

Comparison of escitalopram pharmacokinetics in HIV infected individuals with an uninfected psychiatric cohort

Perrine Courlet¹, Guidi Monia^{1,2}, Anaïs Glatard^{1,3}, Cavassini Matthias⁴, Thierry Buclin¹, Catia Marzolini⁵, Chin B. Eap^{2,3}, Laurent A. Decosterd¹, Chantal Csajka^{1,2}.

¹Service of Clinical Pharmacology, University Hospital Center, University of Lausanne, Lausanne, Switzerland

²School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland

³Unit of Pharmacogenetics and Clinical Psychopharmacology, Center for Psychiatric Neuroscience, Hospital of Cery, University Hospital Center, Prilly, Switzerland

⁴Division of Infectious Diseases, University Hospital Center, University of Lausanne

⁵Departments of Medicine and Clinical Research, University Hospital of Basel and University of Basel, Switzerland

Objectives

- ♦ To analyse the population pharmacokinetics (PK) of escitalopram (metabolized by CYP2C19, 3A4, 2D6) in HIV-infected patients and uninfected psychiatric patients
- ♦ To assess the potential impact of HIV infection and antiretroviral treatments on escitalopram disposition
- ♦ To identify other sources of variability influencing drug exposure, notably drug-drug interactions (DDI)

Methods

Data

- ♦ HIV-infected patients:
 - Swiss HIV Cohort Study (SHCS #815)
 - 39 subjects (18 citalopram and 21 escitalopram), 50 plasma samples under citalopram (n=25) or escitalopram (n=25) intake
 - When only the racemate was available, citalopram doses were divided by 2 and concentrations were derived using an S/R ratio of 0.45 (1).
- ♦ Uninfected psychiatric patients
 - Pharmacogenetic study (PsyMetab) or clinical follow-up
 - 71 subjects (escitalopram), 109 plasma concentrations
- ♦ Plasma concentrations ranged from 4 to 139 ng/mL, collected at unselected times between 0.02 and 29 hours after drug intake.
- ♦ Doses varied between 5 and 40 mg daily for escitalopram and citalopram
- ♦ Therapeutic reference range of escitalopram: 15-80 ng/mL (2)

Structural and error models

- ♦ One-compartment model with first-order absorption and elimination (NONMEM® 7.4 with FOCE-I method) on log-transformed data
- ♦ Absorption rate constant fixed to 0.4 h⁻¹ based on likelihood profile and bootstrap evaluation
- ♦ Additive error model

Covariate model

- ♦ Continuous: age, body weight
- ♦ Discrete: cohort (HIV vs psychiatric), citalopram treatment, sex and comedications (categorized as inhibitors or inducers)

Model validation

- ♦ 151 plasma concentrations from 111 psychiatric patients

Simulations

- ♦ Monte-Carlo simulations were performed for 10 and 20 mg escitalopram regimens to predict the percentage of patients within the therapeutic targets, with and without co-administration of CYP2C19 inhibitors.

Results

Table 1: Population Description

Characteristics	n (%) or median [IQR]	
	Model development (N=110)	Model validation (N=111)
Age (years)	48 [36-56]	46 [35-58]
Body weight (kg)	77 [62-85]	69 [56-81]
HIV cohort	39 (35)	2 (2)
Men	55 (50)	69 (62)
≥ 1 CYP2C19 inhibitors	13 (12)	21 (19)
≥ 1 CYP3A4 inhibitors	17 (16)	2 (2)
≥ 1 CYP2D6 inhibitors	13 (12)	11 (10)
≥ 1 P-glycoprotein inhibitors	39 (36)	34 (31)
≥ 1 CYP2C19 inducers	11 (10)	1 (1)
≥ 1 CYP3A4 inducers	2 (2)	0
≥ 1 P-glycoprotein inducers	4 (4)	0

- ♦ CYP2C19 inhibitors were all represented by proton-pump inhibitors.

Table 2: PK parameters in the final model with bootstrap results

Final population pharmacokinetic model		Bootstrap results (n=2000)	
Parameter	Estimate (RSE %)	Median	CI 95%
k _a (h ⁻¹) FIX	0.4	0.4	
CL/F (L/h)	25.5 (7)	25.7	21.8-29.7
V/F (L)	1270 (37)	1278	569-4414
BSV CL/F (%)	54.1 (11)	51.9	38.2-69.4
θ _{inh2C19}	-0.2 (47)	-0.3	-0.5 to -0.1
Add. residual error (%)	29.6 (17)	41.3	25.9-56.1

- ♦ Except for co-administration of at least one CYP2C19 inhibitor that decreased escitalopram clearance by 20%, no other factors showed any influence on escitalopram PK.
- ♦ The external validation analysis showed a non-significant bias of -1% (CI_{95%}: -4% to 2%) with a precision of 20% for individual predictions.

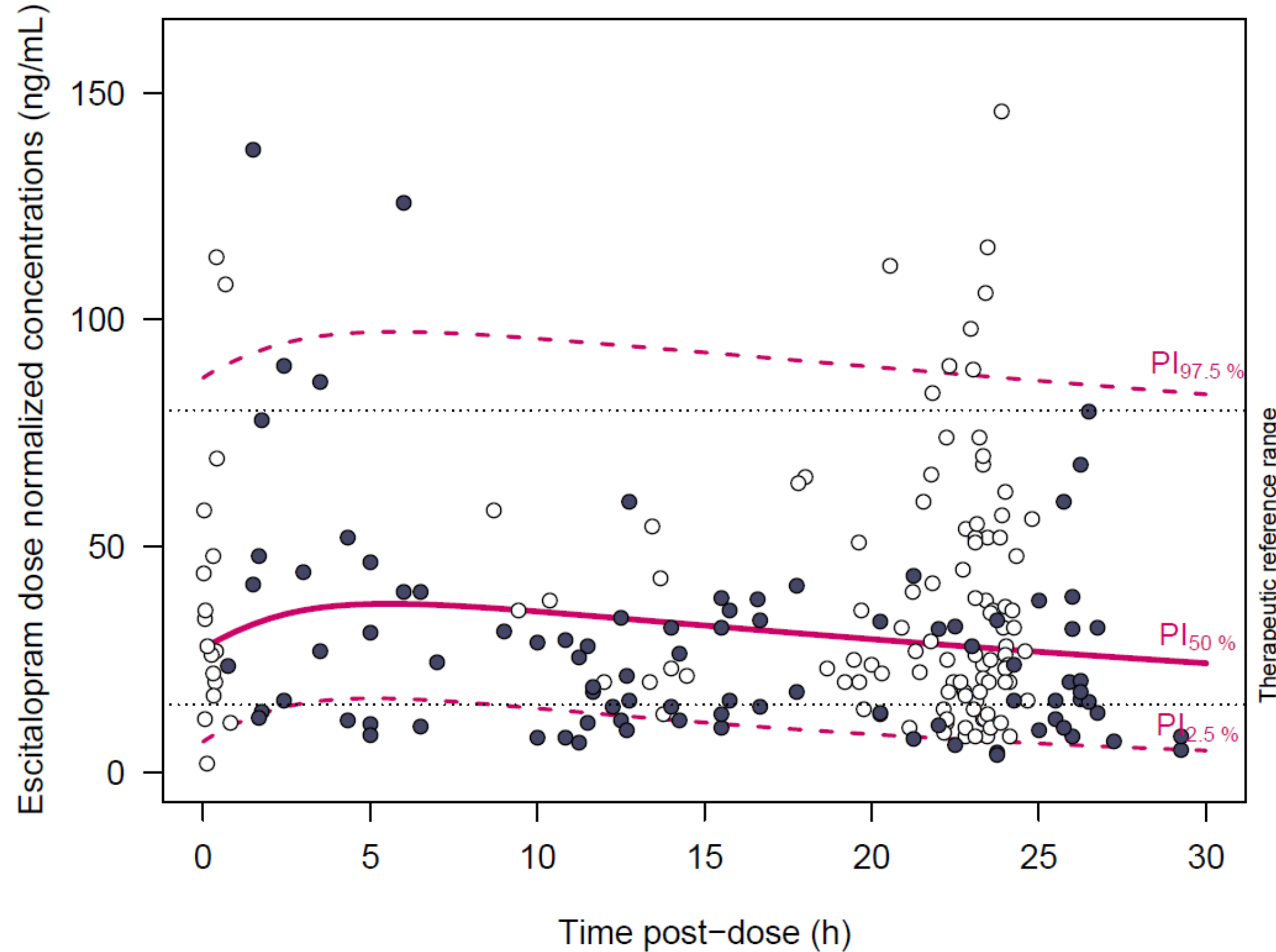


Figure 1: Visual predictive check of observed escitalopram concentrations versus time with the median population predicted concentration (continuous line) and the 95% PI (dashed lines) for the standardized dosing regimen of 20 mg once daily without CYP2C19 inhibitor. Concentrations of HIV-infected patients (full circles) and uninfected psychiatric individuals (empty circles) are shown.

Table 3: Simulated escitalopram plasma concentrations

		10 mg QD		20 mg QD	
		Alone	With CYP2C19 inhibitor	Alone	With CYP2C19 inhibitor
C _{trough} (ng/mL)	PI _{2.5%}	2.9	4.1	5.7	8.3
	PI _{50%}	13.6	17.8	27.3	35.6
	PI _{97.5%}	47.4	60.2	94.7	120.4
% of C _{trough} < 15 ng/mL		56.3	41.5	19.9	10.8
% of C _{trough} > 80 ng/mL		0	0.6	4.6	9.1

Conclusions

- ♦ Escitalopram PK did not differ between antiretroviral treated HIV and uninfected psychiatric patients.
- ♦ PK profile was similar in patients receiving citalopram and those receiving escitalopram, supporting the S/R ratio in plasma of 0.45.
- ♦ Antiretroviral treatments including HIV protease inhibitors did not significantly affect escitalopram concentrations
 - Probably due to the contribution of multiple CYP to escitalopram metabolism and elimination, limiting the impact of DDIs.
- ♦ Inhibitors of CYP2C19 modestly influenced escitalopram elimination, with limited clinical relevance.
- ♦ Our results are reassuring concerning the extent of DDI with escitalopram, not likely to increase the risk of QT prolongation and arrhythmias.

(1) Nikisch G, Eap CB, Baumann P. Citalopram enantiomers in plasma and cerebrospinal fluid of ABCB1 genotyped depressive patients and clinical response: a pilot study. Pharmacol Res. 2008;58(5-6):344-7.

(2) Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62.