Lithium Dosage Optimisation: Why is it so challenging?

A comparison of dosage prediction methods and derivation of pharmacokinetic information from published data

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Background

Lithium salts are the primary treatment for bipolar disorder worldwide. However, it's narrow therapeutic window means clinicians must slowly titrate to a therapeutic dose over a period of weeks.

There are 17 methods for predicting lithium dosage *a priori*, yet none are accurate enough for clinical use due to a lack of pharmacokinetic data[1].

Aims

- Test 4 predictive methods in a recent research sample[2-5]
- Create a simple one compartment model for dose prediction
- Derive pharmacokinetic information using published data[6-8]

Methods

1) 4 predictive methods and a one-compartment model tested using a research sample.
2) Absorption rate constant (Ka) calculated using the method of residuals
3) Bioavailability (F) calculated using oral and IV lithium data
4) Volume of distribution (Vd) was calculated using compartmental and non-compartmental analysis.

1) Dosage Prediction

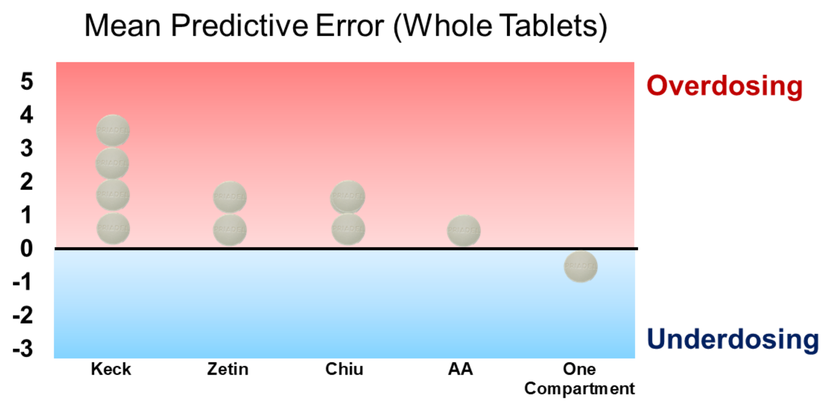


Figure 1. Mean predictive error of 4 existing *a prior* methods and a simple one-compartment model expressed as whole tablets of lithium (200mg)

2) Ka Calculation

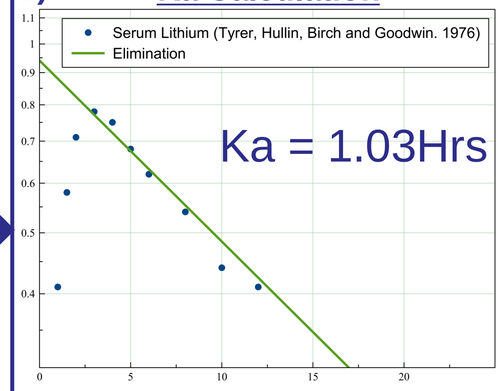
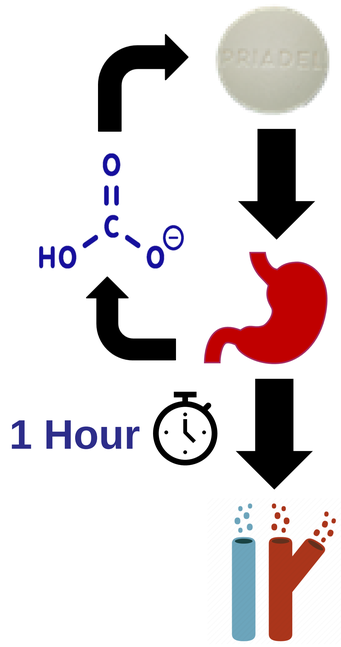


Figure 2. Calculation of Ka through the method of residuals.



3) Bioavailability

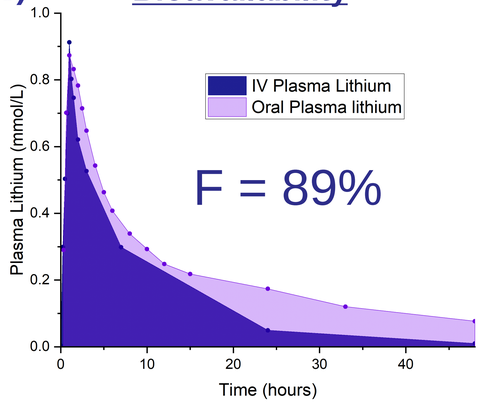


Figure 3. Calculation of F by comparing similar doses of oral and IV lithium carbonate.

4) Volume of Distribution

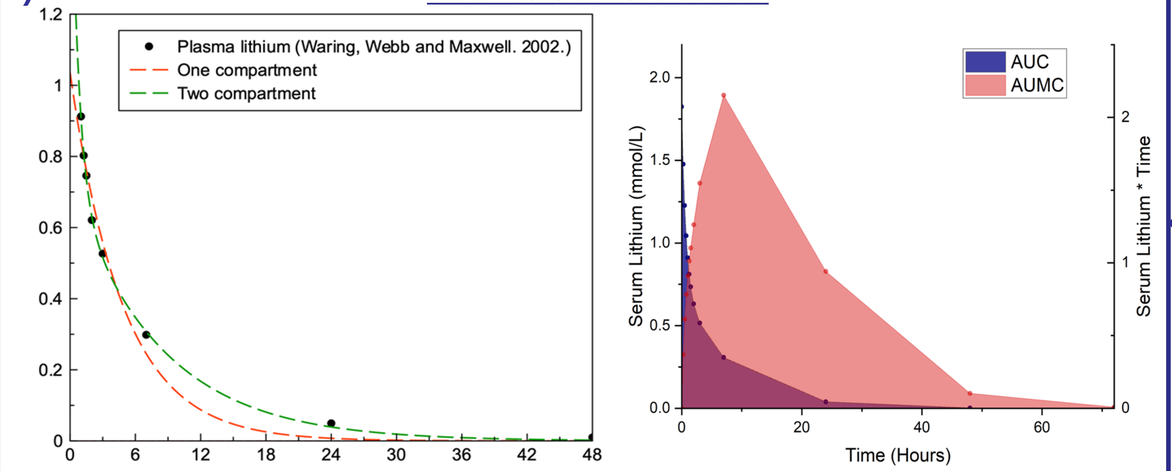
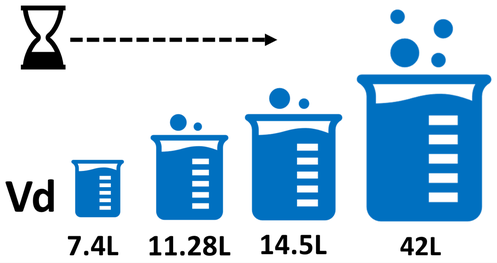


Figure 4. Compartmental and non-compartmental analysis of lithium using published IV lithium 1-hour infusion data to calculate Vd and k.

Future Work

- Bolus dose IV lithium
- More serum measurements in terminal elimination phase



Conclusion

- Lithium absorption is extremely slow– this may mean formulation is arbitrary as it reacts with bicarbonate in the GI tract
- Vd changes drastically over time as lithium distributes into deep compartments
- A one compartment model may be sufficient – more data is needed from the elimination phase

References: 1) Sienaert P, Geeraerts I, Wyckaert S. How to initiate lithium therapy: a systematic review of dose estimation and level prediction methods. Journal of affective disorders. 2013;146(1):15-33 2) Keck Jr PE, Strakowski SM, Hawkins JM, Dunayevich E, Tugrul KC, Bennett JA, et al. A pilot study of rapid lithium administration in the treatment of acute mania. Bipolar Disorders. 2001;3(2):68-72. 3) Zetin M, Garber D, De Antonio M, Schlegel A, Feureisen S, Fieve R, et al. Prediction of lithium dose: a mathematical alternative to the test-dose method. The Journal of clinical psychiatry. 1986;47(4):175-8. 4) CHIU CC, Shen WW, CHEN KP, LU ML. Application of the Cockcroft–Gault method to estimate lithium dosage requirement. Psychiatry and clinical neurosciences. 2007;61(3):269-74. 5) Abou-Auda HS, Al-Yamani MJ, Abou-Shaaban RR, Khoshhal SI. A new accurate method for predicting lithium clearance and daily dosage require-ments in adult psychiatric patients. Bipolar disorders. 2008;10(3):369-76. 6) Waring SW, Webb DJ, Maxwell SR. Lithium carbonate as a potential pharmacological vehicle: intravenous kinetics of single-dose administrationhealthy subjects. European journal of clinical pharmacology. 2002;58:4314.10 7) Guelen PJ, Janssen TJ, De Witte TC, Vree TB, Benson K. Bioavailability of lithium from lithium citrate syrup versus conventional lithium carbonate tablets. Biopharmaceutics & drug disposition. 1992 Oct;13(7):503-11 8) Tyrer S, Hullin RP, Birch NJ, Goodwin JC. Absorption of lithium following administration of slow-release and conventional preparations. Psychological medicine. 1976 Feb;6(1):51-8.