

Prediction of escitalopram and its metabolite exposure in breastfed infants

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Objectives

- ♦ To better characterize the exposure to escitalopram and its metabolite through breast milk
- ♦ To predict the exposure variability and quantify the potential risks associated with the use of this medication during breastfeeding.

Methods

- ♦ Data from women taking selective serotonin reuptake inhibitors (SSRI) while breastfeeding enrolled in the SSRI-Milk cohort study (NCT01796132)
- ♦ Escitalopram (SCIT) and S-desmethylescitalopram (SDCIT) plasma and breast milk concentrations were described using a 2-compartment model with first order absorption and elimination. The volume of distribution of SDCIT, not identifiable, was estimated using a scaling factor (VMR) assuming $V_{SDCIT} = V_{SCIT} \cdot VMR$, with equal metabolization and elimination rate constants ($K_{23} = K_{30}$)
- ♦ Prediction of SCIT and SDCIT milk concentrations was performed using a milk-to-plasma ratios for drug (MPRD) and metabolite (MPRM)
- ♦ Tested covariates:
 - Continuous: age, body weight, milk fat content
 - Discrete: CYP2C19, 2D6 and 3A4/5, P450 oxidoreductase (POR) genotypes
- ♦ Simulations of drug in plasma and milk were performed on 10'000 mother-infants pairs to derive SCIT relative infant dose (RID), using daily infant dosage/weight-adjusted maternal dose

$$\text{Daily infant dosage} = \sum_{i=1}^n C_{milk}^i \cdot V_{milk}$$

Random breastfeeding frequencies/day (6-18) and intervals after the last dose intake and an average milk volume of 150 ml/kg/day were assumed.

- ♦ NONMEM 7.4 and the FOCE-I method; validation by bootstrapping

Results

Data

- ♦ 80 plasma and 104 milk samples taken at unselected time after the last SCIT (n=21) or SDCIT (n=12) intake, obtained from 33 breastfeeding women.

Population Characteristics	n(%) or median [IQR]
	Model development (N=33)
Age (years)	24 [21-43]
Body weight 1st wk postpartum (kg)	68 [53-114]
SCIT treatment	21(64)
Alpha-1-acid-glycoprotein 1st wk postpartum (g/L)	0.80 (0.25-1.47)
CYP2C19 predicted phenotype: Poor, Intermediate, Extensive, Ultrarapid metabolizer	4(12), 5(15), 12(36), 12(36)
CYP2D6 predicted phenotype: Poor, Intermediate, Extensive, Ultrarapid metabolizer	2 (6), 8(24), 23(70), 0(0)
CYP3A4 genotype: *1/*1, *1/*22, *22/*22	30(91), 3(9), 0(0)
CYP3A5 genotype: *1/*1, *1/*3, *3/*3	1(3), 6(18), 26(79)
POR genotype: *1/*1, *1/*28, *28/*28	18(55), 10(30), 5(15)
Breast milk fat content (g/100ml)	3.1 [0.2-9.3]

Structural and covariate model

- ♦ Both parent drug and metabolite were characterized by a MPR of 1.9
- ♦ CYP2C19 PM showed a significant 51% decrease in SCIT clearance compared to the other genotype groups
- ♦ A genetic influence of CYP2C19 on the volume of distribution of SDCIT (VMR) was also observed
- ♦ Increased milk fat content (FAT) was significantly associated with an increased drug transfer into breast milk (+28% for SCIT and +18% for SDCIT when fat amount doubled from 3.1 to 6.2 g/100 ml)

Final Pharmacokinetic parameters

Parameter	Final population parameter		Bootstrap results (n=2000)	
	Estimate	RSE (%)	Median	CI 95%
CL_{scit} (L/h)	32.3	8	32.0	28.4-36.1
CYP2C19 PM	-0.51	17	-0.50	-0.64;-0.34
V_{scit} (L)	1590	14	1474	811-1856
K_{30} (h ⁻¹)	0.67	53	0.59	0.05-1.28
K_a (h ⁻¹)	0.87	36	0.83	0.20-1.73
VMR CYP2C19 PM	4.1	22	4.1	3.0-6.3
VMR CYP2C19 EM/IM	2.4	7	2.4	2.2-2.8
VMR CYP2C19 UM	1.9	7	1.9	1.7-2.1
MPRD	1.9	4	1.9	1.8-2.1
MPRM	1.9	3	1.9	1.8-2.0
FAT on MPRD	0.28	20	0.28	0.20-0.39
FAT on MPRM	0.18	20	0.17	0.11-0.23
ω_{CL} (CV%)	31.1	12	30.5	23.8-36.8
ω_{VMP} (CV%)	21	19	18.9	9.3-24.7
$\sigma_{SCIT_{plasma}}$ (CV%)	33.5	8	33.0	28.7-37.4
$\sigma_{SDCIT_{plasma}}$ (CV%)	20.8	9	20.0	16.7-23.2
$\sigma_{SCIT_{milk}}$ (CV%)	24.0	11	23.1	18.7 - 27.7
$\sigma_{SDCIT_{milk}}$ (CV%)	19.4	9	18.4	14.9-21.6

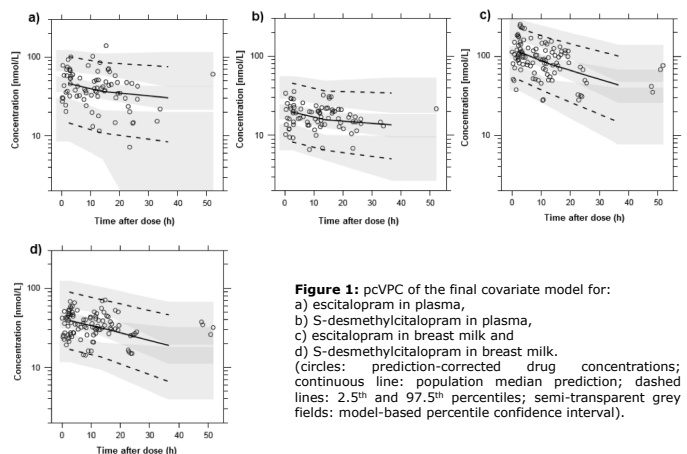


Figure 1: pcVPC of the final covariate model for: a) escitalopram in plasma, b) S-desmethylescitalopram in plasma, c) escitalopram in breast milk and d) S-desmethylescitalopram in breast milk. (circles: prediction-corrected drug concentrations; continuous line: population median prediction; dashed lines: 2.5th and 97.5th percentiles; semi-transparent grey fields: model-based percentile confidence interval).

Simulations of exposure in breast milk

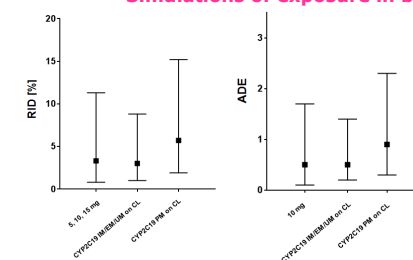


Figure 2: Relative infant dose (RID) and adult dose equivalent (ADE) of SCIT in 10'000 simulated infant pairs under various conditions (median ± range).

Conclusions

- ♦ Escitalopram and its metabolite showed moderate between-subject variability in blood concentrations, partially explained by CYP2C19 genetic polymorphisms.
- ♦ Milk concentrations were similarly variable and mainly influenced by milk fat content.
- ♦ The limited exposure to escitalopram through breast milk, as expected based on previous incomplete data (1-3), could be confirmed
- ♦ These findings provide reassurance with a good level of certainty for clinicians and pregnant women successfully treated with escitalopram or racemic citalopram.

References

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