Prediction of drug-drug interactions with oxycodone as assessed by changes in plasma concentration and pupil constriction using a physiologically based pharmacokinetic-pharmacodynamic model

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Background

Oxycodone is a widely prescribed and potent opioid agonist used to treat acute and chronic pain and is mainly metabolized by CYP3A4 and CYP2D6. An objective biomarker to examine the central effects of oxycodone on the μ-opioid receptor is pupil constriction[1-3] The aim of this study was to develop a physiologically based pharmacokinetic-pharmacodynamic (PBPK-PD) model for oxycodone to assess the impact of CYP2D6 polymorphisms and DDI with CYP3A4 and CYP2D6 inhibitors/inducers on plasma concentrations and pharmacodynamic effect as measured by pupil constriction.

Methods

A minimal PBPK model was developed for oxycodone in Simcyp V21R1. The absorption was described by a first order model with human intestinal permeability predicted using Caco-2 data. *In vitro* kinetic parameters for CYP2D6 and CYP3A4 were estimated by reverse translation using *in vivo* fm[4] and CL_{iv} data from a meta-analysis of 4 clinical studies[5-8]. The pupil constriction effect of oxycodone was modelled using a Sigmoid Emax model with an effect compartment, to take hysteresis between plasma and central oxycodone concentrations into account. The final input parameters are shown in Table 1 below.

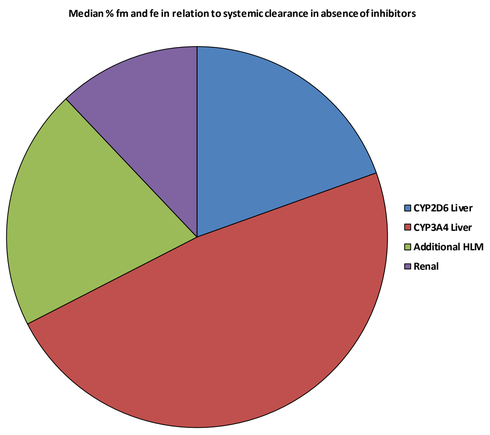

Table 1: Input parameters used in the oxycodone PBPK-PD model.

Input parameters	Value	Comments
Molecular weight	315.4 g/mol	Pubchem
Log P	1.1	Predicted value based on measured LogD at pH 7.4[16]
pKa	8.73	Meta-analysis from 3 measured values [18-20]
fu	0.583	Meta-analysis from 2 measured values[16, 21]
B/P	1.3	measured value[17]
Absorption	predicted fa and ka from Caco-2, Fugut=1, Qgut 4.89 L/h	Caco-2 data[22] , optimized Qgut to capture fg of 0.9
Vss	minimal PBPK with user input 3.1 L/kg	Meta-analysis from 5 measured values [5-8, 15]
CLint CYP2D6	10.7 µL/min/mg protein	estimated from CLiv[5-8] and in vivo fm[4]
CLint CYP3A4	15.93 µL/min/mg protein	
CL additional	6.49 µL/min/mg protein	
CL renal	4.5 L/h	in line with observed data[5]
Pharmacodynamic		
Keo	6 /h	Lalovic et al., 2006[4]
x50	0.1 µM	Lalovic et al., 2006[4]
Emax	-3.56	Hagelberg et al.,2009[9]
E0	0	

Results

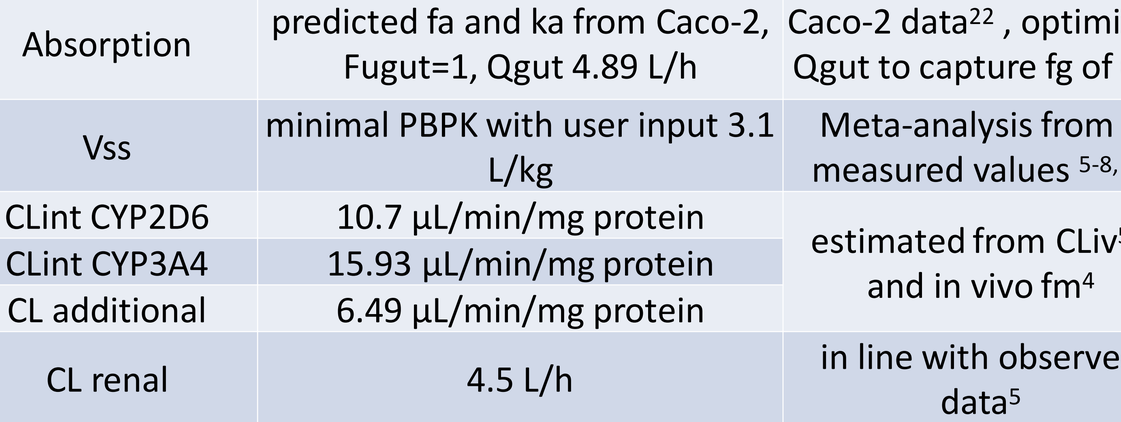

Figure 1. Simulated and observed mean plasma concentration time profiles after a single oral dose of oxycodone (0.18 mg/kg; free base) of in a population with mixed CYP2D6 phenotypes of healthy volunteers (left), and CYP2D6 PMs (grey) and UMs (blue)(right). Solid lines represent predicted profiles in 10 individual virtual trials. Solid circles represent observed data from Samer et al., 2010

Results

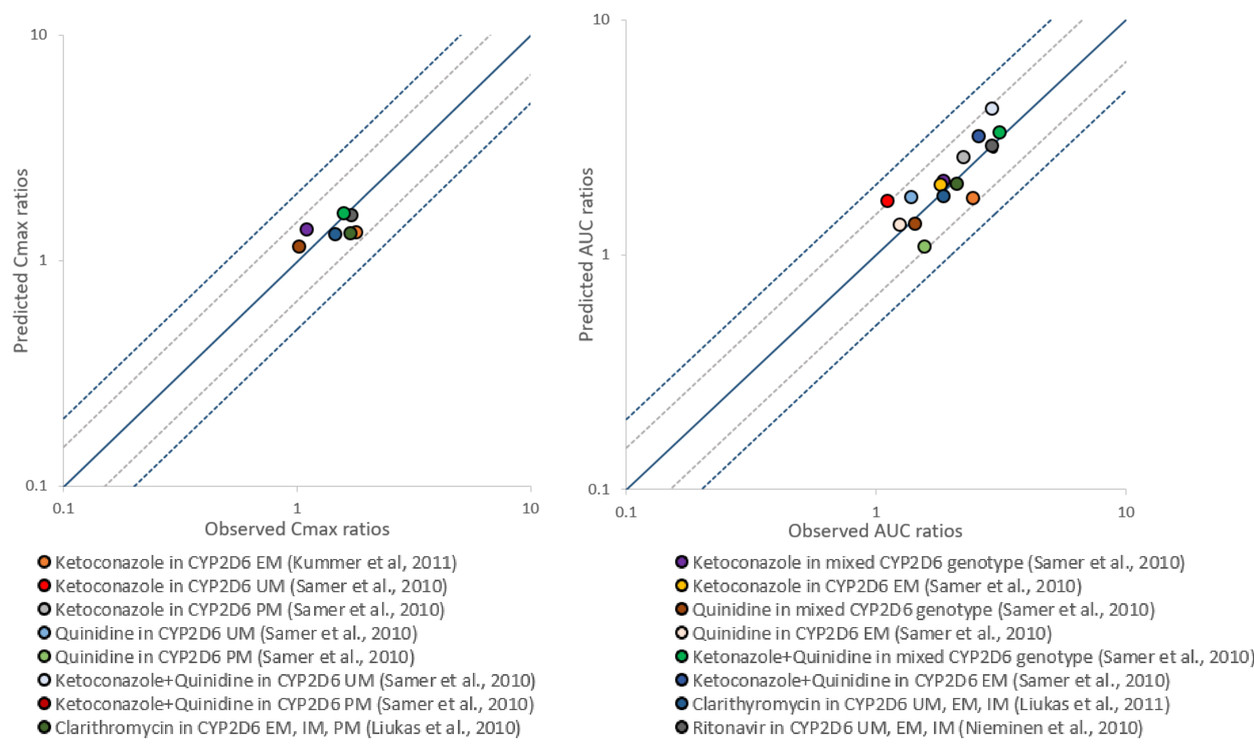

Figure 2. simulated and observed Cmax (left) and AUC (right) ratios of oxycodone in the presence of CYP3A4 and/or CYP2D6 inhibitors. The blue solid line represents unity. The grey and blue dashed lines represent 1.5- and 2-fold deviation from unity.

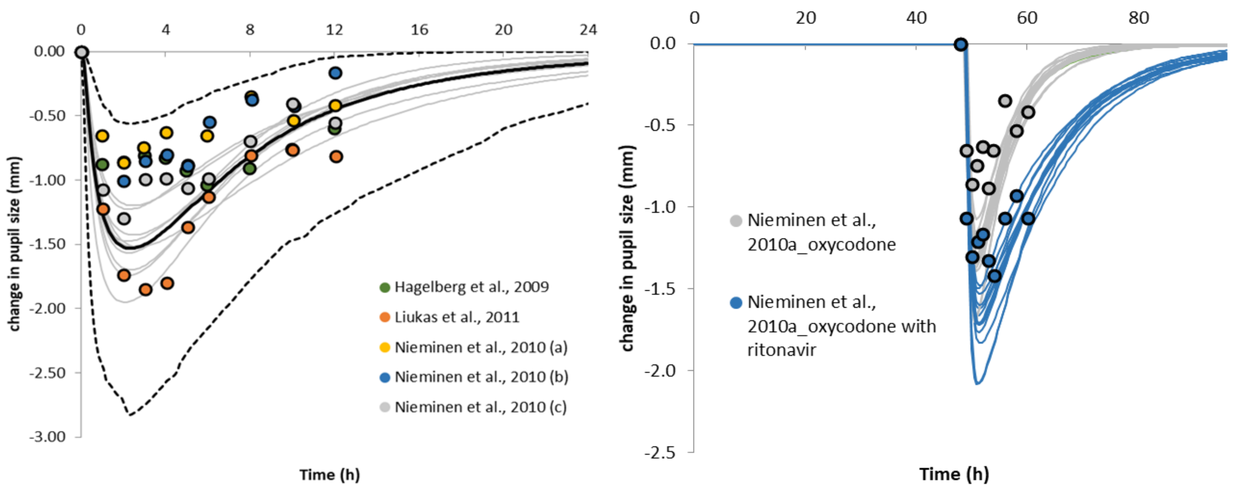

Figure 3. simulated and observed pupillary constriction after 8.89 mg oxycodone (left) and in the presence (blue circles and lines) or absence (grey circles and lines) of ritonavir (right). Solid lines represent predicted profiles in virtual trials. Solid circles represent observed data. Dashed lines represent 5th and 95th percentile of the virtual population.

Conclusions

The present study demonstrated that the developed PBPK-PD model of oxycodone can reasonably recover the impact of CYP2D6 genetic polymorphisms and DDI on oxycodone exposure (Figures 1 and 2).

The plasma exposure was coupled with a PD model and successfully simulated the pupillary constriction effects of oxycodone in subjects with population without CYP2D6 PMs and following the inhibition of oxycodone metabolism by ritonavir (Figure 3).

The current model can provide guidance on dose adjustment of oxycodone in subjects with different CYP2D6 phenotypes and in subjects co-dosed with other CYP3A4 and CYP2D6 perpetrators.

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