Predicting the Influence of Fat Food Intake on the Absorption and Systemic Exposure of Modern Small Drugs using ANDROMEDA by Prosilico Software

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ABSTRACT

Introduction The ANDROMEDA software by Prosilico has previously been successfully applied and validated for predictions of absorption characteristics of small drugs in man. The effects of fat food on the gastrointestinal uptake and systemic exposure of drugs have, however, not yet been evaluated with the software.

Objective and Methodology The main objective was to use ANDROMEDA to predict area under the plasma concentration-time curve ratios in the fed (fat food) and fasted states (AUC_{fed}/AUC_{fast}) for small drugs marketed in 2021 and compare results with corresponding measured clinical estimates. A secondary aim was to make a similar evaluation for a set of selected older small drugs with no and significant food interaction.

Results 17 new drugs with observed AUC_{fed}/AUC_{fast} between 0.4 and 2.0 were found. In addition, 18 older drugs with low (0.5), moderate (1) and high (3.1-5.5) AUC_{fed}/AUC_{fast} were selected. Predicted AUC_{fed}/AUC_{fast} (for all drugs) had mean, median and maximum errors of 1.4-, 1.1- and 3.9-fold, respectively, and the predictive accuracy (correlation between predicted and observed AUC_{fed}/AUC_{fast}; Q^2) was 0.35. For new small drugs, the Q^2 was 0.41. All 10 new drugs with AUC_{fed}/AUC_{fast} between 0.8 and 1.25 were predicted to have AUC_{fed}/AUC_{fast} between 0.6 and 1.5 and all 4 new drugs with $AUC_{fed}/AUC_{fast}<1$ were predicted to have $AUC_{fed}/AUC_{fast}<1.05$. Every predicted value ≥ 1.5 corresponded to a clinically significant food-drug interaction ($AUC_{fed}/AUC_{fast}\geq 1.25$).

Conclusion The results validate ANDROMEDA for prediction of fat food-drug interaction size for small drugs in man. Major advantages with the methodology include that results are produced directly from molecular structure and oral dose and an adequate level of predictive accuracy.

INTRODUCTION

When taken together with drugs, fat food may change their gastrointestinal uptake via changes in motiliy and transit time (reduced time for absorption of compounds with limited permeability) and/or solubility/dissolution (generally enhanced for lipophilic compounds with limited solubility/dissolution) (Deng et al. 2017).

Authorities recommend that drug developers conduct fed bioequivalence studies for orally administered drugs (dosing the drug to individuals in fed and fasted states and evaluating systemic exposures) (FDA 2021). The design of fed bioequivalence studies is usually based on *in vitro* dissolution data. Available absorption data from early clinical studies is also valuable when designing such *in vivo* studies. In cases where the systemic drug exposure is significantly increased (increasing the action of a drug and/or causing unexpected side effects) or decreased (making the drug less effective) in the presence of food a dose adjustment or avoidance of concommittant intake of food and drug is recommended (FDA 2021).

The ANDROMEDA software by Prosilico for prediction, simulation and optimization of human clinical pharmacokinetics (with a major domain for compounds with molecular weight (MW) between 100 and 700 g/mole) has been sucessfully applied and validated for prediction of absorption/biopharmaceutics of small compounds in man in many studies (Fagerholm et al. 2021 and 2022a-c). Predicted absorption properties, including fraction absorbed (f_a), efflux by MDR-1, BCRP and MRP2 and maximum fraction dissolved (f_{diss}), and oral dose can be used to estimate the size of food interaction effect (ratio between area under the plasma concentration-time curves in the fed (fat food) and fasted states (AUC_{fed}/AUC_{fast})). In an internal validation, the predictive accuracy (correlation between predicted and observed AUC_{fed}/AUC_{fast}) was Q^2=0.45 (data on file).

ANDROMEDA has been used to predict the f_a of new small drugs marketed in 2021 (Fagerholm et al. 2022b). The investigation was, however, limited by the few (only 3) new drugs with available measured f_a.

The main objective was to use ANDROMEDA to predict fat food-drug interactions (AUC_{fed}/AUC_{fast}) for small drugs marketed in 2021 and compare results with corresponding measured clinical estimates. A secondary aim was to make a similar evaluation for a set of selected older small drugs with no and significant food interaction.

METHODOLOGY

ANDROMEDA by Prosilico was used to predict absorption parameters (including, for example, f_a, f_{diss} and MDR-1-, BCRP- and MRP2-substrate specificities) and then (based on these data, algorithms and oral dose sizes) AUC_{fed}/AUC_{fast}. In a previous study (Fagerholm et al. 2022b), ANDROMEDA was used to predict f_a for 3 of the small drugs marketed in 2021. These few predicted values were re-used in the present investigation. Clinical food-drug interaction data for new small drugs were taken from FDA-label documents (see Supplementary table). Only drugs with MW 100 to 700 g/mole and oral dose of maximally 1000 mg and not included in training sets of underlying prediction models were selected for the investigation.

RESULTS & DISCUSSION

17 new small drugs with AUC_{fed}/AUC_{fast} between 0.4 and 2.0 qualified for the main evaluation (Table 1, Figure 1).

In total, several hundred absorption estimates were predicted for the investigation (including 3 taken from a previous absorption prediction study with ANDROMEDA (Fagerholm et al. 2022b)).

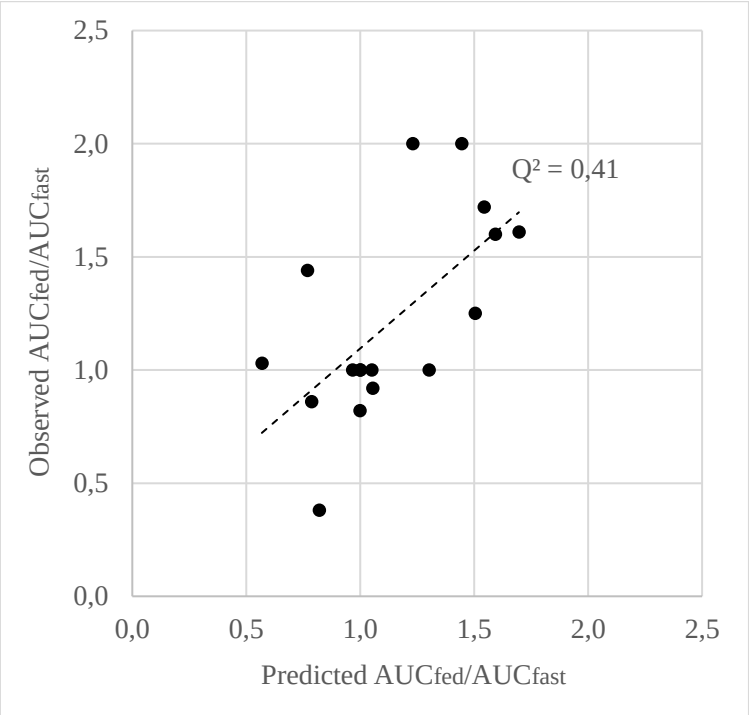

Figure 1. The correlation between predicted and observed AUC_{fed}/AUC_{fast} for the 17 new small drugs.

Mean and median prediction errors for AUC_{fed}/AUC_{fast} were 1.3- and 1.1-fold, respectively. Corresponding estimates for absolute errors were 25 and 18 %, respectively. 76 % of predictions were within 1.3-fold error and the Q^2 was 0.41 (Figure 1; similar to that found in internal cross-

validation study with training set compounds; 0.45). The correlation between predicted and observed AUC_{fed}/AUC_{fast} also showed an intercept of 0.23 and slope of 0.86.

All 10 new small drugs with AUC_{fed}/AUC_{fast} between 0.8 and 1.25 were predicted to have AUC_{fed}/AUC_{fast} between 0.6 and 1.5 and an absolute difference between predicted and observed AUC_{fed}/AUC_{fast} of 0 to 0.46. 6 of 7 new drugs with >1.25 to 2.0-fold AUC_{fed}/AUC_{fast} were also predicted to have higher extent of uptake in the presence of fat food. All 4 new drugs with $AUC_{fed}/AUC_{fast}<1$ were predicted to have $AUC_{fed}/AUC_{fast}<1.05$ *in vivo*.

The largest prediction error (2.2-fold) for new small drugs was found for asciminib, which was predicted to have permeability-limited uptake and a minor (-18 %) food effect. Fat food reduced its absorption by 62 % ($AUC_{fed}/AUC_{fast=}0.38$).

The new drugs fexinidazole (MW 279 g/mole; 1200 mg dose; 3.3-fold increase of AUC with fat food), ibrexafungerp (MW 730 g/mole; 300 mg dose), maralixibat (MW 710 g/mole; 30 mg dose), odevixibat (MW 741 g/mole; 9.6 mg dose) and voclosporin (MW 1215 g/mole; 23.7 mg dose) did not fulfill the inclusion criteria. However, $AUC_{fed}/AUC_{fast}\geq1.4$ was predicted and observed for fexinidazole and ibrexafungerp, $AUC_{fed}/AUC_{fast}<0.75$ was predicted and observed for voclosporin, $AUC_{fed}/AUC_{fast}<0.7$ was predicted and observed for odevixibat and 0.75- to 1.3-fold AUC_{fed}/AUC_{fast} was predicted and observed for maralixibat.

Table 1. The selected 17 new small drugs and *in silico* prediction results.

Drug	**MW** (g/mole)	**Oral dose** (mg)	**High fat food**	**AUC_{fed}/AUC_{fast}** Observed	**AUC_{fed}/AUC_{fast}** Predicted	**Prediction error**
Asciminib	450	40 to 200	Yes	0,38	0,82	2,16
Atogepant	604	10 to 60	Yes	0,82	1,00	1,22
Avacopan	582	30	Yes	1,72	1,54	1,11
Belumosudil	453	200	Yes	2,00	1,45	1,38
Belzutifan	383	120	Yes	1,00	1,05	1,05
Finerenone	378	10 to 20	Yes	1,00	0,97	1,04
Infigratinib	560	125	Yes	2,00	1,23	1,62
Maribavir	376	400	Mod. fat	0,86	0,79	1,09
Mobocertinib	586	160	Yes	1,00	1,30	1,30
Ponesimod	461	20	?	1,00	1,00	1,00
Samidorphan	370	10	?	1,03	0,57	1,81
Sotorasib	561	960	Yes	1,25	1,50	1,20
Tepotinib	493	450	Yes	1,60	1,59	1,00
Tivozanib	455	1,34	Yes	1,00	1,00	1,00
Umbralisib	572	800	Yes	1,61	1,70	1,05
Vericiguat	426	10	Yes	1,44	0,77	1,87
Viloxazine	237	200	Yes	0,92	1,05	1,15
					Mean	1,30
					Median	1,15
					Max	2,16

In addition, 18 older drugs with low (0.5), moderate (1) and high (3.1-5.5) AUC_{fed}/AUC_{fast} were selected (Table 2). Those older drugs with an AUC_{fed}/AUC_{fast} of 0.5, 1 and 3.1-5.5 were predicted to have an AUC_{fed}/AUC_{fast} of 0.5, 0.8-1.1 and 1.25 to 5.7, respectively.

Table 2. The selected 18 older small drugs and *in silico* prediction results.

AUC_{fed}/AUC_{fast} Observed	**Drugs**	**AUC_{fed}/AUC_{fast}** Predicted
Ca 0.5	Didanosine	0,51
	Melphalan	0,45
	Penicillamine	0,47
Ca 1	Bicalutamide	0,79
	Carvedilol	1,00
	Clopidogrel	1,09
	Finasterine	0,91
	Imipramine	1,00
	Letrozole	0,79
	Terfenadine	0,96
	Valproic acid	0,95
	Vardenafil	0,83
3.1-5.5	Albendazole	1,27
	Atavaquone	5,70
	Danazol	1,74
	Etretinate	2,49
	Fenretinide	3,80
	Praziquantel	1,56

When results for both datasets were combined, mean, median and maximum errors and Q^2 of 1.4-, 1.1- and 3.9-fold and 0.35 (n=35) were obtained, respectively. Every predicted value ≥1.5 corresponded to a clinically significant food-drug interaction (AUC_{fed}/AUC_{fast}≥1.25). 27 (77 %) of predictions were correctly classed (significantly decreased exposure by food (AUC_{fed}/AUC_{fast}<0.8), no significant food interaction (AUC_{fed}/AUC_{fast}=0.8-1.25), or significantly increased exposure by food (AUC_{fed}/AUC_{fast}≥1.25)) (Figure 2). Most of those with incorrect predicted class had an AUC_{fed}/AUC_{fast} that was only 1-2 % from correct classing.

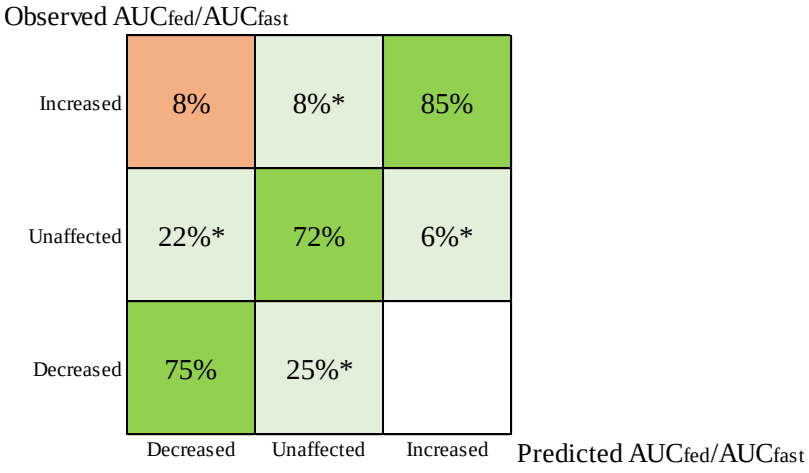

Figure 2. Predicted *vs* observed AUC_{fed}/AUC_{fast}-classes (%) for all the 35 selected drugs. Decreased when AUC_{fed}/AUC_{fast}<0.8; unaffected when AUC_{fed}/AUC_{fast}=0.8-1.25; Increased when AUC_{fed}/AUC_{fast}≥1.25.
*denotes drugs for which predicted AUC_{fed}/AUC_{fast}-class was only 1-5 % from being correct.

A limitation with the study is that no prediction results based on laboratory data (for comparison between *in silico* and *in vitro* methodologies) have been found for the new small drugs.

The results validate ANDROMEDA for prediction of fat food-drug interaction size for small drugs in man. Major advantages with the methodology include that results are produced directly from molecular structure and oral dose and an adequate level of predictive accuracy.

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FDA. 2021. Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA guidance for industry. Draft guidance. https://www.fda.gov/media/87219/download.

Supplementary Table. References for observed human AUC_{fed}/AUC_{fast}-data for the new small drugs.

Drug	**Reference**
Asciminib	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215358s000Orig2lbl.pdf
Atogepant	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215206Orig1s000lbl.pdf
Avacopan	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214487s000lbl.pdf
Belumosudil	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214783s000lbl.pdf
Belzutifan	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215383s000lbl.pdf
Finerenone	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215341s000lbl.pdf
Infigratinib	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214622s000lbl.pdf
Maribavir	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215596lbl.pdf
Mobocertinib	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215310s000lbl.pdf
Ponesimod	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213498s000lbl.pdf
Samidorphan	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213378s000lbl.pdf
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Tepotinib	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214096s000lbl.pdf
Tivozanib	https://www.aveooncology.com/fotivdapi.pdf
Umbralisib	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213176s000lbl.pdf
Vericiguat	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214377s000lbl.pdf
Viloxazine	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211964s000lbl.pdf