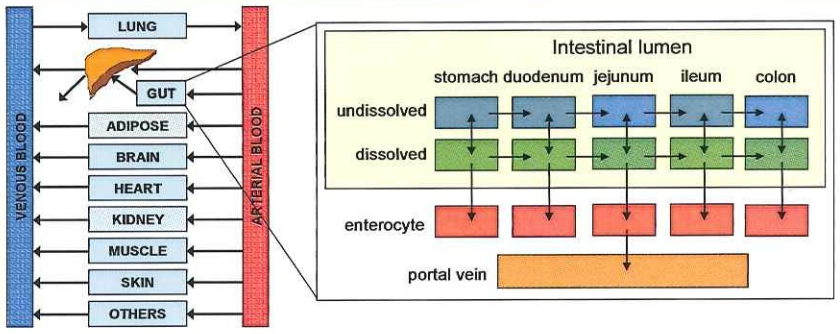
Objectives

- Determine the most predictive method to predict human plasma concentrations time profiles
- Compare predictability of current 1 compartmental approach with 4 commercially available PBPK software programs GastroPlus, SimCYP, PKsim, and ChloePK using 21 Pfizer proprietary compounds where clinical IV and oral data are available:



Model



Commercial packages available that contain PBPK models:

SimCYP: originally developed to study drug-drug interactions in human

GastroPlus: originally developed to predict absorption

PKSim: originally developed to predict distribution

CloePK: semi-empirical PBPK model optimised using a training set of drugs

Clearance estimated from single species scaling body weight$^{0.75}$ or from human liver microsomes for P450 substrates (except SimCYP – CL estimated from HLM or rhCYP within software for P450 substrates)

Distribution characteristics estimated from PPB, bl:pl ratio, LogD, LogP and pKa using published tissue composition equations (except PKSim – propriety methods using membrane affinity data)

Absorption estimated from LogD, LogP, pKa, solubility and permeability (except PKSim – also uses membrane affinity data)

PBPK Model Assumptions:

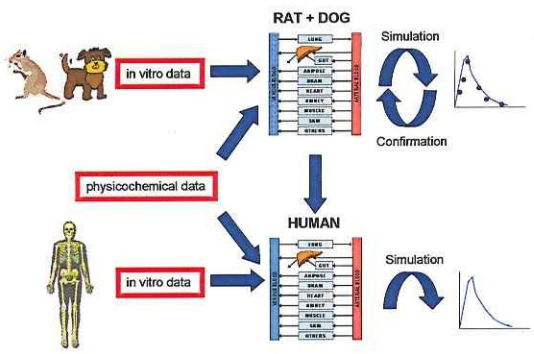
CLEARANCE
- is mainly liver metabolism when scaling from in vitro data
- is determined by BW when scaling from animal data e.g. renal excretion

DISTRIBUTION
- is perfusion limited i.e. blood flow limited, not permeability limited (except PKSim)
- mainly governed by passive processes i.e. no relevant contribution of active transport

ABSORPTION
- mainly governed by passive processes i.e. no relevant contribution of active transport
- in vitro solubility and permeability values are representative of in vivo situation
- relevance of gut metabolism is minimal (except SimCYP)

Method

Initial validation in animals before simulations to human:



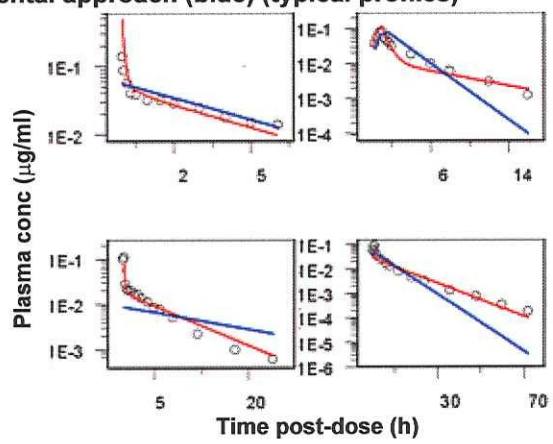
DATA INPUTS:
MW (g/mol; formula and # of halogens)
Log P & D, pKa and acid/base character
Membrane affinity
PAMPA or Caco-2 permeability (10^{-6} cm/sec)
Buffer or biorelevant solubility (mg/mL)
Particle size (um)
Rat, dog, human Cb/Cp ratio, fu(p), fu(mic)
CLint RLM, DLM, HLM (uL/min/mg)
Plasma clearance in rat and dog (mL/min/kg)
Plasma Vss in rat and dog (L/kg)

Accuracy assessment

Accuracy was judged as % within 2 and 3 fold error for CL, Vss, AUC, Terminal T1/2 and Cmax or Average fold error. In addition Residual sum of squares values were standardised across compounds, ranked from highest to lowest and summed across all compounds

Results

Comparison of GastroPlus simulated profiles (red) with current 1-compartmental approach (blue) (typical profiles)



Summary of IV profile prediction accuracy

APPROACH	PROFILE	Vss		CL	
	Weighted sum of squares (RANK)	AFE	% within 2-fold error (3-fold error)	AFE	% within 2-fold error (3-fold error)
GastroPlus	-11.7 (1)	1.4	90 (100)	1.6	80 (85)
PKSim	-6.4 (2)	1.7	70 (90)	1.6	80 (85)
Current Pfizer Approach	-3.8 (3)	1.6	75 (85)	1.6	80 (85)
SimCYP – hlm	5.6 (4)*	1.5	80 (95)	2.5	58 (74)
SimCYP – rhCYP	7.8 (5)*	1.5	80 (95)	2.4	55 (65)
ChloePK	8.5 (6)*	-	-	1.7	70 (80)

Summary of Oral profile prediction accuracy

AFE→ Average Fold Error

APPROACH	PROFILE	AUC		Cmax	
	Weighted sum of squares (RANK)	AFE	% within 2-fold error (3-fold error)	AFE	% within 2-fold error (3-fold error)
GastroPlus	-9.8 (1)	2.7	50 (72)	2.0	67 (72)
Current Pfizer Approach	-5.3 (2)	3.9	33 (56)	2.5	44 (61)
SimCYP - rhCYP	-3.7 (3)	3.0	56 (67)	2.2	61 (72)
SimCYP - hlm	5.7 (4)*	3.6	41 (53)	2.7	53 (59)
PKSim	6.1 (5)*	4.7	22 (39)	5.0	17 (33)
ChloePK	7.0 (6)*	2.8	39 (50)	2.4	50 (61)

Conclusions

- PBPK improved the prediction of profile shape i.e. was able to predict multi-phasic profiles
- GastroPlus was the most predictive in terms of profile, Cmax and AUC
- GastroPlus predictions were consistently superior to current 1-compartmental methods
- Distribution and absorption are well predicted using GastroPlus
- Clearance is the hardest parameter to predict using all approaches

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