Population pharmacokinetic modelling to characterize (es)citalopram exposure in a large cohort of psychiatric patients

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Context and objectives: Citalopram is the racemic combination of R and S-citalopram (escitalopram), the latter being the active form. Both enantiomers are mainly metabolized by *CYP2C19* (≈37%) and to a minor extent by *CYP3A4* (≈35%) and *CYP2D6* (≈28%) (1). Citalopram and escitalopram are widely prescribed for depression with or without anxiety (2). About 30-50% of patients suffering from depression do not respond properly to their antidepressant treatment (3). In 2018, a study found a relationship between *CYP2C19* genotype, escitalopram exposure and treatment failure in a large cohort of patients (4).

The objective of this study was to characterize the pharmacokinetics (PK) of escitalopram in a large cohort of psychiatric patients, to quantify the impact of *CYP2C19* polymorphisms and identify other sources of variability.

Methods: The analysis was performed on steady-state escitalopram plasma concentrations collected in 1744 patients enrolled in an ongoing pharmacogenetic study (PsyMetab) (5) conducted at the Departments of Psychiatry of the Lausanne and of the Geneva University Hospitals and in a private mental health care center (Les Toises; Lausanne, Switzerland) or included in the clinical follow-up study (PsyClin) at the Department of Psychiatry of the Lausanne University Hospital. The population PK (popPK) analyses were performed using the NONMEM program. At first, a base popPK model was built to describe the typical concentration-time profile and the variability in the psychiatric population comparing models of increasing complexity. Due to the paucity of data within a few hours after drug administration, the absorption constant rate (k_a) was fixed at 0.8 h^{-1} according to the literature (6, 7). Second, the effect of covariates, namely age, sex and bodyweight, were investigated on clearance (CL). Finally, a sub-analysis on *CYP2C19* genotyped patients tested the influence of genetics (**1, *2, *3* and **17* alleles) on escitalopram PK. Five phenotypic groups (poor metabolizers (PM), intermediate metabolizers (IM), normal metabolizers (NM), rapid metabolizers (RM) and ultra-rapid metabolizers (UM)) were predicted using genetics.

Results : A total of 2201 escitalopram concentrations (median (range) of 1 (1-22) blood samples per patient) were available for the analysis. The median (range) escitalopram maintenance dose was 20 mg (4 - 60 mg) once daily. A one-compartment model with first-order absorption and elimination best described the escitalopram PK. The base model typical parameter estimates with interindividual variability (IIV, CV%) were: CL, 17.4 L/h (65 %); volume of distribution, 2410 L and k_a, 0.8h^{-1}. None of the studied covariates showed any significant effect on CL.

The reduced model conducted on *CYP2C19* genotyped patients (n=328) showed an influence of *CYP2C19* polymorphisms on CL. Analyses of the influence of each of the five genetic groups indicated a CL of 12.6 L/h in PM (n=9), of 17 L/h in IM (n=99), of 22.4 L/h in NM (n=133), of 22.1 L/h in RM (n=77) and of 19.8 L/h in UM (n=10). No statistical difference was observed between the NM, RM and UM

groups and these data were reduced into a single group. The final model estimated a significant reduction of 43% and 23% in CL between PM (12.6 L/h) and IM (17.1 L/h), respectively, compared to NM, RM and UM (22.2 L/h). The *CYP2C19* genetic polymorphism explained 5.4% of the initial observed variance on CL.

Conclusions : Our popPK model conducted in a large cohort of unselected psychiatric patients is in line with previously published models developed on psychiatric or non-psychiatric patients (6, 8, 9). This analysis confirms the high interpatient variability in escitalopram concentrations described in previous studies (9, 10) and the strong influence of *CYP2C19* polymorphism on its elimination (4, 9). As observed in a previous study, this analysis did not show an influence of age, sex and weight on escitalopram CL (10), which is in contradiction with the findings of another study showing an influence of age and weight (9). Despite the wide recommended concentration targets for this drug (11), some poor metabolizer patients might be overdosed in case of high dosage regimens and are thus at higher risk of therapeutic failure. Our results support the recommendation of a 50% dosage reduction in poor metabolizer (12).

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