PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING OF ZIPRASIDONE IN PREGNANT WOMEN

Carla Biesdorf[1,2], Frederico Martins[3], Andrea Diniz[1]

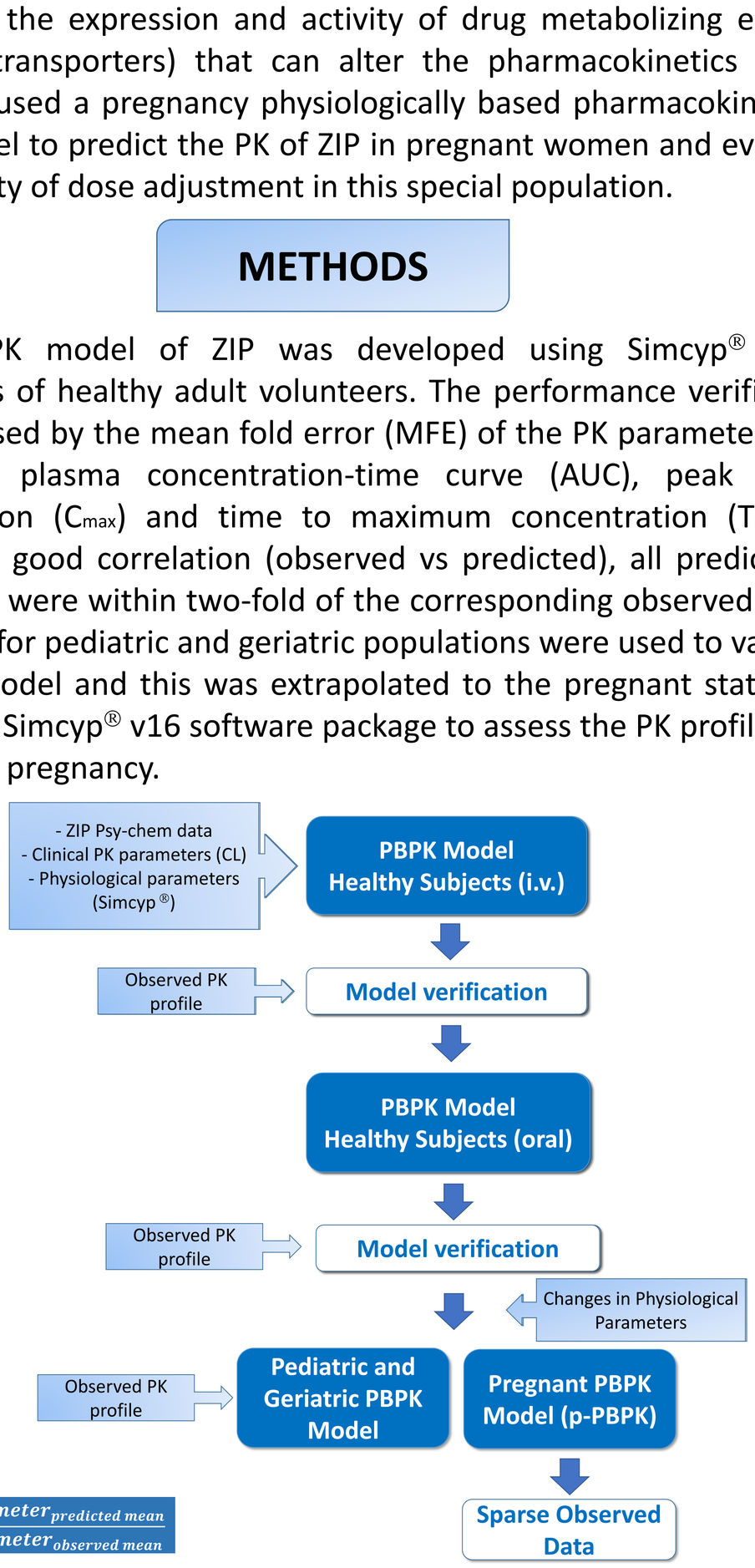
[1]Department of Pharmacy, State University of Maringá, Maringá, Brazil. [2]Indiana University School of Medicine, Indianapolis, USA. [3]Simcyp Limited (a Certara company), Sheffield, UK.

OBJECTIVES

Ziprasidone (ZIP) is an atypical antipsychotic drug used for the treatment of schizophrenia. The age of onset of schizophrenia is between 25 to 35 years old, which matches with the child-bearing potential. Pregnancy can induce physiological changes (i.e. increase in renal filtration, body fluid volume and hepatic portal blood flow, changes in the expression and activity of drug metabolizing enzymes and drug transporters) that can alter the pharmacokinetics (PK) of drugs. We used a pregnancy physiologically based pharmacokinetic (p-PBPK) model to predict the PK of ZIP in pregnant women and evaluated the necessity of dose adjustment in this special population.

METHODS

A full PBPK model of ZIP was developed using Simcyp® virtual populations of healthy adult volunteers. The performance verifications were assessed by the mean fold error (MFE) of the PK parameters: area under the plasma concentration-time curve (AUC), peak plasma concentration (C_{max}) and time to maximum concentration (T_{max}). As criterion of good correlation (observed vs predicted), all predicted PK parameters were within two-fold of the corresponding observed values. Simulation for pediatric and geriatric populations were used to validated the built model and this was extrapolated to the pregnant state using the p-PBPK Simcyp® v16 software package to assess the PK profile of ZIP throughout pregnancy.



$$MFE = \frac{PK\ parameter_{predicted\ mean}}{PK\ parameter_{observed\ mean}}$$

Figure 1: Schematic representation of the workflow of PBPK model development.

Table 1 Parameter Values used for Ziprasidone PBPK model

Parameters	Value
MW (g mol^{-1})	412.94
Log P	3.60
pKa	6.58
Absorption	First-order Model
$P_{eff,man}$ (10^{-4}cm s^{-1})	1.66
$P_{app,\ Caco\text{-}2}$ (10^{-6} cm s^{-1})	12.30
f_a	0.90
k_a (h^{-1})	0.32
Distribution	Full PBPK Model
V_{ss} (l kg^{-1})	1.03
f_u	0.01
B:P	0.64
Elimination	
CL_{iv} (l h^{-1})	22.80
% contribution 3A	33.00

Figure 2: Schematic illustration of the Simcyp pregnancy physiologically based pharmacokinetic (p-PBPK) model [1].

RESULTS

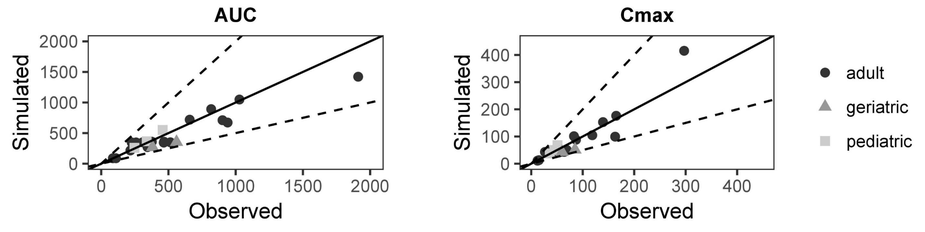


Figure 3: Comparison between simulated and observed PK parameters from several studies in the literature for non-pregnant population. Solid lines represent line of unity, dashed lines represent 2-fold difference.

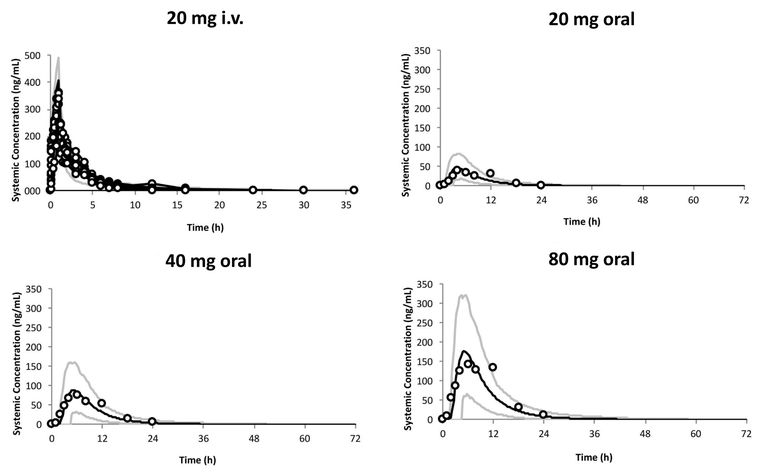


Figure 4: PK profiles in non-pregnant population. Simulation (mean predictions in black lines and 5^{th}-95^{th} percentiles of predictions in grey lines) of PK profiles for an i.v. administration of 20 mg infused over one hour and for oral administrations of 20, 40 and 80 mg of ziprasidone (under fed conditions). Simulations were compared with observed clinical data (circles) from 20 mg i.v administration [2], 20, 40, 80 mg oral administration [3].

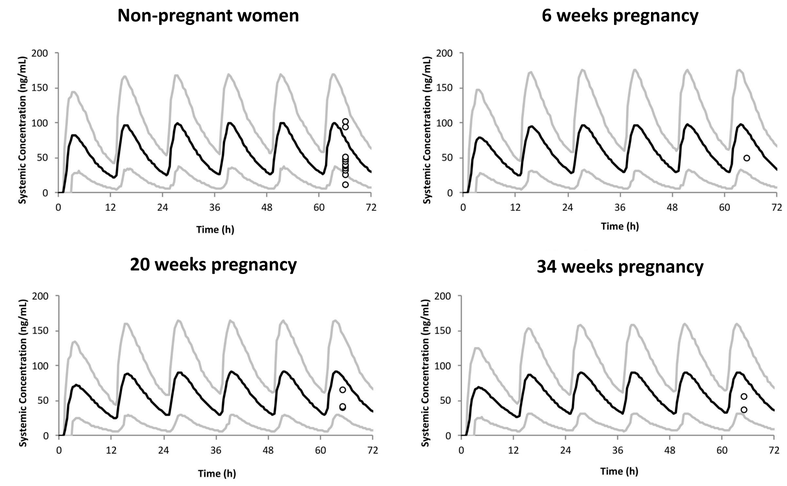


Figure 5: PK profiles in non-pregnant and pregnant women. Simulation (mean predictions in black lines and 5^{th}-95^{th} percentiles of predictions in grey lines) of PK profiles for oral administration of 40 mg twice daily, in non-pregnant situation and during the sixth, twentieth and thirty-fourth weeks of pregnancy. Simulations were compared with the observed clinical data (circles) after 40 mg oral twice-daily administration [4] .

Table 2 Predicted steady-state PK parameters of Ziprasidone during different periods of pregnancy (expressed as mean data)

Parameters	Baseline[a]	6 weeks[a]	20 weeks[a]	34 weeks[a]
Dose	40 mg, b.i.d.	40 mg, b.i.d.	40 mg, b.i.d.	40 mg, b.i.d.
f_a	0.81	0.81	0.81	0.81
f_u	0.01007	0.01038	0.01131	0.01285
CL_{int} (l h^{-1})	3914.11	3690.45	3461.41	3115.07
CL/F (l h^{-1})[b]	69.94	71.23	74.41	71.48
$AUC_{0\text{-}12h,ss}$ (ng ml^{-1} h^{-1})	655.39	666.64	641.00	656.12
C_{max} (ng ml^{-1})	96.57	92.11	86.17	85.99
C_{trough} (ng ml^{-1})	22.15	24.77	25.55	27.68
T_{max} (h)	3.22	3.32	3.33	3.34
V_{ss} (l kg^{-1})	1.15	1.19	1.29	1.43

$AUC_{0\text{-}12h,ss}$, area under the plasma concentration-time curve from 0-12 h at steady-state; b.i.d., twice daily; CL_{int}, intrinsic clearance; C_{max}, maximum concentration; C_{trough}, trough concentration; f_a, fraction absorbed from dosage form; f_u, fraction of drug unbound in plasma; V_{ss}, volume of distribution at steady-state; T_{max}, time to maximum concentration;
[a]baseline, non-pregnant women; 6 weeks, first trimester pregnancy; 20 weeks, second trimester pregnancy; 34 weeks, third trimester pregnancy
[b] Clearance computed as F x Dose/AUC.

CONCLUSION

The p-PBPK model predicted the impact of physiological changes during pregnancy on PK and exposure of ziprasidone, suggesting that dose adjustment is not necessary in this special population.

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References:

[1] Gaohua L, et al. A pregnancy physiologically based pharmacokinetic (p-PBPK) model for disposition of drugs metabolized by CYP1A2, CYP2D6 and CYP3A4. British Journal of Clinical Pharmacology 2012; 74: 873–885.
[2] Sutton SC, et al. The impact of gastric pH, volume, and emptying on the food effect of ziprasidone oral absorption. The AAPS journal 2017; 19: 1084-90.
[3] Miceli JJ, et al. The effect of food on the absorption of oral ziprasidone. Psychopharmacology bulletin 2007; 40: 58-68.
[4] Westin AA, et al. Treatment With Antipsychotics in Pregnancy: Changes in Drug Disposition. Clinical pharmacology and therapeutics 2018; 103: 477-84.