INTRODUCTION

Lithium is an antidepressant used as primary treatment for the prevention of episode recurrences in bipolar disorder, acute treatment of mania and to a lesser extent depression. Due to its relatively narrow therapeutic range and high inter-individual (IIV) and residual (RSV) variability, routine therapeutic drug monitoring (TDM) of lithium is therefore necessary to ensure dosing schedules with satisfactory result and without severe side effects and toxicity. 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 [1-2]. Steady-state levels are likely to be reached approximately 5 days after dose adjustment.

OBJECTIVE

The objective of this work is to develop a population pharmacokinetic model, including the covariates analysis, and to assess the adherence to treatment of patients.

MATERIAL AND METHODS

96 psychiatric patients were enrolled in this study and all individuals signed or declared informed consent. All patients were diagnosed with bipolar disorder and they attended the Psychiatric Department in Hospital of Gandia. Lithium carbonate was administered to all patients at different dose levels (200, 300, 400, 600 and 800 mg) and administration intervals (8, 12 and 24 h). Different demographic, biochemical and anthropometric covariates were selected. Patients received several treatment cycles and one plasma concentration measurement for each patient was obtained always before starting next cycle (pre-dose) at steady state. Due to no experimental observations were measured before steady-state conditions, the analysis was performed assuming intravenous perfusion administration of lithium carbonate. In order to capture the concentration-time course at the individual level, different approaches were developed (Figure 1). Experimental data were fitted using non-linear mixed-effects modelling implemented in NONMEM 7.2 [3]. Inter-individual variability was described using an exponential model, inter-occasion (IOV) and residual variability were implemented using an additive model. Different approaches were implemented in order to capture the concentration profiles observed: (1) addition of IIV on CL, (2) use of Prior information and (3) IOV on bioavailability dose fraction (F1). Model selection was based on the lowest and significant OFV and goodness-of-fit (GOF) plots. Covariate analysis was performed manually, adding the covariates into the final base model. Final model evaluation was carried out using prediction corrected-visual predictive check (pc-VPC) (n=1000) and Bootstrap (n=1000) analysis.

RESULTS

Plasma observations were described using a two-compartment model. Creatinine clearance (CrCl) was selected as significant covariate on typical clearance parameter analysis was performed manually, adding the covariates into the final base model. Final model evaluation was carried out using prediction corrected-visual predictive check (pc-VPC) (n=1000) and Bootstrap (n=1000) analysis.

CONCLUSIONS

- The addition of inter-occasion variability on the bioavailability dose fraction (F1) allowed for a better characterization of the individual profiles and to assess drug compliance.
- Nearly half of the F1 estimated (46%) were different from ±10%, representing that patients did not meet the prescribed dose regimen along all monitored cycles.
- The final model was able to characterize the number of individuals/observations out of the therapeutic interval with more precision compared to the other approaches proposed.
- Therapeutic drug monitoring of lithium carbonate in bipolar patients needs better administration regimen assessment in order to keep individual concentration measurements at steady-state within the therapeutic interval.
- Future analysis might include the therapeutic interval as a clinical predictor of the drug compliance in order to guarantee better efficacy and safety outcomes.

REFERENCES