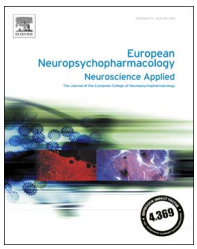
European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮



www.elsevier.com/locate/euroneuro

Population pharmacokinetic model of lithium and drug compliance assessment

Isabel Pérez-Castelló[a,b], Víctor Mangas-Sanjuan[a,c], Ignacio González-García[d,1], Isabel Gonzalez-Alvarez[a], Marival Bermejo[a], Jose Luis Marco-Garbayo[b,2], Iñaki F. Trocóniz[c,*,2]

[a]*Program of Molecular and Cellular Biology, Department of Engineering, University Miguel Hernández de Elche, Carretera Alicante Valencia km 87, San Juan de Alicante, 03550 Alicante, Spain*
[b]*Department of Clinical Pharmacy, Hospital of Francesc de Borja, Av/ de la Medicina 6, Gandia, 46702 Valencia, Spain*
[c]*Pharmacometrics and Systems Pharmacology, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Irunlarrea 1, 31008 Pamplona, Navarra, Spain*
[d]*Pharmacy and Pharmaceutical Technology Department, University of Valencia, Av/ Vicent Andres Estelles, s/n. 46100, Burjasot, 46100 Valencia, Spain*

Received 4 May 2016; received in revised form 19 October 2016; accepted 8 November 2016

KEYWORDS
Lithium;
Drug compliance;
TDM;
Population pharmacokinetic analysis;
Markov modelling

Abstract
Population pharmacokinetic analysis of lithium during therapeutic drug monitoring and drug compliance assessment was performed in 54 patients and 246 plasma concentrations levels were included in this study. Patients received several treatment cycles (1–9) and one plasma concentration measurement for each patient was obtained always before starting next cycle (pre-dose) at steady state. Data were analysed using the population approach with NONMEM version 7.2. Lithium measurements were described using a two-compartment model (CL/F=0.41 L h^{-1}, V_1/F=15.3 L, Q/F=0.61 L h^{-1}, and V_2/F = 15.8 L) and the most significant covariate on lithium CL was found to be creatinine clearance (reference model). Lithium compliance was analysed using inter-occasion variability or Markovian features (previous lithium measurement as ordered categorical covariate) on bioavailability parameter. Markov-type model predicted the lithium compliance in the next cycle with higher success rate (79.8%)

Nonstandard abbreviations: −2LL, 2xlog(likelihood); BD, bipolar disease; CrCL, creatinine clearance; EBE's, Empirical Bayes Estimates; IIV, inter-individual variability; IOV, inter-occasion variability; NONMEM, Non-Linear Mixed Effect Models; pc-VPC, prediction-corrected visual predictive checks; PDV, previous dependent variable; TDM, therapeutic drug monitoring; TI, therapeutic interval; TVF, typical value of bioavailability.

*Corresponding author. Fax: +34 948425740.
E-mail address: itroconiz@unav.es (I.F. Trocóniz).
[1]Current address: Clinical Pharmacology, PharmaMar, Spain.
[2]These two authors co-supervised equally this work.

http://dx.doi.org/10.1016/j.euroneuro.2016.11.005
0924-977X/

Please cite this article as: Pérez-Castelló, I., et al., Population pharmacokinetic model of lithium and drug compliance assessment. European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.11.005

compared to IOV model (65.2%) and reference model (43.2%). This model becomes an efficient tool, not only being able to adequately describe the observed outcome, but also to predict the individual drug compliance in the next cycle. Therefore, Bipolar disorder patients can be classified regarding their probability to become extensive or poor compliers in the next cycle and then, individual probabilities lower than 0.5 highlight the need of intensive monitoring, as well as other pharmaceutical care measurements that might be applied to enhance drug compliance for a better and safer lithium treatment.

1. Introduction

Lithium is an alkaline metal used as primary treatment for the prevention of episode recurrences in bipolar disease (BD), acute treatment of mania and to a lesser extent depression. Lithium remains by most experts and guidelines as the first-choice mood stabilizer, protecting against both depression and mania and reducing the risk of suicide and short-term mortality (Cipriani et al., 2005; Geddes et al., 2004; Grunze et al., 2013; Yatham et al., 2013). Due to its relatively narrow therapeutic range, routine therapeutic drug monitoring (TDM) of lithium is therefore necessary to ensure dosing schedules with satisfactory result avoiding severe side effects. Lithium concentrations usually range from 0.4–1.2 mEq/L in bipolar patients, however due to the increased risk of renal toxicity after chronic lithium administration, psychiatrists commonly choose a range between 0.4–0.8 mEq/L (Grandjean and Aubry, 2009; Sproule et al., 2000). Steady-state levels are likely to be reached approximately 5 days after dose adjustment. Lithium has been classified as a highly variable drug by some authors, but this variability could be related to a lack of adequate compliance of patients in some stages of the disease (Goodwin, 1999). Adherence to treatment is crucial in TDM and clinical trials because it can undermine or overestimate drug effects, and has been investigated in the past from a model-based perspective (Fellows et al., 2015; Levy, 1993).

Only few reports have analyzed the pharmacokinetics of lithium, most of them after single dose administration in healthy adults using non-compartmental analysis (Altamura et al., 1977; Findling et al., 2010; Hunter, 1988; Potkin et al., 2002). Lithium is rapidly and completely absorbed after oral administration in the upper gastrointestinal tract, with oral bioavailability of 80–100%. Other pharmacokinetic parameters are volume of distribution of 1 L/Kg and lithium clearance ranges from 0.6 to 2.4 L/h, with large inter-individual variability associated (Grandjean and Aubry, 2009; Sproule et al., 2000). Low protein binding was reported (~15%) and the excretion of lithium is almost exclusively via the kidney as a free ion. Age, creatinine clearance and body weight have been identified as predictor covariates of the pharmacokinetic parameters (Findling et al., 2010; Grandjean and Aubry, 2009; Sproule et al., 2000).

Nonlinear mixed-effects modelling method has increased its impact on TDM in the last decades (Gotta et al., 2012; Johansson et al., 2011; Kelley et al., 1997; Kim et al., 2015; van Hest et al., 2005; Zhao et al., 2013). Benefits of this methodology vs two-stage approaches are described elsewhere (Dartois et al., 2007). However, only two references are available describing the clinical routine administration of lithium using this modelling approach (ElDesoky et al., 2008; Yukawa et al., 1993). Moreover, there is a lack of references dealing with the pharmacokinetics of lithium in patients at steady-state conditions (Hunter, 1988). Therefore, the aims of the present study were: (i) to develop a population pharmacokinetic model of lithium in patients after multiple-dose schedule over a 3-months period, and (ii) to assess drug compliance in the population studied after the ambulatory administration of lithium at each treatment cycle.

2. Experimental procedures

2.1. Patient population and study design

Data were collected from patients of the Psychiatric Department in Hospital of Francesc de Borja (Spain). All patients enrolled during the study satisfied the inclusion criteria previously established: adult patients ($\geq$ 18 years old, and diagnosed with bipolar disorder) with maintenance treatment of lithium. Based on the individual pre-dose levels of lithium plasma concentration, doses levels of 200, 300, 400, or 800 mg and dosing regimens of 8, 12, or 24 h were adapted at each cycle. One plasma concentration measurement for each patient was obtained before starting next cycle (pre-dose) at steady state. Patients were provided with the number of doses prescribed for the next cycle of treatment at the Pharmacy service according to the dosing regimen established. 54 patients were enrolled in the study at cycle 1, but patients dropped out the study throughout the following cycles. Each cycle of administration was defined as 10 days of treatment. The Psychiatric Committee of the Hospital of Francesc de Borja established a therapeutic interval (TI) of 0.4–0.8 mEq/L for chronic administration of lithium in bipolar patients. All procedures were approved by each participating investigator's Institutional Review Board for Human Investigation. Different demographic, biochemical and anthropometric covariates that were not considered as inclusion/exclusion criteria were collected at each cycle and appear listed in Table 1.

2.2. Analytical determination of Lithium concentrations in plasma

Lithium plasma concentrations were analysed using the ion-selective electrode method (SpotLyte©, Menarini Diagnostics). Potentiometric quantitative lithium detection was performed using a reference electrode and membrane-indicator electrode, which is related to the drug concentration in the sample. The difference in membrane potentials shows a logarithmic relationship with lithium concentrations divided by the lithium concentration in the standard solution. SpotLyte© system calibrates itself automatically and

Please cite this article as: Pérez-Castelló, I., et al., Population pharmacokinetic model of lithium and drug compliance assessment. European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.11.005