AAPS Poster Number 3635

Why multiple dosing of a victim drug with auto-inhibition exhibits lower drug-drug interaction in comparison to its single dose regimen?

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Purpose

Drug-drug interaction (DDI) depends on the fraction of the victim drug metabolised by the inhibited enzyme (fm). For a victim drug which also exhibits auto-inhibition fm changes over time. We investigated the impact of such changes in single and multiple dosing (SD and MD) regimens and its impact on the DDI using a mechanistic dynamic model in the Simcyp Simulator (V12 R2) using drug X as an example.

Input data for elimination:

CYP recombinant enzyme phenotyping:

CYPs	Vmax (1/min)	Km (μM)	ISEF	fu(inc)
CYP3A4	12.3	6.68	0.157	0.830
CYP1A2	1.11	48.0	0.372	0.860
CYP2J2	3.35	11.8	1.00	0.860
CYP3A5	0.732	23.9	0.157	0.870

ISEF: inter systemic extrapolation factor
fu(inc): unbound fraction in incubates

Other elimination property:

In vitro	*Uptake hep* (total/passive hepatic uptake ratio)	1.60
	Human liver microsomes CLint (μL/min/mg) [1)]	5.28 (CV: 30%)
	Human liver microsomes fu(inc)	0.81
	Biliary clearance (μL/min/10^6 cells)	0 [2)]
In vivo	CLr (L/h)	0 [2)]

1) FMO-3 contribution suggested from heat-treated HLM and recombinant enzyme
2) Assumption: CLbile(rat)=CLbile(human)=0; CLr(rat)=CLr(human)=0

The victim drug X is cleared by CYP1A2, 2J2, 3A4, 3A5 and FMO-3. The *in vitro* contribution of hepatic CYP3A4, FMO-3 and other CYP enzymes was 78%, 20%, and 2%, respectively.

In vitro CYP inhibition constants:

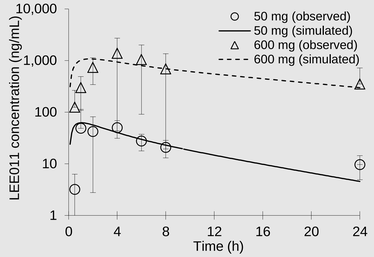
CYPs	Competitive		Time-dependent		
	Ki (μM)	fu(inc)	KI (μM)	kinact (1/h)	fu(inc)
CYP1A2	16	0.82	Not observed	Not observed	-
CYP2E1	31 (=IC50/2)	0.80	Not observed	Not observed	-
CYP3A4	35	0.86	5.06	1.47	0.80

Inhibitory effects of drug X on the metabolism of probe substrates were investigated in HLM.

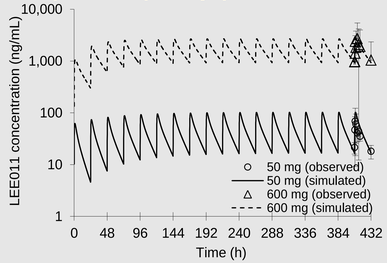
Drug X is a mechanism-based inhibitor of CYP3A4.

PK model validation:

Single dose



Multiple dose (18 days)



		N	Cmax (ng/mL)	AUC (0-24h) (ng·h/mL)	Tmax (h)
600 mg, p.o., single dose	Simulated	24	1134.8 (475.7-2757.0)	14375.8 (2963.6-47664.7)	1.99 (0.76-4.65)
	Observed	4	1443 (455-3200)	15220 (3857-34992)	3.00 (2.00-4.00)
600 mg, p.o., q.d. multiple dose	Simulated	24	2727.4 (996.0-5380.7)	39421.1 (9465.6-93965.8)	1.83 (1.09-2.90)
	Observed	4	2728 (943-5860)	39761 (9968-89685)	4.00 (2.00-4.00)

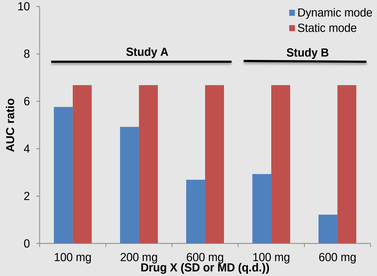
Data expressed as mean with range in parenthesis.

The predicted AUC and Cmax using the established dynamic model of drug X were in line with the clinical observations available after single and multiple dosing (50-600 mg p.o.).

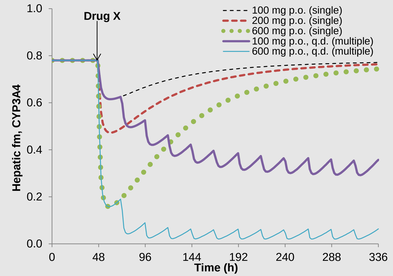
Effect of time-dependent fm change on DDI prediction:

	Drug X	Ketoconazole	Volunteer
Study A	SD at day 3	MD (200 mg, p.o., b.i.d.), 15 days	Healthy, Caucasian (n=24)
Study B	MD (q.d.) at day 3-15		

AUC ratio of drug X with ketoconazole



fm,CYP3A4 of drug X without ketoconazole



The dynamic simulation of Study A changed a 5.76-, 4.92- and 2.69-fold (geometric mean) in the AUC ratio after SD of drug X at 100, 200 and 600 mg p.o., respectively. In Study B, the predicted AUC ratios of drug X (100 and 600 mg p.o.) changed to 2.93- and 1.22- fold, respectively. As a result of victim drug auto-inhibition in Study A, there was a dose-dependent decrease in the fraction of the CYP3A4 contribution to the total hepatic intrinsic clearance. The decrease was profound and sustained in Study B where multiple doses of the victim drug were administered.

Conclusion

In static DDI models fm is assumed to be constant. However, this assumption is not valid when the victim drug also exhibits auto-inhibition (or auto-induction). Only mechanistic dynamic models can incorporate time-varying nature of fm values. Such models can provide reliable prediction of DDI and also explain the reduced level of DDI in MD compared to SD administration of the victim drug with a dose-dependent manner.

Funding/Grants/Encore reference

No external fund was used to carry this research study.