Challenges in predicting the drug-drug interaction between dextromethorphan and rifampicin using a physiologically based pharmacokinetic (PBPK) model that includes three metabolites of dextromethorphan

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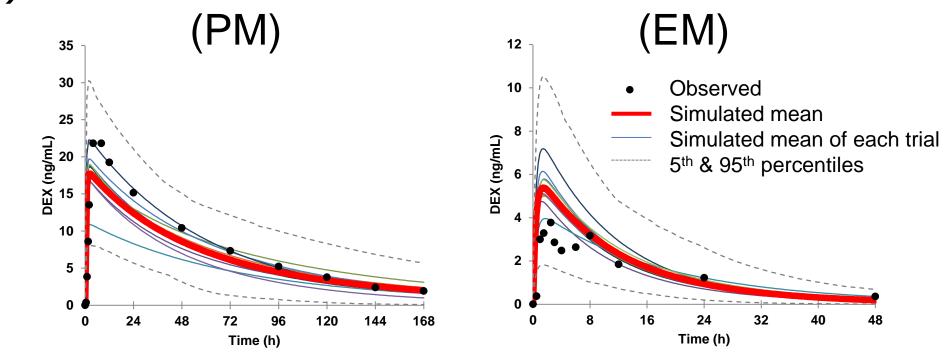
Background

A significant drug-drug interaction (DDI) was observed between dextromethorphan (DEX, a CYP2D6 substrate) and rifampicin (RIF, a well-known CYP3A4 inducer)[1]. The finding is surprising in that CYP2D6 plays a major role in the metabolism of DEX while CYP3A4 plays a minor role and it is generally perceived that CYP2D6 is non-inducible. The current study aims to use physiologically-based pharmacokinetic (PBPK) modelling to investigate the complex mechanism of clinical DEX-RIF DDI. For this purpose, the Simcyp Simulator (V14R1) was used to develop PBPK models for DEX and its 3 metabolites using prior *in vitro* and *in vivo* data and utilise these to explain clinically observed DEX-RIF DDI.
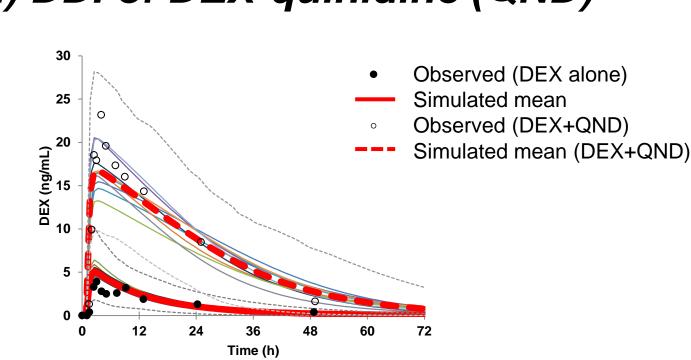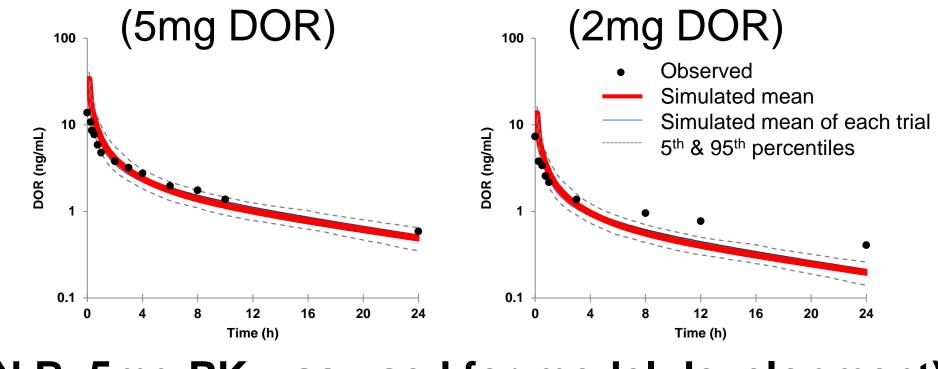
Method

DEX and its 3 metabolites

As an *in vitro* and *in vivo* probe substrate for CYP2D6, DEX undergoes O-demethylation to dextrorphan (DOR) and N-demethylation to 3-methoxymethorphinan (3MM)[2,3]. Both metabolites are then further metabolised to 3-hydroxymorphinan (3HM). In addition to CYP2D6, CYP3A4 and UGTs are also involved in the elimination of DEX and its metabolites.
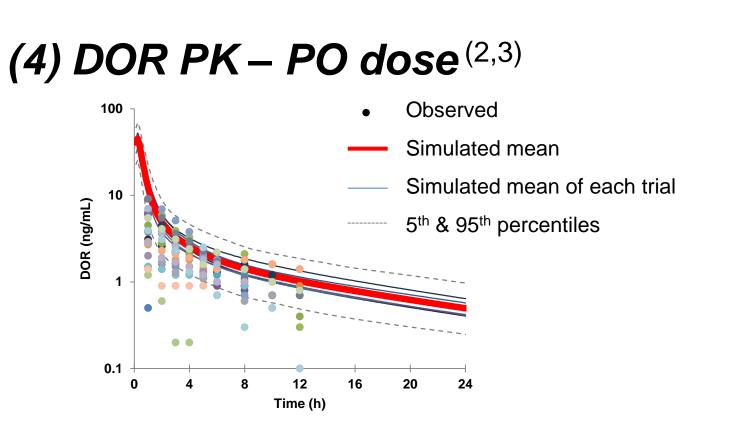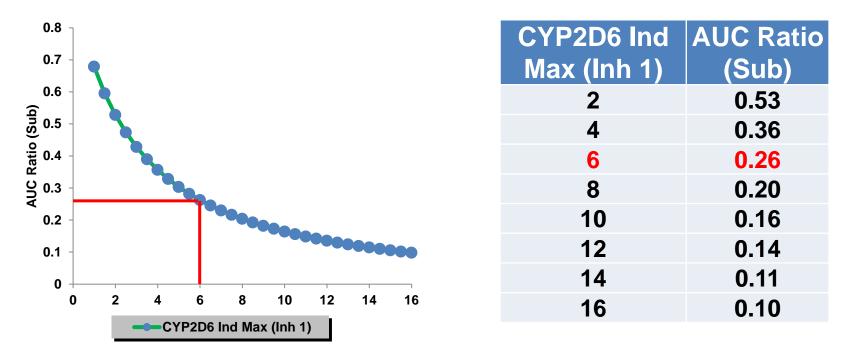

Model development

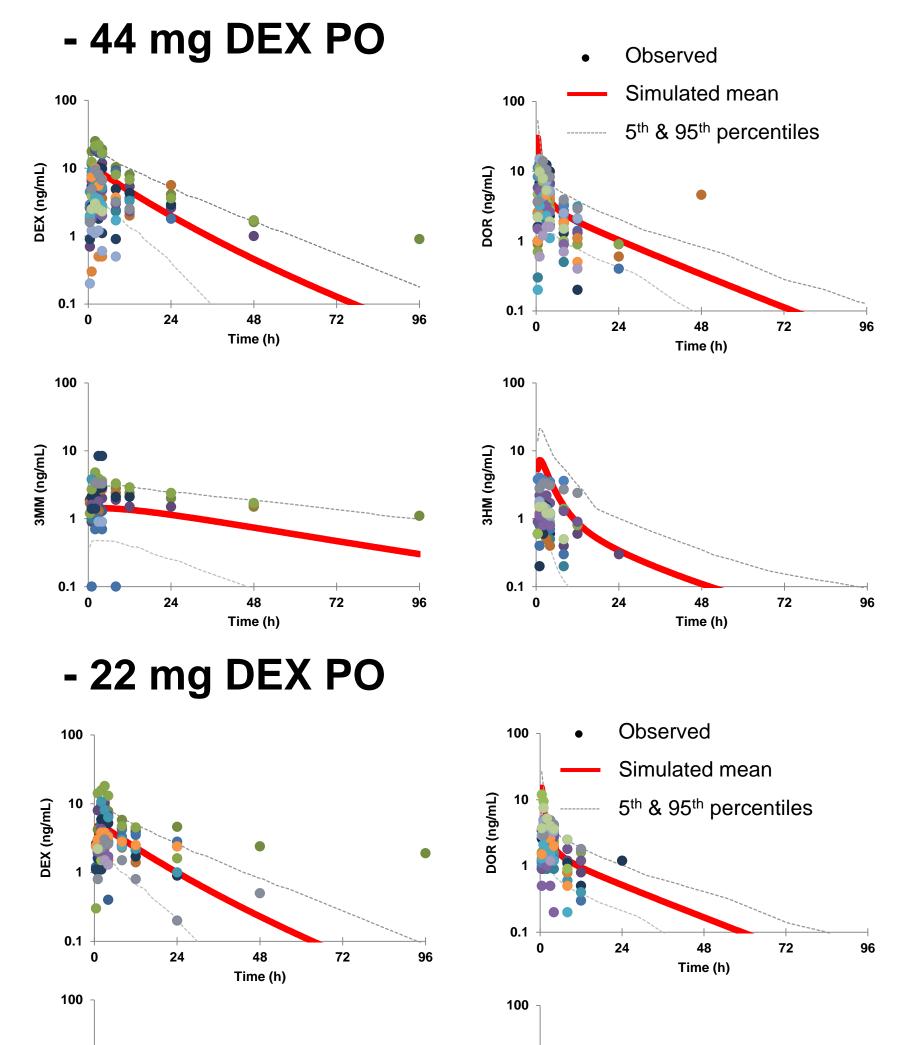The Simcyp Simulator (V14R1) was used to build the PBPK model for each of the moieties.

(1) The elimination data of the currently available DEX compound model in the Simulator library were revised using *in vivo* data for the major contributing enzyme CYP2D6 and *in vitro* data for the relative contributions of minor metabolic enzymes, collectively represented by CYP3A4.

(2) The DOR PBPK model was developed based on the clinical PK profiles after IV and PO dosing of DOR.

(3) Where relevant data for 3MM and 3HM were lacking the parent's data were used.

(4) The DEX PBPK model is linked to the 3 metabolite PBPK models via its elimination pathways.

Model performance verification

The performance of the PBPK models as a whole in CYP2D6 EM and PM subjects alone and with quinidine (QND) were verified using independent clinical data sets that had not been used in the model development.

Model application

The PBPK model of DEX and its metabolites with the default RIF library file in the Simcyp Simulator were used to simulate the clinical DEX-RIF DDI. Sensitivity analysis was used to explore the potential for 2D6 induction by RIF as a possible mechanism to recover the extent of observed DEX-RIF DDI level.

Simulation results

Model performance verification

(1) DEX PK in CYP2D6 PM and EM [4]

(2) DDI of DEX-quinidine (QND) [4]

(3) DOR PK – IV dose [5]

(N.B. 5mg PK was used for model development)

(4) DOR PK – PO dose [2,3]

(5) DEX and 3 metabolites PK [2,3]

- 44 mg DEX PO

- 22 mg DEX PO

(6) DDI DEX-QND [2,3]

Model application

(7) DDI DEX-RIF [1]

(8) Sensitivity analysis

CYP2D6 Ind Max (Inh 1)	AUC Ratio (Sub)
2	0.53
4	0.36
6	0.26
8	0.20
10	0.16
12	0.14
14	0.11
16	0.10

	DEX AUC$_{0-inf}$ ratio
Observed Mean (90% CI) [1]	0.27 (0.17-0.42)
Simulated Mean (90% CI) CYP3A4 induction alone	0.67 (0.65-0.70)
Simulated Mean (90% CI) With CYP2D6 induction	0.30 (0.28-0.31)

The whole PBPK model including DEX and its 3 metabolites was verified using various clinical studies in CYP2D6 EM and PM subjects, as well as a DDI between DEX and quinidine (QND).

Simulating only EM subjects, the observed DEX-RIF DDI could not be fully explained by induction of CYP3A4 alone (AUC ratio=0.67 simulated vs. 0.27 observed). Sensitivity analysis indicated that induction of CYP2D6 by RIF can recover the extent of clinical DDI, if no other mechanism were involved.

Discussion

It is generally accepted that CYP2D6 is non-inducible which presents a dilemma in explaining the observed DEX-RIF DDI data.

The simulated PK in CYP2D6 EM and PM subjects and clinical DEX-QND DDI observations support a CYP2D6 fm value of ~94% and a minor role for CYP3A4 in CYP2D6 EM subjects. RIF was adequately staggered 12 hours from DEX dosing in the DDI simulation, similar to the clinical study[1], so the possible effect of CYP2D6 inhibition can be ruled out.

Knowing that only limited *in vitro* and *in vivo* data have been reported on CYP2D6 induction[6,7] further studies are warranted.
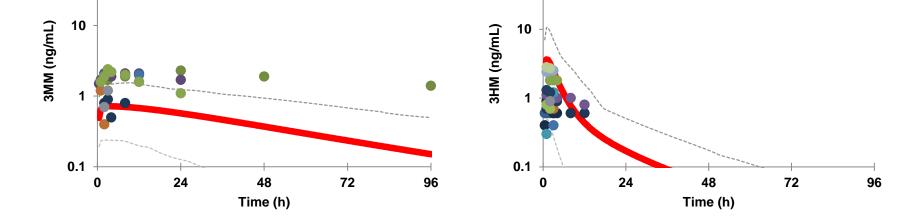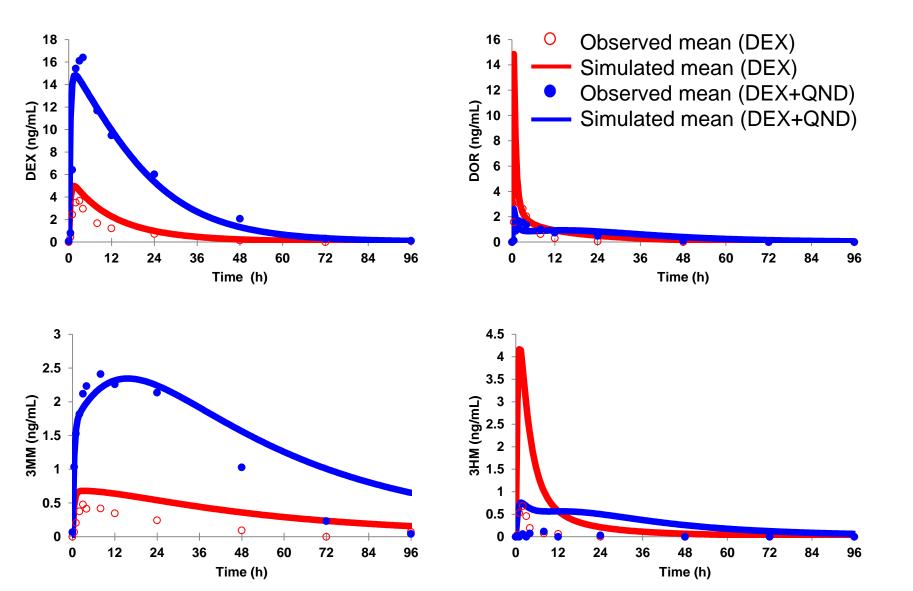
Conclusion

(1) A set of PBPK models has been developed for DEX and its 3 metabolites based on *in vitro* and *in vivo* data and used to explore the mechanism of the DEX-RIF DDI.

(2) The observed DEX-RIF DDI could not be fully explained by CYP3A4 induction alone.

(3) Apart from CYP3A4 induction, clinical DEX-RIF DDI may involve other unknown mechanisms.

References

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