Varenicline exposure is associated with abstinence from smoking in a cohort of smokers from the general population

Anaïs Glatard[1,2], Monia Guidi[2,3], Maria Dobrinas[1], Jacques Cornuz[4], Chantal Csajka[2,3*] and Chin B. Eap[1,3*]

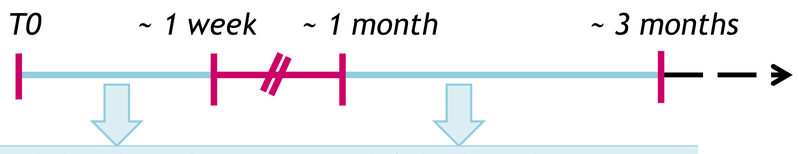
(1) Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Hospital of Cery, Prilly, Switzerland
(2) Division of Clinical Pharmacology, Service of Biomedicine, Department of Laboratory, Lausanne University Hospital, Lausanne, Switzerland
(3) School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland
(4) Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland
*joint corresponding authors

Introduction & Objectives

- Varenicline is a partial agonist of the α4ß2 nicotinic acetylcholine receptor.
- 90% of the dose is eliminated unchanged in urine, notably via OCT2 transporters and the most abundant metabolite is obtained by glucuronidation via UGT2B7[1].
- The overall abstinence rate after varenicline treatment at the effective dose is reported to be less than 35%.
- This work aimed to characterize the sources of variability of varenicline pharmacokinetics and to relate them to drug effectiveness measured by expired carbon monoxide (CO) and cotinine plasma levels.

Methods

Data: 82 subjects received varenicline during a 6-month smoking cessation program (0.5 mg/day x 3 days, 0.5 mg 2/day x 4 days then 1 mg 2/day until 3 months)



Data	1st blood sample N values	2nd blood sample N values
Varenicline concentrations	70	51
Expired carbon monoxide levels (CO, half-life:4-8h) (Figure 2)	65	49
Cotinine plasma levels (half-life : 16-17 h) (Figure 2)	67	43

- 19 single nucleotide polymorphisms of notably the OCT2 and UGT2B7 were genotyped using the Cardio-MetaboChip (Illumina)

Pharmacokinetic-pharmacogenetic model :

- Non-linear mixed effect modelling using NONMEM® v. 7.2.
- Tested covariates: SNPs and clinical covariates: body weight (BW), age, sex, etc.
- VPC was performed by simulations based on the final model with variability using 1000 UGT2B7 rs7439366 TT/TC individuals.

Exposure-response analysis:

- Varenicline AUC0-24 was computed in NONMEM analytically based on the dose history and the pharmacokinetic parameters.
- CO and cotinine levels were modeled in NONMEM using the AUC0-24 in $ng^{-1}.h^{-1}.mL$ and the treatment duration (Time in days). Models were evaluated by the AIC. The final model for CO and cotinine was the following:

  CO (or cotinine) = a x AUC0-24 + b x Time + c

  Where: a is the effect of varenicline AUC0-24 and b is the effect of the treatment duration on the biomarker and c is the baseline level.

Results

- A one-compartment model with first order absorption and elimination appropriately described varenicline concentrations.
- Varenicline CL increased by 68% upon BW doubling.
- *UGT2B7* rs7439366 C/C carriers represented 26% of the sample analysis and were found to have 21% higher CL than T/T and C/T carriers (Table 1).

Table 1: Final varenicline population pharmacokinetic parameter estimates and their bootstrap evaluations.

Parameter	Final population parameter		Bootstrap evaluation (n=2000 samples)	
	Estimate	RSE[a] (%)	Median	$CI_{95\%}$
CL_0 (L/h)	$8.5 \cdot (BW/70)^{0.75}$	4	$8.5 \cdot (BW/70)^{0.75}$	(7.9; 9.2)
$\theta^{b}_{UGT2B7\ rs7439366\ CC}$ (%)	21	49	21	(0.4; 44)
V (L)	228	8	229	(192; 275)
k_a (h^{-1})	0.98 fixed	--	0.98	--
IIV^{c}_{CL} (CV%)	19	22	18	(9; 26)
σ^{d} (CV%)	23	18	23	(19; 27)

CL_0, typical apparent clearance for *UGT2B7* rs7439366 TT or TC carrier, function of patients' body weight (BW); V, typical apparent volume of distribution; k_a, typical absorption rate constant.
[a]Relative standard errors of the estimates; [b]Relative deviation of CL due to *UGT2B7* rs7439366 CC; [c]Interpatient variability; [d]Residual intrapatient variability.

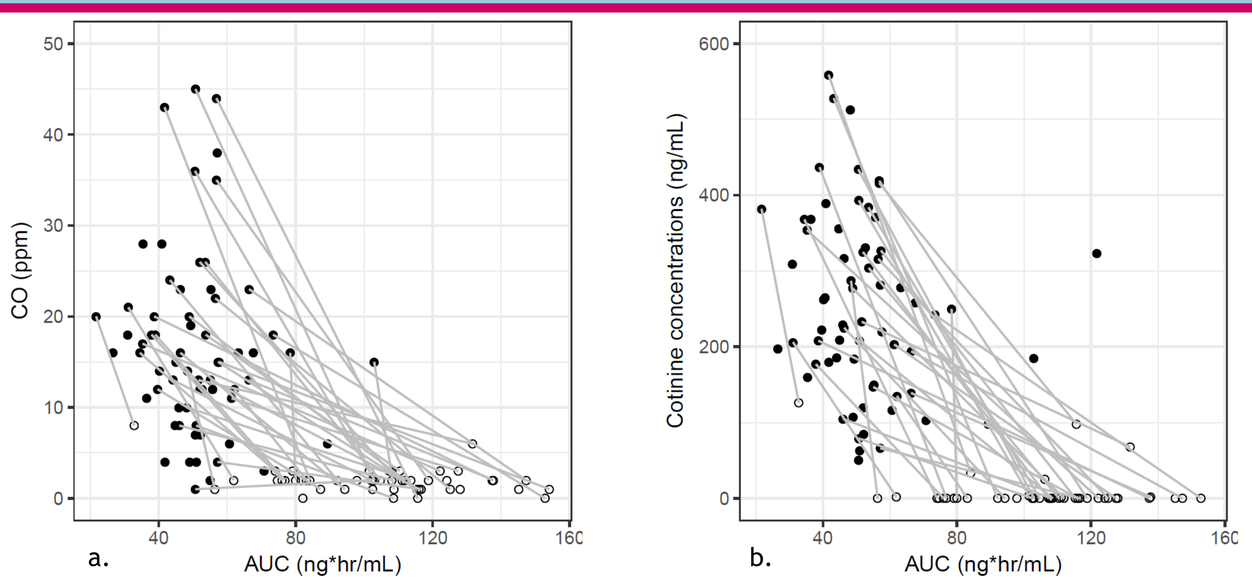


Figure 1: Observed CO and cotinine levels versus varenicline AUC0-24. Full and empty circles represent the observation of the first and the second blood sample, respectively. Two observations of the same subject are linked by a grey line.

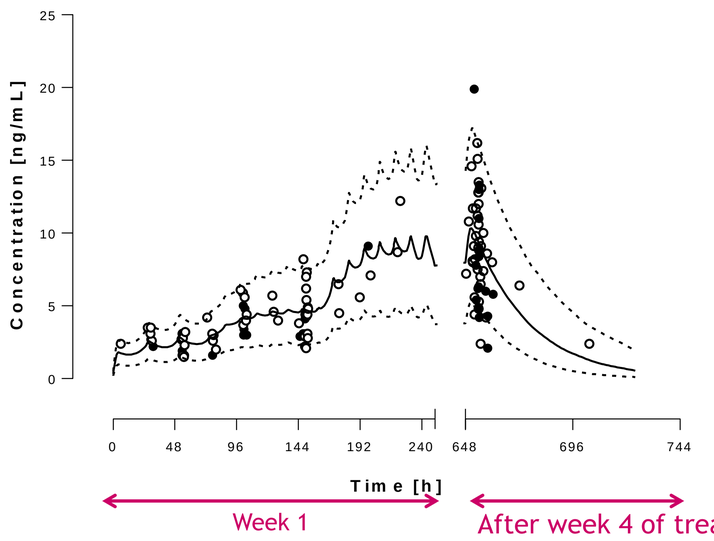


Figure 1: Observed dose-normalized varenicline concentrations versus time from the beginning of the treatment. Mean population prediction (solid lines) and 95% prediction intervals (dotted lines) computed for a *UGT2B7* rs7439366 TT or TC carrier weighting 77 kg (mean population body weight). Empty and full circles represent respectively TT or TC and CC subjects.

Table 2: Parameters estimates of the exposure-response models

Model equations	a (IIV)*	b (IIV)*	c (IIV)*	Residual Error**	AIC
CO = a x AUC0-24 + c	-0.17 (68%)	-	22.4 (59%)	5.2	577
CO = b x Time + c	-	-0.29 (86%)	14.8 (66%)	2.3	528
CO = a x AUC0-24 + b x Time + c	**-0.06 (90%)**	**-0.22 (64%)**	**17.9 (65%)**	**2.7**	**509**
cotinine = a x AUC0-24 + c	-3.2 (42%)	-	385 (34%)	98	1154
cotinine = b x Time + c	-	-6.3 (36%)	260 (42%)	49	1086
cotinine = a x AUC0-24 + b x Time + c	**-0.63 (90%)**	**-5.3 (35%)**	**287 (50%)**	**38**	**1069**

*IIV: inter-individual variability expressed as CV%; Additive residual error in ppm for the CO model and in $ng^{-1}.h^{-1}.mL$ for the cotinine model

- For an AUC0-24 increase of 10 $ng^{-1}.h^{-1}.mL$, CO level was decreased by 0.6 ppm (95%CI= -0.7 ; -0.4) and cotinine level was decreased by 6.3 ng/mL (95%CI= -8.6 ; -4.0) significantly.
- For one week of treatment, CO level was decreased by 1.5 ppm (95%CI= -1.9 ; -1.2) and cotinine level was decreased by 37 ng/mL (95%CI= -43 ; -32) significantly.

Conclusions

- An effect of treatment duration and a more modest effect of varenicline AUC were identified on CO and cotinine levels.
- Body weight and a genetic polymorphism of *UGT2B7* significantly contribute to varenicline plasma concentrations variability.
- In clinical practice, dosage titration based on body weight and on carbon monoxide or cotinine measurement might help the treatment monitoring.

References
1. Cahill K, Stead LF, Lancaster T, et al. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2012;4:CD006103.