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Review

How to initiate lithium therapy: a systematic review of dose estimation and level prediction methods

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ABSTRACT

Background: Throughout the past decades, several methods have been developed to achieve therapeutic lithium blood levels as quick and safe as possible. The present study will systematically review the methods developed and studied for lithium dose estimation or level prediction at the initiation of therapy.
Methods: A systematic computerized Medline search was performed for papers published in English, French or Dutch between 1966 and April 2012 describing or studying methods for dosing lithium or predicting the lithium level on a certain dosage. References of relevant articles were screened for additional papers.
Results: Of 273 unique references retrieved, 65 met the inclusion criteria. Apart from the empirical titration method, 38 predictive methods for initiating lithium were identified. These methods can be classified into two categories: the *a priori* predictive methods, and the *test-dose* predictive methods requiring the administration of a test dose of lithium prior to starting treatment.
Limitations: The methodological strength was not taken into account for a study to be included in the review.
Conclusions: The most important distinction between the empirical titration method and the predictive methods appears to be the shorter time the latter need to achieve the targeted lithium level. The vast majority of predictive methods, however, show inconsistent or poor results or have not been replicated since their initial description. The empirical titration method, although not extensively studied, appears to be a time-honored method that can be recommended for use in daily clinical practice.

Contents

1. Introduction

Since the psychiatric use of lithium was first described in 1949 (Cade, 1949), lithium has become an established therapeutic agent for the treatment of both acute manic, mixed and depressive

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episodes and the maintenance treatment of bipolar disorder (APA, 2002). In addition, it is often used as an augmentation agent in antidepressant-resistant major depressive disorder and in prophylaxis of recurrent depressive disorders, schizoaffective psychosis and pathologic aggressive behavior (Bauer et al., 2006). Despite wide experience and proven efficacy, the use of lithium has not remained undisputed, mainly because of potential renal impairment and dangerous toxicity. The specific pharmacokinetic and pharmacodynamic properties of lithium complicate its therapeutic use (Malhi et al., 2011, 2012). Lithium has a narrow therapeutic index and there is a wide interindividual variation in renal clearance of lithium and response to treatment (Grandjean and Aubry, 2009). This implies that for each patient, an appropriate dose has to be determined, and regular monitoring of blood levels has to be ensured. The most widely used method to start lithium therapy is the clinical titration method (Bauer et al., 2006). Lithium is started at a low dose, and a 12-hour serum level is measured after steady-state concentrations are reached, i.e. after one week. The daily dose is then adjusted, with gradual increments, to reach the desired serum level. This procedure is based on the linear relationship between lithium dose and blood levels at steady-state (Bauer et al., 2006).

Throughout the past decades, several methods have adressed the question of how to achieve therapeutic blood levels as quick and safe as possible. These methods provide formulas to predict the dosage an individual patient will require to achieve a preset lithium blood level or calculate the expected steady state level on a certain dosage of lithium. Seventeen of these predictive methods were reviewed before, in 1988 (Lobeck, 1988). It was concluded that all methods had considerable shortcomings and should be used with due caution (Lobeck, 1988).

The present study will systematically review all methods for lithium dose estimation or level prediction at the initiation of therapy, developed and/or studied to date. The clinical usefulness of these lithium initiation methods, i.e. their accuracy and practical value, will be discussed.

2. Methods

A systematic computerized Medline search was performed for papers published between 1966 and April 2012, using the search terms 'lithium' and 'dose/dosage prediction', 'dose/dosage

Table 1
Characteristics of a priori predictive methods.

Method	Analytical approach	Parameters included	Number of articles studying the method
Pepin et al. (1980)	M/PK D	Creatinine clearance (Cockcroft–Gault, with use of ideal body weight)	12
Sampath et al. (1981)	LRA (187)	Body weight	4
Zetin et al. (1983)	LRA (100)	Lithium formulation (carbonate, citrate, extended release), use of TCA, age, sex, body weight	6
Lesar et al.(1985)	LRA (71)	Sex, weight, age, depression/use of TCA, state (acute/nonacute), creatinine clearance (Cockcroft-Gault)	1
		Sex, weight, age, depression/use of TCA, state (acute/nonacute)	1
Kook *Loading dose* (Kook et al., 1985)	NM	Body weight	1
Zetin et al. (1986)	LRA (548)	Age, body weight, inpatient/outpatient, sex, use of TCA	18
Higuchi *Mason*[*a] (**Higuchi et al., 1988**)	M/PK D	Body weight	1
Groves et al. (1991)	Based on Stokes' 76 observations[b]	Body weight	2
Jermain *NONMEM* (Jermain et al., 1991)	NONMEM (79)	Lean Body weight (calculated from body weight and height), creatinine clearance (Cockcroft-Gault)	4
Moscovich *Loading dose* (Moscovich et al., 1992)	NM	Clinical considerations (age, body size, past history of tolerance,…)	1
Yukawa *NONMEM* (Yukawa et al., 1993)	NONMEM (90 patients, 303 data sets)	Age, body weight, serum creatinine level	2
Sproule *Fuzzy logic* (Sproule et al., 1997)	Fuzzy logic modeling (10 patients, 87 data sets)	Time since last dose, serum creatinine level	1
Terao et al., 1999	LRA (70)	Age, body weight, BUN	4
Keck *Loading dose* (Keck et al., 2001)	M/PK D	Body weight	2
Chiu et al. (2007)	M/PK D	Body weight, creatinine clearance (Cockcroft-Gault)	1
Abou-Auda et al. (2008)	LRA (60)	Age, body weight, sex, BUN, use of TCA, creatinine clearance (Cockcroft-Gault), inpatient/outpatient	2
Huang et al. (2008)	M/PK D	Age, body weight, sex, serum creatinine level	1

NM: not mentioned in the article.
LRA: linear regression analysis based upon patient data (the number of patients used for analysis is noted between brackets).
M/PK D: mathematical/pharmacokinetic derivation.
NONMEM: non-linear regression analysis with the Non-linear Mixed Effects Model Program, based upon patient data (the number of patients used for analysis is noted between brackets).
Fuzzy logic modeling: predictions based on the creation of a knowledge base of prediction rules by the principles of fuzzy logic modeling, (the number of patients used for creation of the knowledge base is noted between brackets).
Loading dose: methods used to give a loading dose of lithium, to rapidly attain therapeutic levels, in the case of acute mania.
BUN: blood urea nitrogen.
TCA: tricyclic antidepressants.

[a] Mean lithium population pharmacokinetic parameters by Mason et al. were used to derive estimates of lithium clearance and volume of distribution, dependent on the body weight of the patient.
[b] Manic patients were designated to alternatingly placebo, low, medium or high doses of lithium chloride, as calculated according to body weight. High and medium dosages appeared to be more efficacious in improving manic ratings.