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Development of a PBPK model for the prediction of Amiodarone pharmacokinetics in fed and fasted state using the Advanced Dissolution, Absorption and Metabolism (ADAM) model

Peter J Kilford[1], Xian Pan[1], Sumit Arora[1], Iain Gardner[1]

[1]Certara UK Ltd, Simcyp Division, Sheffield, United Kingdom

CONTACT INFORMATION: peter.kilford@Certara.com

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PURPOSE

Amiodarone is an antiarrhythmic drug, prescribed for the treatment of prophylaxis of ventricular tachycardia or fibrillation. Amiodarone is poorly soluble and variable bioavailability has been observed in the clinical setting. In addition food has been shown to enhance the absorption of the drug with up to a two to three fold increase in systemic exposure noted in clinical studies [1, 2].

OBJECTIVE(S)

The aim of this work was to construct a mechanistic physiologically based absorption model that will account for the low solubility and bioavailability of Amiodarone in both the fed and fasted conditions and to subsequently investigate the drug-drug interaction potential of amiodarone in the fed and fasted state [3].

METHOD(S)

A model of Amiodarone (AMIO) and its major metabolite, mono des-ethylamiodarone (MDEA), was built using parameters from the literature [3] and further optimised.

A retrograde calculation of clearance was determined using the Simcyp simulator based on the total intravenous clearance and calculated fraction metabolised data from liver enzymes (50% CYP3A4 and 30% CYP2C8).

Further optimisation was conducted to capture the solubility (intrinsic solubility of 4.5x10-6 mg/ml) and absorption of amiodarone from the intestine (bile micelle:buffer coefficient 9.3:6.9 in fasted state).

The simulation was conducted using Simcyp (V18R2) with a single oral dose of 564mg amiodarone (free base), and a trial size of 10 x 30 subjects using both the fasted and fed states and a healthy volunteer population.

DDIs were evaluated based on the clinical trial designs for Simvastatin [4], S-Warfarin [5] and Metoprolol [6] with AMIO as the perpetrator under fed and fasted conditions. Key model parameters are shown in Table 1.

RESULT(S)

Table 1: Parameters for AMIO and MDEA used in model development

Parameter	AMIO	MDEA
Molecular Weight	645.32	617.25
Log P	7.57	7.32
pKa	6.56	5.58
B/P	0.73	3.3
fu	0.0009	0.0009
Absorption	ADAM Immediate Release	First Order
Intrinsic Solubility (mg/ml)	4.5 x 10^{-6}	NA
Bile:micelle partition coeff	9.29:6.89	NA
Model	Full PBPK	Minimal PBPK
Vss (Liver tissue:plasma coeff)	10.8 (140)	46.9 (23)
Cl_{IV} (L/h)	19.5	12.8
CL_{int} CYP3A4, 2C8, 1A2, 2C19, Add CL (µL/min/pmol enzyme)	33.5, 134, 10.2, 47.1, 867	NA
CYP2C9 Ki (µM), K_{app} (µM), K_{inact} (/h)	47.4, 0.044, 4.35	1.19
CYP2D6 Ki (µM), K_{app} (µM), K_{inact} (/h)	22.6	2.27, 0.10, 3.93
CYP3A4 Ki (µM), K_{app} (µM), K_{inact} (/h)	136, 0.86, 3.6	6.11

Clinical DDIs

- The AUC ratio was increased to a maximum of 1.5-fold for Metoprolol when a fed state was simulated compared to DDIs evaluated in a fasted state (Table 2).

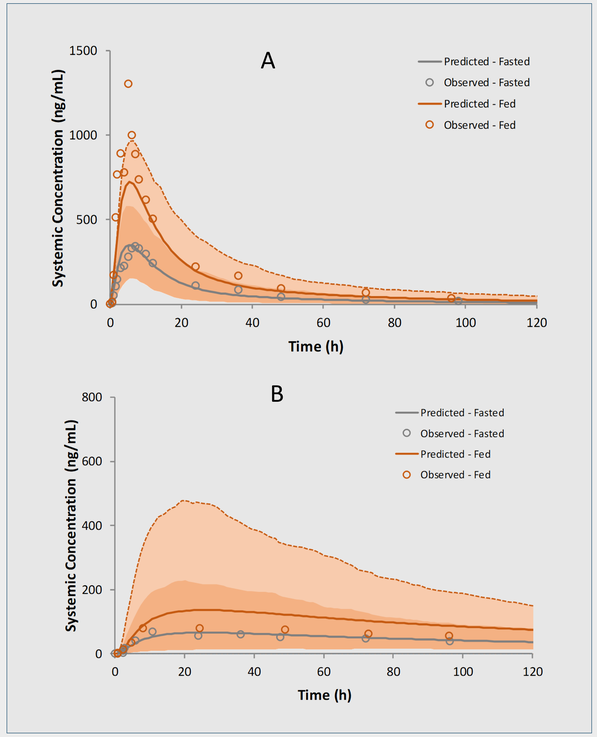
Table 2: Clinical DDI with AMIO: Impact of Fed state of AUC Ratio of victim drugs

Interaction	AUC Ratio Obs Fasted	AUC Ratio Pred Fasted	AUC Ratio Pred Fed	Fold Increase (Fed/Fasted)
Simvastatin	1.76 [4]	1.78	1.98	**1.11**
S-Warfarin	1.27 [5]	1.31	1.49	**1.14**
Metoprolol	1.81 [6]	1.79	2.71	**1.52**

Model Development

- The combined AMIO and MDEA model was developed based on information available in the literature [1]
- Model was further optimised based on the clinical study data where both fed and fasted conditions were evaluated.
- The model was able to simulate the clinical data picking up a 2.1- and 1.9-fold increase AUC for AMIO and MDEA, respectively, after amiodarone was dosed in fed state (Figure 1).
- This was comparable to the observed clinical data where a 2.5-and 1.6-fold increase was observed in AMIO and MDEA AUC, respectively [1].

Figure 1: Simulation of AMIO (A) and MDEA (B) in fed and fasted conditions after a single oral dose of 600mg



CONCLUSION(S)

- Current work focussed on developing a mechanistic physiologically based model which is able to simulate the magnitude of the increase in exposure after AMIO is administered with food.
- When AMIO is administered after a subject has eaten a high fat meal there is an apparent 2-3 fold increase in systemic exposure[1].
- This may have implications in clinical setting where: increased AMIO exposure could lead to increased DDIs.
- AMIO is a poorly soluble drug, determining the intrinsic solubility and distribution were key to ensure accurate performance of the model.
- Distribution of the metabolite MDEA, also needed to be incorporated to fully capture the pharmacokinetic and DDI profiles
- Current model captured both the PK profile in fasted and fed state
- Magnitude of the food effect was simulated to be 2.1- and 1.9-fold increase in AMIO and MDEA systemic exposure, respectively.
- Simulation of the clinical DDIs showed an increase in the magnitude of the interaction when AMIO was dosed in fed state
- Up to 1.5-fold increase in AUC ratio observed for Metoprolol when dosed with AMIO after a high fat meal

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