Population pharmacokinetic modelling of sustained-release lithium in the serum, erythrocytes and urine of patients with bipolar disorder

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Introduction

Background: Bipolar disorder is a major affective disorder. Sustained-release lithium (srLI) is now the first-line treatment. SrLI has a narrow therapeutic margin adapted empirically from studies of the immediate-release form looking at the concentration at H12 post evening intake [1].

→ No specific pharmacokinetics (PK) studies for srLI administered once a day

Objectives:

- To build a joint PK model of srLI using serum (S), erythrocyte (E) and urinary (U) samples collected in 17 bipolar patients, after 15 days of morning intake once a day
- To optimize the sampling times for a large PK study of N=100 patients (study PopKLI, sponsor French Health ministry, PI Dr Sportiche)

Methods

Clinical study prospectively conducted in French bipolar disorder centres in patients treated with srLI for at least two years.

- Patients received their usual dose
- S and E samples collected before drug intake and at H1, H4, and H8
- U samples between H0 and H8

Adherence recorded over the 15 days using with MEMS (monitoring electronic medical system) [2]

Population PK model:

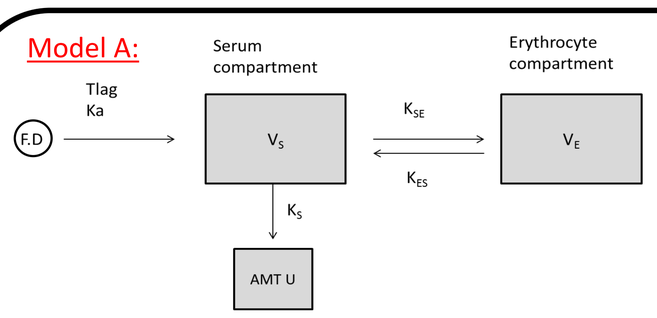
Estimation using the SAEM algorithm [3] in the software Monolix 4.3.3s

Three candidate structural joint models were evaluated:

- The most appropriate model was selected on the basis : (i) BIC; (ii) GOF plots; (iii) RSE of PK parameter estimates
- Exponential model for the between-subject random effects except for the bioavailability, F modelled with a logit function
- Between-subject correlations were tested across PK parameters

Design Optimization using PFIM 4.0 [4]

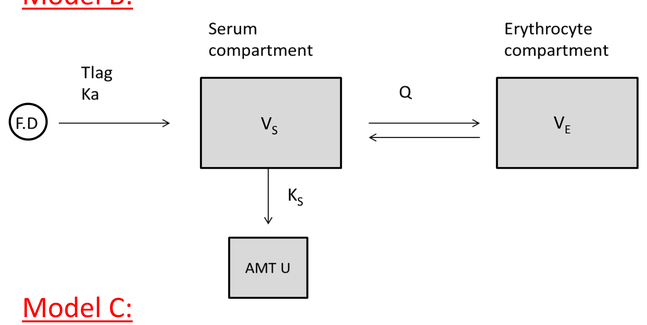
Model A:



Equation:

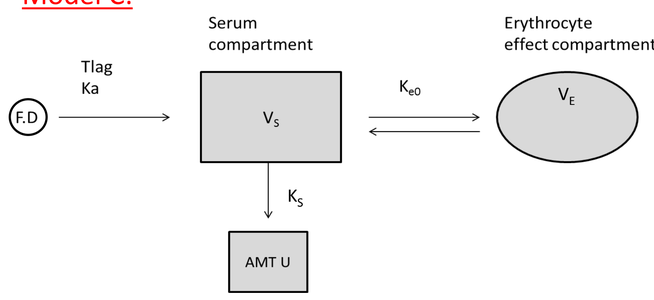
$$\frac{dG}{dt} = -ka \cdot G \; with \; G(0) = FD$$
$$\frac{dA_S}{dt} = ka \cdot G - k_{SE} \cdot A_S + k_{ES} \cdot A_E - k_S \cdot A_S$$
$$\frac{dA_E}{dt} = -k_{ES} \cdot A_E + k_{SE} \cdot A_S$$
$$\frac{dA_U}{dt} = k_S \cdot A_S$$
$$k_S = Cl_S/V_S$$
$$k_{SE} = Cl_{SE}/V_S \text{ and } k_{ES} = Cl_{ES}/V_E$$
$$C_S = A_S/V_S \text{ and } C_E = A_E/V_E$$

Model B:



$$k_{SE} = Q/V_S \text{ and } k_{ES} = Q/V_E$$

Model C:



$$k_{E0} = k_{SE} = k_{ES}$$
$$V_E = 1$$

Supplementary clinical routine data :

- 12h-serum concentrations, post evening intake in 11 patients
- Wilcoxon signed rank test comparison to individual-level model predictions of 12h-serum concentrations

Results

Study Data: 17 patients (6 males) with median [range] age: 40 years [27-63], Alda scale: 7 [0-9] and dose: 1000 mg [600-1600] i.e. 27.03 meq [16.22-43.24].

Adherence: Dosing interval was 24.02 hours [23.97-26.01] with only two patients having forgotten one dose.

Population PK model:

The srLI PK was best described by the Model A

	Estimate	RSE (%)
Fixed effects		
F	0.62	12
Tlag (h)	0.92	5
Ka (h^{-1})	2.22	60
V_S (L)	23.0	16
Cl_S (L h^{-1})	1.21	8
Cl_{SE} (L h^{-1})	3.63	22
Cl_{ES} (L h^{-1})	9.46	23
V_E (L)	64.7	21

	Estimate	RSE (%)
Between-subject variability		
w_F(%)	0.98	21
w_{Ka} (%)	0.72	26
$w_{V\,S}$ (%)	0.30	43
$W_{Cl\,S}$ (%)	0.20	28
$w_{Cl\,ES}$(%)	0.27	19
Residual variability		
σ_s (%)	10	13
σ_E (mEq/L)	0.02	10
σ_U (mEq)	1.78	29

table: **Population pharmacokinetic parameter estimates of sustained-release lithium in 17 bipolar patients (one dose per day after 15 days)**

Secondary PK model:

- The ratio of exposition to srLI in E over S (as measured by the ratio of predicted $AUCss = AUC_E/AUC_S$) is of 0.38 (BSV 20%)
- The Tmax was calculated at 3 hours and five minutes.

Model evaluation:

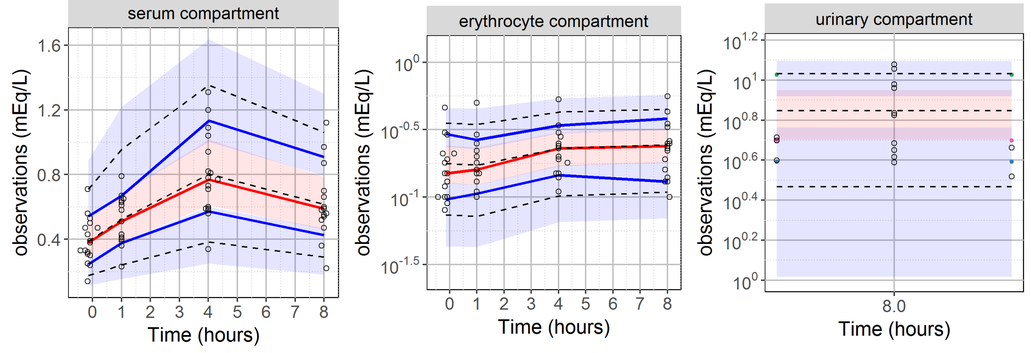


Figure: **VPC plots of the population PK model for the 17 bipolar patients for the S, E and U compartments. The color lines or points are the observed percentiles (10, 50, 90th percentiles), the blue and red ribbons are the corresponding 95% confidence intervals. The dashed black lines are predicted percentiles.**

Design optimization:

For N=100 bipolar patients and only four PK samples, the D-optimal design was H1,H3,H8,H24, RSE < 20% for all paramters only the RSE(V_S) = 26%.

Comparison to clinical routine 12h-serum concentrations post evening intake:

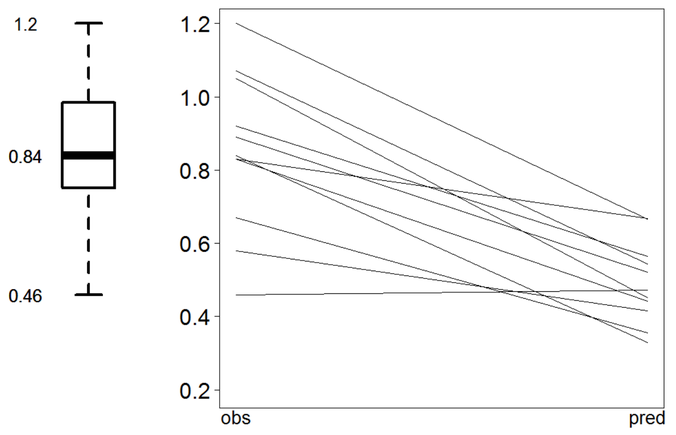


Figure: **Boxplot of observed serum concentration of srLI after an evening intake (obs; left), stripchart of segments connecting observed and predicted concentrations from the same patient (middle) and boxplot of model predicted serum concentration of srLI after a morning intake (pred; right) in 11 patients.**

- Difference estimated median at 0.37 [IQR 0.23-0.52] (p-value < 0.001)

Results

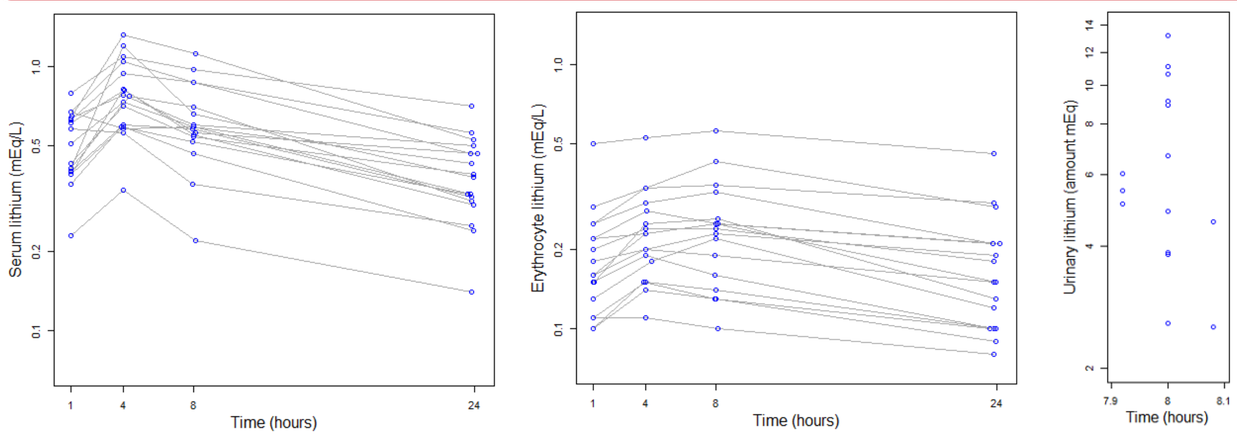


Figure: **Spaghetti plots of serum (left), erythrocyte lithium concentrations (middle) and urinary amount (right) versus time for the 17 bipolar patients included in the pharmacokinetic analysis. The 24h point is the trough concentration of the previous dose.**

Conclusion

- First PK model of srLI in bipolar patients describing lithium concentrations in S, E and U using a population approach jointly and providing an estimate of the ratio of exposition to srLI in E over S, deemed to be a proxy of brain impregnation [5].
- Next step will be to study how srLI PK variability associate with response using data from PopKLi after an evening intake (sponsor French Health ministry, PI Dr Sportiche) which uses the optimal sampling design based on the present model.

References

1. Grandjean EM, Aubry J-M. Lithium: updated human knowledge using an evidence-based approach. Part II: Clinical pharmacology and therapeutic monitoring. CNS Drugs. 2009;23(4):331–49. 2. Vrijens B, Goetghebeur E. The impact of compliance in pharmacokinetic studies. Stat Methods Med Res. 1999 Sep;8(3):247–62. 3. Kuhn E, Lavielle M. Maximum likelihood estimation in nonlinear mixed effects models. Comput Stat Data Anal. 2005 Jun 15;49(4):1020–38. 4. www.pfim.biostat.fr. 5. Sproule B. Lithium in bipolar disorder: can drug concentrations predict therapeutic effect? Clin Pharmacokinet. 2002;41(9):639–60