ANDROMEDA by Prosilico Software Successfully Predicts Human Clinical Pharmacokinetics of 300 Drugs Out of Reach for *In Vitro* Methods

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ABSTRACT

Introduction *In vitro* measurements and predictions of human clinical pharmacokinetics (PK) are sometimes hindered and made impossible due to factors such as extensive binding to materials, low methodological sensitivity and large variability.

Methods The objective was to find compounds out of reach for *in vitro* PK-methods and (if possible) predict corresponding human clinical estimates using the ANDROMEDA by Prosilico software. *In vitro* methods selected for the investigation were human microsomes and hepatocytes for measuring and predicting intrinsic hepatic metabolic clearance (CL_{int}), Caco-2 and Ralph Russ canine kidney cells (RRCK) cells for measuring apparent intestinal permeability (P_{app}) for prediction of fraction absorbed (f_a), plasma for measurement and estimation of unbound fraction (f_u), and water and buffers for measuring solubility (S) for prediction of *in vivo* dissolution potential (f_{diss}).

Results and Conclusion As many as 329 non-quantifiable *in vitro* PK-measurements for 300 compounds were found in the literature: 191 for CL_{int}, 101 for P_{app}, 11 for f_u and 26 for S. ANDROMEDA was successful in predicting all corresponding clinical PK-estimates for the selection of compounds with non-quantifiable *in vitro* PK, and predicted estimates (1.6-fold median prediction error; n=159) were generally in line with observed *in vivo* data and results/problems at *in vitro* laboratories. Thus, ANDROMEDA is applicable for predicting human clinical PK for compounds out of reach for laboratory methods.

INTRODUCTION

Various *in vitro* methods are used to measure and screen pharmacokinetic (PK) properties of drug candidates, including human microsomes and hepatocytes for measuring and predicting intrinsic hepatic metabolic clearance (CL_{int}), Caco-2, Madin Darby canine kidney (MDCK) and Ralph Russ canine kidney (RRCK) cells for measuring apparent intestinal permeability (P_{app}) for prediction of fraction absorbed (f_a), plasma for measurement and estimation of unbound fraction (f_u), and water and buffers for measuring solubility (S) for prediction of *in vivo* dissolution potential (f_{diss}).

In vitro measurements and *in vivo* predictions are commonly hindered and made impossible due to extensive binding to materials, low methodological sensitivity and large variability between laboratories and method set-ups. For example, the *in vitro* PK for about every other compound could not be quantified with human microsomes and hepatocytes (CL_{int}<limit of quantification (LOQ)) and Caco-2 cells (low recovery) in studies by Stringer et al. (2008) and Skolnik et al. (2010), respectively. This has recently also been investigated and shown by Fagerholm et al. (2022a-c).

Lack of preclinical PK data/information could jeopardize drug discovery and development, for example, causing systemic underexposures (and many dosing arms) or unwanted overexposures (side-effects) in first clinical trials with candidate drugs, resulting in selection of compounds with inadequate *in vivo* PK and making optimization of PK-properties difficult/impossible. Thus, it is important to improve and develop new methodologies so that useful PK-data can be produced for compounds that are out of reach for the conventional *in vitro* methods.

The ANDROMEDA software by Prosilico for prediction, simulation and optimization of human clinical PK has been applied and validated in many studies (Fagerholm et al. 2021a,b and 2022a,d,e). It has been shown to outperform (higher accuracy) laboratory methods in 13 comparisons out of 17 (76 %; on par in 12 % of cases) and to have a wider prediction domain (with ability to predict human clinical PK for compounds with good metabolical stability (low CL_{int}), extrahepatic elimination and low P_{app}, S and recovery) (Fagerholm et al. 2022a,e)).

The objective of this investigation was to - via literature search - find compounds out of reach for *in vitro* PK-methods (human microsome and hepatocyte CL_{int}, P_{app}, plasma f_u and aqueous S) and then to (if possible) predict corresponding human clinical estimates using ANDROMEDA.

MATERIALS & METHODS

The literature was searched for compounds with non-quantifiable human microsome and hepatocyte CL_{int} and P_{app}, uncertain f_u (below a certain limit) and reported insolubility in water (including lack of S-data). Useful data were found in the following references: microsome and hepatocvte CL_{int} (Stringer et al. 2008; Sohlenius-Sternbeck et al. 2010; Obach 1999; Riley et al. 2005; McGinnity et al. 2007; Keefer et al. 2023; own non-published data), Caco-2 and RRCK P_{app} (Irvine et al. 1999; Fagerholm and Björnsson 2005; Sköld et al. 2006; Alsenz and Haenel 2003; Keefer et al. 2023), f_u (Fagerholm el al. 2021c; FDA drug labels) and S (Pham-The et al. 2013; Jiménez et al. 2022; Newby et al. 2023; Prosilico data bank).

ANDROMEDA software by Prosilico for prediction, simulation and optimization of human clinical PK) was applied to predict the main parameters for the study: *in vivo* CL_{int}, f_a (permeability-based f_a), f_u, and f_{diss} (at a default oral dose of 50 mg).

RESULTS, DISCUSSION & CONCLUSION

In total, 329 non-quantifiable *in vitro* PK-measurements for 300 compounds were found: 191 for CL_{int}, 101 for P_{app}, 11 for f_u and 26 for S (Table 1).

The minimum, median and maximum predicted CL_{int} were 8, 442 and 35645 mL/min, respectively. 78 (60 %) of the compounds with *in vitro* CL_{int}<LOQ had an *in vivo* CL_{int}<500 mL/min, a limit that is slightly below the median *in vivo* CL_{int} for drugs (738 mL/min) and about 100-fold higher that lowest reported clinical values (Fagerholm 2022b,c; Varma et al. 2010). 55% of CL_{int}-predictions had an error of <2-fold (n=130), which in consistent with previous prediction results with ANDROMEDA (Fagerholm et al. 2022a,e). For these low CL_{int}-compounds it is common with contribution by elimination via excretion (Fagerholm 2022b). Thus, human microsomes and hepatocytes are generally insufficient for measuring and predicting elimination of such compounds. Validated prediction models for renal and biliary excretion are included in ANDROMEDA.

The predicted and observed f_a for the compounds lacking P_{app}-data due to low recovery or sensitivity limitations were ca 0 to 1.00. The median-fold prediction error for f_a was 1.4-fold (n=29). For the hydrolysis sensitive naproxen-prodrug AZD3582 (naproxinod) an intrinsic f_a (in case of absence of gastrointestinal degradation) of 1.00 was predicted. The passive f_a of actively absorbed ACE-lisinopril was predicted to 0.01. Considering the active component a f_a of 0.25 was predicted.

The overall median prediction error for CL_{int} and f_a was 1.57-fold.

Predicted f_u-values ranged between 0.0033 and 0.049 and were generally close to reported maximum f_u-estimates (<0.001 to <0.01). In 3 cases predicted estimates were lower than measured upper limits (<X), and in 6 cases they were above them.

For compounds with unmeasurable S, f_{diss} at the 50 mg oral dose level ranged between 0.01 (beta-carotene) and 1.00, with 8 (31 %) of compounds with f_{diss}<0.5. Incomplete f_{diss} was predicted for 17 (65 %) of the 26 compounds. As described in recent papers, there is very weak correlation between the clinical solubility/dissolution parameter f_{diss} and *in vitro* S (Fagerholm 2022b,c).

In conclusion, ANDROMEDA was successful in predicting all the corresponding clinical PK-estimates for the selection of 300 compounds with non-quantifiable *in vitro* PK, and predicted estimates were generally in line with observed *in vivo* data and results/problems at *in vitro* laboratories. Thus, this software is applicable for predicting human clinical PK for compounds out of reach for laboratory methods.

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TABLE

Table 1 300 compounds with non-quantifiable *in vitro* PK and corresponding *in silico* predicted estimates.

	CL_{int} (mL/min)		**f_u**		**f_a**		**Sol.** *(in vitro) vs* **f_{diss}** *(in silico)*	
	In vitro[1]	*In silico*	*In vitro*	*In silico*	*In vitro*[2]	*In silico*	*In vitro*[3]	*In silico*
(-)dOTC	Non-quant.	84						
Acarbose	Non-quant.	53						
Acecainide	Non-quant.	883						
Acetaminophen	Non-quant.	676						
Albuterol	Non-quant.	469						
Alosetron	Non-quant.	2541						
Amdinocillin	Non-quant.	285						
Amifloxacin	Non-quant.	221						
Amygdalin	Non-quant.	385						
Antofloxacin	Non-quant.	238						
Apixaban	Non-quant.	3698						
Argatroban	Non-quant.	171						
Astragaloside IV	Non-quant.	3733						
Atenolol	Non-quant.	232						
Azapropazone	Non-quant.	1914						
Azithromycin	Non-quant.	5715						
Azlocillin	Non-quant.	184						
Baclofen	Non-quant.	394						
Betaxolol	Non-quant.	676						
Bidisomide	Non-quant.	1560						
Bisoprolol	Non-quant.	315						
Bosentan	Non-quant.	4385						
Buthionine sulfoximine	Non-quant.	60						
Butylbiguanide	Non-quant.	136						
Caffeine	Non-quant.	95						
Cefadroxil	Non-quant.	43						
Cefazolin	Non-quant.	74						
Cefbuperazone	Non-quant.	96						
Cefetamet	Non-quant.	42						
Cefixime	Non-quant.	83						
Cefoperazone	Non-quant.	189						
Cefotetan	Non-quant.	25						
Cefotiam	Non-quant.	139						
Cefpiramide	Non-quant.	341						
Ceftezole	Non-quant.	41						
Ceftriaxone	Non-quant.	65						
Cefuroxime	Non-quant.	21						
Cefuzonam	Non-quant.	54						
Cephalexin	Non-quant.	39						
Cephaloridine	Non-quant.	212						
Chlorpheniramine	Non-quant.	288						
Chlorpropamide	Non-quant.	123						
Chlorthalidone	Non-quant.	200						
Cilazaprilat	Non-quant.	42						
Cilengitide	Non-quant.	397						
Citalopram	Non-quant.	2099						
Clopidogrel	Non-quant.	4571						
Colchicine	Non-quant.	1242						
Dapsone	Non-quant.	252						
Deacetyl metipranolol	Non-quant.	1641						
Delafloxacin	Non-quant.	865						
Demethylchlor tetracycline	Non-quant.	573						
Desvenlafaxine	Non-quant.	2382						
Diatrizoic acid	Non-quant.	18						
Didanosine	Non-quant.	339						
Disopyramide	Non-quant.	219						

Distigmine	Non-quant.	1462						
Dofetilide	Non-quant.	355						
Doxofylline	Non-quant.	135						
Doxycycline	Non-quant.	664						
DX9065a	Non-quant.	2679						
Edoxaban	Non-quant.	940						
Edrophonium	Non-quant.	887						
Enalaprilat	Non-quant.	8						
Enalkiren	Non-quant.	7798						
Enprofylline	Non-quant.	98						
Erlotinib	Non-quant.	7603						
Ethambutol	Non-quant.	94						
Faropenem	Non-quant.	179						
Finasteride	Non-quant.	1545						
Flecainide	Non-quant.	548						
Flucytosine	Non-quant.	28						
Fludarabine	Non-quant.	102						
Flumazenil	Non-quant.	6026						
Fluvoxamine	Non-quant.	1365						
Furosemide	Non-quant.	103						
Gabapentin	Non-quant.	62						
Galantamine	Non-quant.	589						
Garenoxacin	Non-quant.	442						
Gliclazide	Non-quant.	783						
Glipizide	Non-quant.	679						
Glycopyrrolate bromide	Non-quant.	1995						
Glycyrrhizin	Non-quant.	2965						
Granisetron	Non-quant.	2089						
Heptaminol	Non-quant.	110						
Hydrocortisone	Non-quant.	3622						
Hydroflumethiazide	Non-quant.	50						
Ifosfamide	Non-quant.	52						
Imipramine N-oxide	Non-quant.	14555						
Iopromide	Non-quant.	85						
Iothalamic acid	Non-quant.	22						
Isoxicam	Non-quant.	748						
Ketoprofen	Non-quant.	8128						
Ketorolac	Non-quant.	1259						
Lamivudine	Non-quant.	94						
Levofloxacin	Non-quant.	182						
Levoleucovorin	Non-quant.	86						
Levoprotiline	Non-quant.	6761						
Licarbazepine	Non-quant.	951						
Lidocaine	Non-quant.	497						
Linagliptin	Non-quant.	1521						
Linezolid	Non-quant.	160						
Lomefloxacin	Non-quant.	84						
Lorazepam	Non-quant.	1023						
Melphalan	Non-quant.	3388						
Mepindolol	Non-quant.	1213						
Mepivacaine	Non-quant.	2163						
Meptazinol	Non-quant.	1242						
Mercaptopurine, 6-	Non-quant.	117						
Metadoxine	Non-quant.	303						
Metazosin	Non-quant.	1479						
Metformin	Non-quant.	56						
Methotrexate	Non-quant.	194						
Metocloprimide	Non-quant.	545						
Metolazone	Non-quant.	502						
Metronidazole	Non-quant.	155						
Minocycline	Non-quant.	536						
Nadolol	Non-quant.	521						
Nalbuphine	Non-quant.	843						
Naloxone	Non-quant.	1208						
NK 611	Non-quant.	404						
Odanacatib	Non-quant.	735						
Ofloxacin	Non-quant.	182						

Oleandomycin	Non-quant.	6339						
Olmesartan	Non-quant.	15668						
Ondansetron	Non-quant.	2399						
Ornidazole	Non-quant.	261						
Oxprenolol	Non-quant.	2203						
Oxytetracycline	Non-quant.	264						
Palonosetron	Non-quant.	2188						
Panipenem	Non-quant.	163						
Pefloxacin	Non-quant.	246						
Pelrinone	Non-quant.	296						
Penciclovir	Non-quant.	123						
Penicillin G	Non-quant.	729						
Phenacetin	Non-quant.	1824						
Phenazepam	Non-quant.	569						
Phenprocoumon	Non-quant.	1706						
Phenytoin	Non-quant.	413						
Pidotimod	Non-quant.	22						
Pindolol	Non-quant.	708						
Pipecuronium	Non-quant.	5610						
Piperacillin	Non-quant.	222						
Pirenzepine	Non-quant.	577						
Pralatrexate	Non-quant.	202						
Pravastatin	Non-quant.	1096						
Prazosin	Non-quant.	5248						
Prednisolone	Non-quant.	1069						
Primaquine	Non-quant.	248						
Promethazine	Non-quant.	3750						
Propionyl-L-carnitine	Non-quant.	201						
Proxyphyllin	Non-quant.	142						
Prucalopride	Non-quant.	1099						
Pyridostigmine	Non-quant.	241						
Pyrimethamine	Non-quant.	1164						
Rabeprazole	Non-quant.	11749						
Ribavirin	Non-quant.	49						
Ribostamycin	Non-quant.	18						
Ropinirole	Non-quant.	2564						
Rosuvastatin	Non-quant.	2570						
Safinamide	Non-quant.	608						
Sematilide	Non-quant.	89						
Sotalol	Non-quant.	44						
Sulbactam	Non-quant.	77						
Sulfasalazine	Non-quant.	518						
Sulfinpyrazone	Non-quant.	417						
Sulfisoxazole	Non-quant.	174						
Tacrine	Non-quant.	1276						
Talinolol	Non-quant.	592						
Temazepam	Non-quant.	1585						
Tenofovir	Non-quant.	50						
Tenoxicam	Non-quant.	200						
Teriflunomide	Non-quant.	450						
Theophylline	Non-quant.	104						
Tiapride	Non-quant.	513						
Timolol	Non-quant.	661						
Tinidazole	Non-quant.	222						
Tizanidine	Non-quant.	1694						
Tolbutamide	Non-quant.	372						
Toloxatone	Non-quant.	3864						
Trospectomycin	Non-quant.	300						
Vaborbactam	Non-quant.	302						
Valsartan	Non-quant.	14322						
Vancomycin	Non-quant.	4178						
Warfarin	Non-quant.	1542						
Venlafaxine	Non-quant.	2360						
Vismodegib	Non-quant.	984						
Vosaroxin	Non-quant.	275						
Zafirlukast	Non-quant.	35645						
Zaleplon	Non-quant.	1426						

Zonampanel	Non-quant.	338						
Tivozanib			<0,01	0,0490				
Avacopan			<0,001	0,0099				
DDT			?	0,0067				
Ganaxolone			ca 0.01	0,0084				
Ibrexafungerp			<0,01	0,0167				
Lumefantrine			<0,01	0,0033				
Odevixibat			<0,003	0,0112				
Ponesimod			<0,01	0,0180				
Umbralisib			<0,003	0,0037				
Zafirlukast			<0,01	0,0064				
AZD3582[4] (prodrug)			?	0,0073				
Aclidiniumbromide					Non-quant.	0,70		
Acyclovir					Non-quant.	0,41		
Albuterol					Non-quant.	0,60		
Almitrine					Non-quant.	0,75		
Amdinocillin					Non-quant.	0,17		
Amifloxacin					Non-quant.	0,68		
Amiodarone					Non-quant.	0,57		
Amygdalin					Non-quant.	0,02		
Anidulafungin					Non-quant.	0,08		
Astragaloside IV					Non-quant.	0,03		
Atovaquone					Non-quant.	0,53		
AZD3582 (naproxinod; prodrug)					Non-quant.	1,00		
Aztreonam					Non-quant.	0,18		
Bilobalide					Non-quant.	0,54		
Bivalirudin					Non-quant.	0,00		
Cangrelor					Non-quant.	0,00		
Cefbuperazone					Non-quant.	0,00		
Cefepime					Non-quant.	0,00		
Cefmenoxime					Non-quant.	0,00		
Cefodizime					Non-quant.	0,00		
Cefoperazone					Non-quant.	0,00		
Cefotaxime					Non-quant.	0,00		
Cefotiam					Non-quant.	0,00		
Cefprozil					Non-quant.	0,02		
Ceftriaxone					Non-quant.	0,00		
Cephapirin					Non-quant.	0,01		
Cephradine					Non-quant.	0,03		
CGP36742					Non-quant.	0,70		
Cilengitide					Non-quant.	0,16		
Clevidipine					Non-quant.	0,90		
Dalbavancin					Non-quant.	0,00		
Dehydroandrographolide succinate					Non-quant.	0,44		
Deoxycytidine					Non-quant.	0,42		
Desferrioxamine					Non-quant.	0,54		
Diatrizoic Acid					Non-quant.	0,47		
Dicloxacillin					Non-quant.	0,13		
Didanosine					Non-quant.	0,38		
Dobutamine					Non-quant.	0,65		
Dronedarone					Non-quant.	0,70		
Eptifibatide					Non-quant.	0,02		
Estramustine phosphate					Non-quant.	0,63		
Ethambutol					Non-quant.	0,65		
Etilefrine					Non-quant.	0,47		
Evacetrapib					Non-quant.	0,57		
Faropenem					Non-quant.	0,42		
Fenofibrate					Non-quant.	0,99		
Folinic acid					Non-quant.	0,15		
GSK2251052					Non-quant.	0,80		
Hydralazine					Non-quant.	0,93		
Hydroxysafflor yellow A					Non-quant.	0,01		
Ibandronic Acid					Non-quant.	0,01		
Indocyanine green					Non-quant.	0,33		

Isoglycirrhizinate					Non-quant.	0,03		
KW2478					Non-quant.	0,87		
Lamivudine					Non-quant.	0,65		
Lisinopril					Non-quant.	0,25[5]		
Meclizine					Non-quant.	1,00		
Metadoxine					Non-quant.	0,75		
Metaproterenol					Non-quant.	0,26		
Metocurine					Non-quant.	0,84		
Metrizoate					Non-quant.	0,50		
Nedocromil					Non-quant.	0,55		
Nelarabine					Non-quant.	0,16		
Octreotide					Non-quant.	0,18		
Olcegepant					Non-quant.	0,44		
Olsalazine					Non-quant.	0,69		
Ombitasvir					Non-quant.	0,11		
Paclitaxel					Non-quant.	0,59		
Paeoniflorin					Non-quant.	0,22		
Pelrinone					Non-quant.	0,64		
PF05212384					Non-quant.	0,73		
Pidotimod					Non-quant.	0,24		
Piperacillin					Non-quant.	0,01		
Piroximone					Non-quant.	0,77		
Pixantrone					Non-quant.	0,59		
Practolol					Non-quant.	0,67		
Pravastatin					Non-quant.	0,40		
Promethazine					Non-quant.	1,00		
Propionyl-L-carnitine					Non-quant.	0,59		
Raltitrexed					Non-quant.	0,26		
Ranitidine					Non-quant.	0,64		
Ribostamycin					Non-quant.	0,00		
Romidepsin					Non-quant.	0,36		
Salvianolic acid B					Non-quant.	0,21		
Scutellarin					Non-quant.	0,16		
Sumatriptan succinate					Non-quant.	0,74		
Suramin					Non-quant.	0,25		
Tanshinol					Non-quant.	0,52		
Tazarotene					Non-quant.	0,89		
Temoporfin					Non-quant.	0,20		
Terbutaline					Non-quant.	0,57		
Terlipressin					Non-quant.	0,00		
Tetracycline					Non-quant.	0,57		
TH302					Non-quant.	0,63		
Tiopronin					Non-quant.	0,34		
Tirilazad					Non-quant.	0,76		
Trospectomycin					Non-quant.	0,28		
Valspodar					Non-quant.	0,16		
Vancomycin					Non-quant.	0,00		
VerteporfinMac					Non-quant.	0,32		
Vincristine					Non-quant.	0,62		
ACBI1[6]							<0,72 µM	>0,5
Amlodipine							<0.01 g/L	1,00
Aripiprazole							<0.0003 g/L	>0,5
Artemether							insol.	<0,5
ARV-825[6]							<0,32 µM	<0,5
Atovaquone							<0.0001 g/L	<0,5
Azathioprine							insol.	1,00
Azithromycin							<0.003 g/L	1,00
Beta-carotene							insol.	<0,5
Bicalutamide							<0.005 g/L	>0,5
Chlorphenesin							<10 g/L	1,00
Conivaptan							<0.001 g/L	>0,5
Daridorexant							low	>0,5
Lomustine							<0.05 g/L	1,00
Lumefantrine							insol.	<0,5
Mcl1 degrader-1[6]							<0,87 µM	<0,5
MD-224							<0,23 µM	<0,5
Paricalcitol							insol.	>0,5

Posaconazole							<0.002 g/L	>0,5
Pranoprofen							insol.	1,00
Pseudoephedrine							<0.5 g/L	1,00
Pyrantel							insol.	>0,5
Rebamipide							low	>0,5
Venlafaxine							<0.1 g/L	1,00
Vitamin D2							insol.	<0,5
Zolpidem							<0.01 g/L	1,00

[1] Non-quantifiable (including <LOQ) with human microsomes or hepatocytes.
[2] Non-quantifiable P_{app} with Caco-2 or RRCK cells.
[3] Solubility (µM or g/L)
[4] Naproxinod (naproxen prodrug).
[5] Including prediction of active uptake (passive f_a=0,014).
[6] PROTAC.