

Population pharmacokinetics of risperidone and 9-hydroxy-risperidone in psychiatric patients

M. Guidi^{1,2}, F. Vandenberghe³, E. Choong³, T. Buclin¹, C.B. Eap^{2,3}, C. Csajka^{1,2}

¹Division of Clinical Pharmacology, University Hospital Center, University of Lausanne, Lausanne, Switzerland; ²School of Pharmacy, Department of Pharmaceutical Sciences, University of Geneva and Lausanne, Geneva Switzerland; ³Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, University Hospital Lausanne, Prilly-Lausanne, Switzerland.

OBJECTIVES

- To characterize the pharmacokinetics of risperidone (RISP) and 9-hydroxy-risperidone (9OHRISP).
- To test the influence of genetic polymorphism along with non-genetic factors on drug and metabolite levels.
- To compare the active moiety (AM=RISP+9OHRISP) expositions between metabolic groups (drug and metabolite have the same affinity for the D₂ receptor).

METHODS

Data

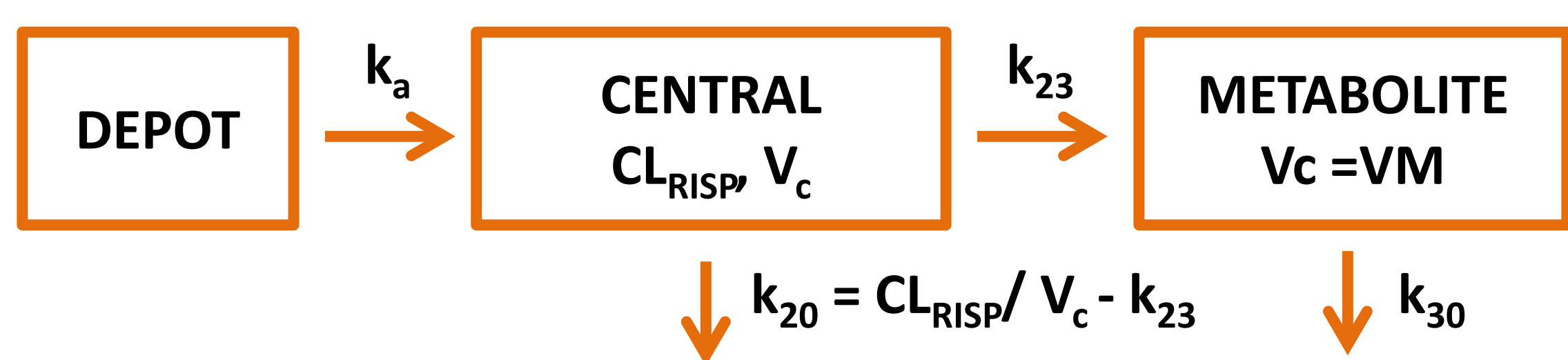
- 144 concentrations of both RISP and 9OHRISP from 127 patients.

Covariates

- Demographic: gender, race, age, body weight, height.
- Co-medications: inducers and inhibitors of P-glycoprotein (PGP) and cytochromes (CYP) 3A4 and 2D6.
- Clinical variables: liver function tests (ALT and AST) and creatinine clearance.
- Genetic polymorphisms: *CYP2D6*, *CYP3A4* rs4646437 C>T, *CYP3A4**1B, *CYP3A5**3, *CYP3A7**1C, *POR* rs1057868 (*28 C>T), *PXR* rs7643645, *PXR* rs1523130 and *PXR* rs2472677.

Data analysis

- One-compartment model with first-order absorption and elimination for both RISP and 9OHRISP, with linear metabolization from drug to metabolite (NONMEM®).
- Same distribution volumes were associated to RISP and 9OHRISP because of identifiability problems.



- Derived parameters: drug over metabolite concentrations ratio (D/M), drug, metabolite and active moiety AUC₀₋₂₄ (AUC_{0-24, AM}=AUC_{0-24, RISP}+ AUC_{0-24, 9OHRISP}).
- Interpatient variability was assigned to CL_{RISP} and k₂₃.
- An additive error model was employed to describe intra-patient variability for both drug and metabolite.

Covariates analyses

- Linear models were used for demographic, clinical variables and co-administered drugs (coded as 0 or 1) on both CL_{RISP} and k₂₃.
- A fixed effect was associated to each genotype group to assess genetic impact on CL_{RISP} and k₂₃ (rich model). Linear models as a function of the number of functional alleles were eventually employed.

RESULTS

- *CYP2D6* poor metabolizer (PM, n=8) phenotype had the most significant impact on CL_{RISP} and k₂₃.
- No difference between *CYP2D6* intermediate (IM, n=33), extensive (EM, n=81) and ultra (UM, n=5) metabolizers were observed.
- CL_{RISP} was also affected by AGE.
- The significant covariates explained altogether 48% and 66% of the interpatient variability on CL_{RISP} and k₂₃.

Parameter	Population mean			
	Estimate	SE(%)	IIV (%)	SE(%)
CL _{RISP, IM/EM/UM} (l/h)	22.9	7	40	52
θ _{AGE, CL_{RISP}}	-0.26	31		
θ _{PM, CL_{RISP}}	-0.79	5		
V _c (l)	184	9		
k _a (h ⁻¹) (FIX)	3.11			
k _{23, IM/EM/UM} (h ⁻¹)	0.13	24	25	76
θ _{PM, k₂₃}	-0.92	4		
k ₃₀ (h ⁻¹)	0.045	24		
σ _{add, RISP} (ng/ml)	0.039	11		
σ _{add, 9OHRISP} (ng/ml)	0.034	16		

- CL_{RISP} and D/M were estimated to be respectively 4.8 l/h and 4.2 in PM and 22.9 l/h and 0.34 in IM/EM/UM patients.

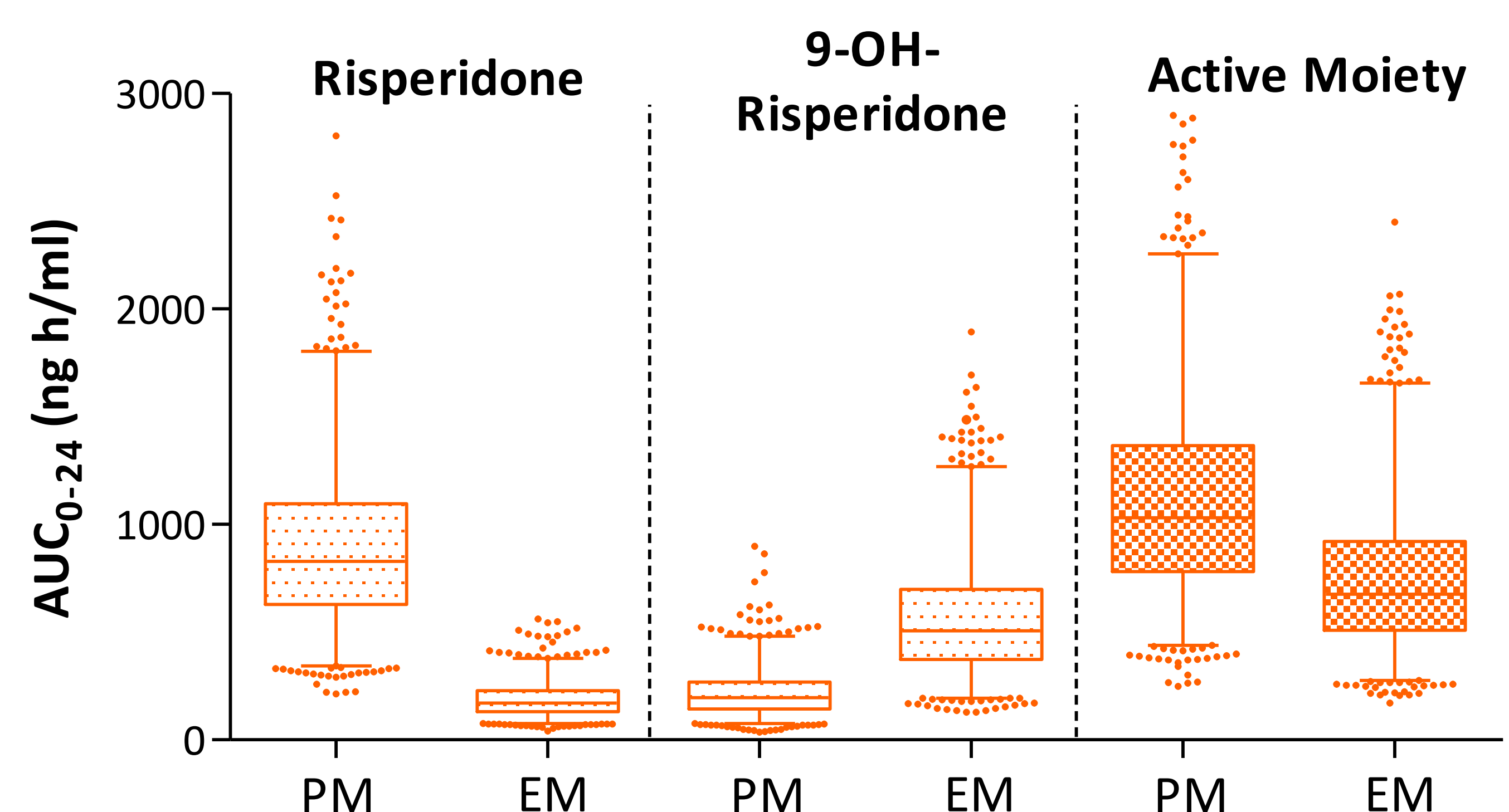
Final model equations:

$$CL_{RISP} = CL_{RISP, IM/EM/UM} * (1 + \theta_{PM, CL_{RISP}} * I_{PM}) * (1 + \theta_{AGE, CL_{RISP}} * (AGE - MAGE) / MAGE)$$

$$k_{23} = k_{23, IM/EM/UM} * (1 + \theta_{PM, k_{23}} * I_{PM})$$

with I_{PM} indicator variable taking the value of 1 for poor metabolizers (PM), 0 otherwise; and MAGE = 37 years, mean age of our population.

- AUC₀₋₂₄ of the active moiety derived by simulation for the PM is significantly higher than that estimated for the IM/EM/UM patients:



CONCLUSIONS

- *CYP2D6* polymorphisms accounts for the majority of the variation in risperidone and 9-hydroxy-risperidone levels.
- The significant difference found in the active moiety exposure between poor and intermediate or good metabolizers might explain reported higher rates of side-effects and drop-out in risperidone poor metabolizers [1].

[1]de Leon, J., et al., *The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation*. J Clin Psychiatry, 2005. 66(1): p. 15-27.