

A One Compartment Model Provides Benchmark Lithium Dose Prediction

Oisín N Kavanagh¹ Elliott M Asprey², Katinka A Edelmann⁶, Philipp Ritter^{6,7}, David A Cousins^{3,4,5} Victoria C Wing^{3,5}

¹School of Pharmacy, ²School of Medicine, ³Translational and Clinical Research Institute, Faculty of Medical Sciences, ⁴Newcastle MR Centre, Newcastle University, UK; ⁵CNTW NHS Trust, UK; ⁶Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany; ⁷Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

BACKGROUND

- ❑ **Lithium** is a very **effective mood stabiliser**¹ but **under-prescribed** due to its narrow therapeutic window and need for regular blood monitoring.
- ❑ **Lithium dose prediction methods** try to calculate the dose an individual will require to reach therapeutic levels in the blood.
- ❑ There are at least 65 publications reporting 38 different methods, but **none have been adopted into clinical practice**.²
- ❑ Previous models fail to consider the pharmacokinetics (PK) of lithium relying on linear regression in small samples, or use population PK methods, which **struggle to extrapolate to more diverse populations**.

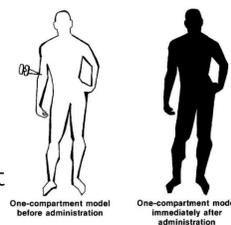
OBJECTIVES

- 1) **Develop a PK model of lithium** to predict the dose required for an individual to reach a therapeutic plasma level.
- 2) **Test the accuracy of the PK model** compared to existing methods.

METHODS

Constructing a one-compartment model for lithium

- ❑ A 1-compartment model assumes the body can be described as a single, uniform compartment.
- ❑ Lithium's PK parameters were taken from the product literature³ or we extracted from PK studies.
- ❑ Preliminary work using volume of distribution (0.7L/kg)³ systematically underestimated lithium dose.
- ❑ Instead, we **assumed that lithium distributes to total body water** (TBW), and equated TBW to V_d at steady state giving:



$$C_t = \frac{\text{Dose}}{V_d} \times e^{-Kt}$$

$$C_t = \frac{[Li] \times F}{\text{Total body water}} \times e^{-0.0289 \times t}$$

Where for lithium: C=concentration; t=time post-dose; [Li]=dose in mmols; F=bioavailability (90%); half-life is 24 hours ($k=0.0289$)
TBW is calculated from simple body measurements (height, weight, age, sex)⁴

Testing the one-compartment model

- ❑ Lithium dosing and biometric data from two independent samples of patients enrolled in ⁷Li-MRI studies were used to test the model.⁶
- ❑ Using the BLISS dataset, we compared the performance of our one-compartment model to six commonly cited dose prediction formulae.

Characteristics of the test cohorts

- ❑ All had bipolar disorder, euthymic mood, and were on a stable once daily dose of lithium carbonate. Serum levels were taken 12-hours post-dose.

Characteristic	BLISS (n=36)	BIPOLITH (n=18)
Sex (female/male)	20/16	10/8
Age (years)	51 ± 11	40 ± 10
Height (cm)	170 ± 10	175 ± 11
Weight (kg)	85 ± 16	81 ± 20
BMI	29 ± 5	26 ± 6
Lithium dose (mg/day)	794 ± 220	846 ± 230
Creatinine clearance (CrCl, mL/min)	113 ± 35	-
Serum lithium (mmol/L)	0.75 ± 0.14	0.69 ± 0.13

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RESULTS

Comparison of the 1-compartment model to previous methods

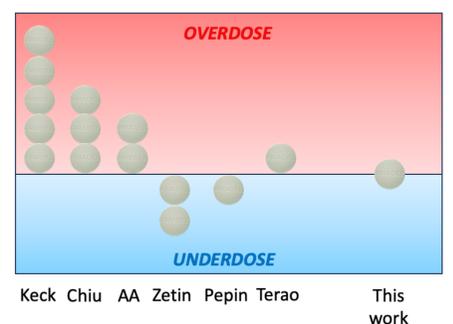
Method	Factors Included	Mean prediction error ± Std Dev	
		Lithium carbonate (mg)	Nearest whole tablet (200mg)
* Keck ⁶	Weight	901 ± 299	5 ± 1
* Chiu ⁷	Body weight, CrCl Desired Li concentration	693 ± 626	3 ± 3
* Abou-Auda ⁸	Ideal body weight, CrCl Desired Li concentration	307 ± 210	2 ± 1
* Zetin ⁹	Weight, Age, Gender Hospitalization, TCA use Desired Li concentration	-327 ± 211	-2 ± 1
Pepin ¹⁰	mmol Li in formulation Weight, Height Time of plasma sample	-284 ± 102	-1 ± 1
* Terao ¹¹	Desired lithium concentration Blood urea nitrogen Age, Weight	145 ± 173	1 ± 1
This work	mmol Li in formulation Weight, Height, Sex, Age Time of plasma sample	10 ± 148	0 ± 1

* Include one or more constants derived from linear regression

Our model predicted lithium dose within a 200mg tablet.

Remaining error may be due to:

- Variability in time of serum level in relation to last dose.
- Serum lithium was reported to only 0.1mmol/L accuracy.



Developing a lithium dose calculator

- ❑ The 1-compartment model is embedded in an Excel-based calculator which can be applied to different lithium formulations (carbonate, citrate, sulphate), dosage regimens (OD or BD), and target ranges.
- ❑ It can also be used to predict serum levels across the day, which if robust could allow for samples to be taken outside the 12-hour window.

Patient Public Involvement and Engagement

- ❑ Focus groups with both service users and doctors were positive about the potential for the lithium dose calculator to improve clinical care.
- ❑ Based on clinician feedback we are developing a user-friendly 'app'

CONCLUSIONS

- ❑ **Our lithium dose calculator requires only simple body measurement and sets a new benchmark for predictive accuracy.**
- ❑ Future work will look to validate it in a controlled human PK laboratory study, as well as in larger more diverse samples.
- ❑ **A user-friendly reliable lithium dose calculator could facilitate collaborative planning between clinicians and patients and increase confidence in lithium prescribing.**
- ❑ **This work has implications for UK and global clinical practice by reducing barriers to lithium initiation.**

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