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Predicting Human Oral Bioavailability: Comparison of *In Vivo* Animal (Rat- Dog- and Monkey) Studies versus Mechanistic *In Vitro In Vivo* Extrapolation (IVIVE) Based Predictions

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PURPOSE

Identifying critical factors affecting bioavailability (F) and predicting the human oral bioavailability (F_{human}) before first-in-human trials are very important to prioritize and support drug discovery and development projects. At preclinical stage, animal *in vivo* pharmacokinetic studies and/or various *in vitro* measurements such as solubility and permeability (affecting absorption into the gut-wall), metabolism (first pass-elimination in gut-wall and liver) are conducted to understand/estimate the human oral bioavailability. Carefully collated dataset of 184 compounds by Musther et al. demonstrated no strong or predictive correlations between animal and human bioavailability for all species, individually and combined [1]. This comprehensive analysis showed that bioavailability estimated in animal studies are poorly reflecting that of humans. This raised a question if the mechanistic *in vitro* to *in vivo* extrapolation (IVIVE) commonly employed in the physiologically based pharmacokinetics (PBPK) modelling for human pharmacokinetics (PK) simulations can be used as an alternative to predict F_{human}.

OBJECTIVE(S)

Here, we present the preliminary results of a proof-of-concept study t to assess the utility of mechanistic IVIVE to predict F_{human} for 25 compounds where we had access to in vitro data to parametrize the model.

METHOD(S)

We have chosen 25 compounds out of the 184 compounds of Musther et al. that exist in the Simcyp compound library or a published PBPK model is available. Simcyp library compounds were chosen for this preliminary study as the required *in vitro* and physchem data were readily available. Fraction absorbed into the gut-wall (f_a) was estimated using the method proposed by Matsumura et al. [2]. This method requires solubility of a given drug in FaSSIF (3mM bile salts and pH 6.5) for fasted oral dose and FeSSIF (15mM bile salts and pH 5) for fed state dosing and effective permeability (P_{eff}). FaSSIF and FeSSIF solubility were predicted using the Glomme et al. [3] QSAR method as implemented within the Simcyp Simulator predicting partitioning of the drug in bile micelles ($K_{micelle:water}$) using the molecule's lipophilicity (LogP). Permeability was either scaled from *in vitro* P_{app} to human P_{eff} using the regression equations available in the Simcyp Simulator or estimated from polar surface area (PSA) and hydrogen bond donor (HBD) using QSAR method reported by Winiwarter *et al.* [4]. First-pass liver metabolism (F_H) was predicted using well-stirred liver model. The unbound human liver microsomal (HLM) $CL_{int,u}$ values for a given drug were obtained from the Simcyp Simulator compound database or published PBPK models. Fraction of drug metabolised by CYP3A4 ($f_{m,3A4}$) with respect to the total unbound HLM $CL_{int,u}$ was obtained from the Simcyp database or from Yau *et al* [5]. Fraction of drug escaping first-pass gut-wall metabolism (F_g) was calculated using the 'Qgut' model [6] where the $f_{m,3A4}$ values used to determine the CYP3A4 contribution in the gut metabolism. Then F_{human} was calculated using $F_{human,pred} = f_a * F_g * F_H$. Some of the $CL_{int,u}$ and $f_{m,3A4}$ values were informed or verified using clinical data which improves $F_{human,pred}$. To compare the predictions against the data solely measured in vitro, $CL_{int,u}$ values measured in *in-vitro* assays were obtained from literature [5,7,8] and bottom-up IVIVE predictions were compared to observed F_{human}.

RESULT(S)

Predicted F_{human} values using IVIVE (with verified/refined *in vitro* $CL_{int,u}$ from the Simcyp library and literature *in vitro* $CL_{int,u}$) compared with the observed F_{human} from are reported in Figure 1 A and B, respectively. Figure 2 A, B and C shows the rat, dog and monkey F versus F_{human} for the same drugs where data were available in individual species. The IVIVE based predictions showed a good correlation with F_{human} close to line of identity with R^2 of more than 0.8 while animal predicted F showed relatively poorer correlation with human F. Figure 2D also demonstrates poor between-species (here rat and dog) correlation for animal F.

Name	Dose (mg)	F (Pred)	F (Obs)	LogP	MW	So (mg/mL)	Peff (cm/s)	HLM Clint (ul/min/mg)	fm3A4	MAD (mg) (Calculated)	fa (Pred)	Fg (Pred)	Fh (Pred)
Nifedipine	20	0.49	0.50	2.69	346.30	0.02	5.69E-04	141	0.94	68.10	1.00	0.72	0.68
acyclovir (high dose)	800	0.23	0.20	-1.56	225.21	2.50	2.26E-05	0.166	0	188.98	0.24	1.00	0.99
acyclovir (low dose)	350	0.54	0.52	-1.56	225.21	2.50	2.26E-05	0.166	0	188.98	0.54	1.00	0.99
Alprazolam	1	0.95	0.92	2.12	308.80	0.01	9.55E-04	3.69	0.67	57.45	1.00	1.00	0.95
cyclosporin (fed)	800	0.27	0.20	2.96	1202.00	0.01	2.65E-04	94.53	1	257.54	0.32	0.87	0.96
Erythromycin	250	0.44	0.36	2.50	733.90	0.04	2.39E-05	32.8	1	826.72	1.00	0.66	0.67
Fluconazole	65	1.00	0.90	0.20	306.30	1.39	3.57E-04	0.09	0	1678.55	1.00	1.00	1.00
Ibuprofen	200	1.00	0.90	3.23	206.27	0.02	5.27E-04	93.22	0.14	3908.42	1.00	0.98	0.93
itraconazole (fed)	200	0.48	0.55	4.47	705.60	0.00	9.85E-04	1730	0.97	329.48	1.00	0.98	0.49
metformin	500	0.71	0.55	-1.43	129.16	1.38	4.11E-05	1.662	0	378.32	0.76	1.00	0.94
Metoprolol	50	0.50	0.55	1.88	267.40	500.00	2.42E-04	31.18	0.07	1380801.61	1.00	0.99	0.51
midazolam	15	0.28	0.34	3.53	325.80	0.01	6.37E-04	392	0.98	1133.25	1.00	0.56	0.51
moxifloxacin	100	0.93	0.82	0.83	401.40	1.15	1.92E-04	5.36	0	15151653.49	1.00	1.00	0.93
omeprazole	40	0.48	0.49	2.23	345.40	0.36	3.24E-04	303.64	0.13	1398.07	1.00	0.91	0.52
phenobarbital	100	1.00	1.00	1.47	232.24	1.11	1.17E-04	0.125	0	715.70	1.00	1.00	1.00
phenytoin	322	0.71	0.78	2.47	252.28	0.03	4.86E-04	4.639	0	235.19	0.73	1.00	0.97
Quinidine	261.8	0.76	0.70	2.81	324.40	0.14	3.47E-04	24.17	0.96	1257442.54	1.00	0.95	0.80
Ranitidine	150	0.89	0.54	0.27	314.40	43.39	3.70E-05	3	0	8526511.63	1.00	1.00	0.89
Rifampin	600	0.99	0.95	4.01	823.00	1.40	2.44E-04	2.84	0	2683090209.48	1.00	1.00	0.99
rosiglitazone	4	0.93	0.99	2.88	357.40	0.02	6.50E-04	289.9	0	1201.78	1.00	1.00	0.93
rosuvastatin	40	0.47	0.20	2.40	481.54	0.09	9.57E-06	17	0	27.15	0.68	1.00	0.70
sildenafil	50	0.54	0.40	2.97	474.58	0.00	7.55E-05	98	0.82	67.55	1.00	0.67	0.81
tacrolimus	5	0.10	0.16	3.30	804.03	0.01	4.59E-06	54.8	0.63	1.90	0.38	0.27	1.00
triazolam	0.25	0.61	0.53	2.42	343.20	0.01	9.55E-04	45.21	0.9	67.72	1.00	0.94	0.65
warfarin	15	0.94	0.94	2.70	308.30	0.00	3.00E-04	7.66	0	14.11	0.94	1.00	1.00
zolpidem	50	0.66	0.66	2.42	307.39	0.07	1.10E-03	89.69	0.63	6243.64	1.00	0.92	0.72

Table 1. *List of 25 compounds with observed and predicted human oral bioavailability with physicochemical, permeability and metabolism inputs and calculated f_a, F_g and F_H from mechanistic IVIVE (yellow column headings indicate input data)*

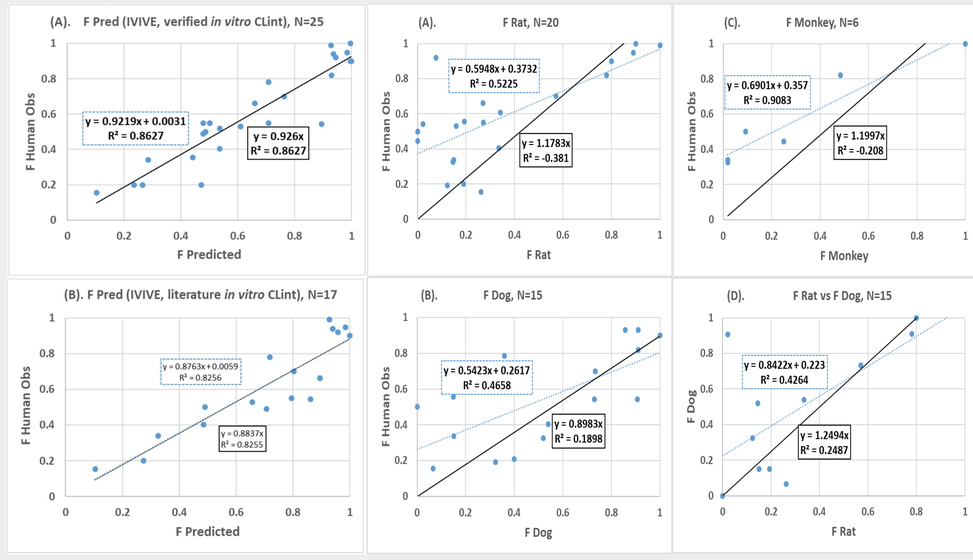

Figure 1. *Mechanistic IVIVE predicted versus observed F_{human} (dotted trend line has unrestricted intercept while the solid black line has an intercept of zero)*

Figure 2. *Animal versus human and between animal species oral bioavailability (dotted trend line has unrestricted intercept while the solid black line has an intercept of zero)*

CONCLUSION(S)

The preliminary analysis of 25 drugs, which spans various BCS and BDDCS classes and diverse chemical nature (Log P range -1.6 to 4.8; MW 129 to 1202; PSA 37.6 to 279; HBD 0 to 5), showed mechanistic IVIVE predictions of human oral bioavailability are significantly better compared to the animals based predictions (Table 1). Using high quality *in vitro* data improves the IVIVE approach predictions, which in turn can reduce, refine and replace animal use in the research where there is known poor predictions in humans. We will further expand the compound database to investigate the approach for a wider dataset.

REFERENCE

[1] Musther et al. Eur J Pharm Sci. 2014 Jun 16;57:280-91. [2] Matsumura et al. J Pharm Sci. 2018 Sep;107(9):2489-2496. [3] Glomme et al. J Pharm Sci. 2005 Jan;94(1):1-16. [4] Winiwarter et al. J Med Chem. 1998 Dec 3;41(25):4939-49. [5] Yau et al. Biopharm Drug Dispos. 2017 Apr;38(3):163-186. [6] Yang et al. Curr Drug Metab. 2007 Oct;8(7):676-84. [7] Wood et al. Drug Metab Dispos. 2017 Nov;45(11):1178-1188. [8] Riley et al. Drug Metab Dispos. 2005 Sep;33(9):1304-11.

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The Simcyp Simulator is freely available, following completion of the relevant workshop, to approved members of academic institutions and other not for-profit organizations for research and teaching purposes.