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

Lu Gaohua1, Kim Crewe1, Rachel Rose1, Amin Rostami-Hodjegan1,2, Karen Rowland Yeo1, Masoud Jamei1

Simcyp Limited, Sheffield, UK & 2University of Manchester, Manchester, UK

Background

A significant drug-drug interaction (DDI) was observed between dextromethorphan (DEX, a CYP2D6 substrate) and rifampicin (RIF, a well-known CYP3A4 inducer)11. 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-methoxyxymethorphan (3MM)(2,3). Both metabolites are then further metabolised to 3-hydroxyxymethorphan (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 D6 induction by Rif as a possible mechanism to recover the extent of observed DEX-RIF DDI level.