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First-Dose Pharmacokinetics of Lithium Carbonate in Children and Adolescents

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INTRODUCTION

Bipolar I disorder (BP-I) in children and adolescents is associated with substantive psychosocial dysfunction and human suffering [1,2]. Safe and effective treatments are needed to reduce symptomatology and improve quality of life for the vulnerable youngsters and families impacted by this illness.

Lithium is a benchmark treatment for adults suffering from bipolar illness [3], with evidence of benefit dating back almost 60 years [4]. However, there has been relatively little research regarding the use of lithium in the treatment of youths suffering from mania [5]. Given this paucity of information, a Written Request (WR) was issued by the Food and Drug Administration (FDA) under the auspices of the Best Pharmaceuticals for Children Act (BPCA) (FDA 2002) for the study of this agent in youths. In response, a contract was awarded to rigorously study lithium in children and adolescents with mania.

A key step in developing evidence-based dosing paradigms for any compound is the characterization of the drug's pharmacokinetics (PK) [6]. Therefore, two of the goals of this contract were to characterize the pharmacokinetics of lithium and to develop evidence-based dosing for lithium in children and adolescents [7].

Although many studies have examined the PK of lithium in adults [8–10], relatively little is known about the PK of lithium in pediatric patients. Vitiello et al. [11] described lithium PK in nine children (aged 9–12 years) with a *DSM-III-R* primary diagnosis of conduct disorder or adjustment disorder. Subjects received one single 300 mg dose of lithium carbonate. The disposition of lithium in these children appeared to generally be similar to that seen in adults. However, their elimination half-life and greater total lithium clearance were shorter than reported in adult studies.

The present study was performed in order to describe the first dose PK of lithium in children and adolescents. In addition to characterizing the disposition of lithium in children and adolescents with BP-I, we also explored whether patient-specific characteristics (e.g. age, gender and weight) influence the PK of lithium in this patient population.

MATERIALS & METHODS

The data presented herein were collected as part of an open-label clinical trial [7]. All procedures were approved by each participating investigator's Institutional Review Board for Human Investigation. The parents/guardians of all study subjects provided written informed consent and all youths provided written assent before participation.

Study Subjects

Youths aged 7 to 17 years who met *DSM-IV* (APA 1994) criteria for BP-I in a current manic or mixed state without active psychotic symptoms were eligible to participate. Subjects underwent a psychiatric interview by a child and adolescent psychiatrist. In addition, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (KSADS-PL) [12] was administered by a trained interviewer to confirm the clinician's diagnosis. Subjects also needed to receive a score of 20 or greater on the Young Mania Rating Scale (YMRS) [13] both at screening and at the initiation of lithium dosing. Subjects were required to be in good physical health and capable of swallowing study medication as whole lithium carbonate capsules.

Subjects with a current diagnosis of schizophrenia, schizoaffective disorder, a pervasive developmental disorder, anorexia nervosa, bulimia nervosa, substance dependence, or

obsessive-compulsive disorder were excluded. Also, subjects with an intelligence quotient less than 70 based on the results of the Wechsler Abbreviated Scales of Intelligence (WASI) Vocabulary and Matrix Reasoning Subscales [14] were not included. Other exclusion criteria included positive screens for drugs of abuse during screening and at retest 1 to 3 weeks later, current general medical conditions and unstable medical illnesses that might be affected adversely by lithium or could influence the efficacy or safety of lithium, a previous trial with lithium lasting at least 4 weeks with trough serum concentrations between 0.8–1.2 mEq/L, or a history of an allergy or adverse reaction to lithium. Furthermore, subjects could not be taking: psychotropic agents other than stimulants within the preceding 2 weeks, stimulants within the preceding week, or fluoxetine or depot antipsychotics within the past month.

Potential subjects that had a psychiatric hospitalization within 1 month of screening for psychosis or serious homicidal/serious suicidal ideation or who were currently experiencing active hallucinations or delusions were also excluded. Youth with symptoms of mania that may be attributable to a general medical condition or secondary to use of medications were not eligible. Sexually active females who were not using adequate forms of birth control were not eligible. Additionally, female subjects were ineligible if they were currently pregnant or lactating.

The screening period to determine subject eligibility was 3–28 days in duration. Subjects currently receiving fluoxetine at the screen were able to have an extended screening period lasting up to, but not exceeding, 6 weeks.

Medication Dosing and Sample Collection

Prior to their first dose, subjects were required to fast for at least 8 hours. Eligibility criteria were reviewed and confirmed prior to receiving the first dose of medication. Subjects weighing less than 20 kg were to receive a single dose of 300 mg (arm I). Subjects weighing 20 kg or more were randomly assigned to receive either a single 600 mg (arm I) or 900 mg (arm II) dose of lithium. Randomization assignments were stratified by age (children: 7–11 years vs. adolescents: 12–17 years) and sex.

Blood samples for lithium serum levels were obtained pre-single dose, and at 0.5, 1, 1.5, 2, 4, 8, 12, and 24 hours post-dose. The patients were admitted to the clinical research center for the first 24 hours of the study. In addition, subjects were randomly assigned in a 1:1 ratio to return to the study site for collection of a single blood sample to assess lithium serum concentration at either 48 or 72 hours post-dose.

Safety Assessments

Prior to the subject receiving lithium, an electrocardiogram (ECG), a physical examination, and a determination of sexual maturation [15,16] was performed. Blood pressure and pulse were measured prior to receiving lithium and at 2, 8, and 24 hours after the single dose.

Additionally, laboratory examinations, including a chemistry profile, complete blood count with differential, urine toxicology screen, urinalysis, thyroid stimulating hormone (TSH), triiodothyronin (T3), serum thyroxine (T4), anti-thyroid antibody, urine (on the day of dosing) and a serum (during the screening process) pregnancy test for females was obtained prior to subjects receiving their first dose of lithium carbonate. The collection of a 24 hour urine sample was also initiated immediately prior to the first dose of lithium in order to determine creatinine clearance. Spontaneously reported adverse events were recorded during the blood sample collection period.

Lithium Assays

Lithium concentrations in serum were measured using standard clinical chemistry methods available at each site. These included: the LI Flex reagent cartridge (Dade Behring) used on the Dimension Clinical Chemistry System, a lithium Ion-Specific Electrode in a DuPont Na/K/Li Analyzer, the colorimetric Vitros Li Slide method on a Vitros chemistry system at 3 sites, and a spectrophotometric method on the Beckman Coulter Synchron chemistry analyzer at 2 sites. Concentrations were reported in a format with 2 significant digits after the decimal point from centers 1, 2, and 4, and with one such significant digit from centers 3, 6, 7, and 8. The lower limit of quantification was 0.20 mEq/L for samples which were analyzed at centers 1, 3, 4, 7 and 8, and was 0.25 mEq/L at centers 2 and 6.

Pharmacokinetic Analyses

The creatinine clearance was both measured directly and calculated using the Schwartz method [17,18] in subjects under 12 years of age. The Cockcroft-Gault method [19] was used for all other subjects.

Statistical Analyses

Nominal data are reported as frequencies and percents and continuous data are reported as means and standard deviations unless otherwise noted.

Population Pharmacokinetic Analyses

One-, two-, and three-compartment disposition models with first-order, zero-order, sequential zero- and first-order, and mixed-order absorption, with or without lag-time of oral absorption were considered. First-order, mixed-order, and parallel first-order and mixed-order elimination were assessed. Competing models were evaluated by their predictive performance assessed via visual predictive checks, NONMEM's objective function, and residual plots.

A model with two disposition compartments and first-order absorption and elimination was chosen as the structural model (base model). The amount of lithium in the absorption compartment (A_{gut}) and initial condition is

$$\frac{dA_{gut}}{dt} = -k_a \cdot A_{gut} \qquad A_{gut}(0) = \text{Dose}$$

where k_a (h^{-1}) is the absorption rate constant for lithium. The amount of lithium in the central compartment (A_c) is

$$\frac{dA_c}{dt} = k_a \cdot A_{gut} - \frac{CL + CL_{ic}}{V_c} \cdot A_c + \frac{CL_{ic}}{V_p} \cdot A_p \qquad A_c(0) = 0$$

where CL (L/h) is the apparent elimination clearance of lithium, CL_{ic} (L/h) is the apparent intercompartmental clearance, and V_c (L) and V_p (L) are the apparent volumes of distribution of the central and peripheral compartments. The total volume of distribution is described by $V_c + V_p$. The amount in the peripheral compartment (A_p) is

$$\frac{dA_p}{dt} = \frac{CL_{ic}}{V_c} \cdot A_c - \frac{CL_{ic}}{V_p} \cdot A_p \qquad A_p(0) = 0$$

For the visual predictive check, the plasma concentration profiles were simulated for 20,000 subjects for each competing model and assessed for the whole dataset and for each dose separately. From these data the median, the nonparametric 80% prediction interval (10% to 90% percentile), and the nonparametric 50% prediction interval (25% to 75% percentile) were calculated for the predicted plasma concentrations. These prediction interval lines were then over-laid on the original raw data. If the model described the data adequately, then 20% of the observed data points should fall outside the 80% prediction interval at each time point and 50% of the data should fall outside the interquartile range. The median predicted concentrations and the prediction intervals were compared with the observed data. It was assessed whether the median and the prediction intervals mirrored the central tendency and the variability of the observed data for the various models.

The between subject variability (BSV) was estimated for all PK parameters with an exponential parameter variability model. The residual unidentified variability was described by a combined additive and proportional error model.

Possible relationships between patient specific covariates such as body size, age, gender, sexual maturation and renal function, and the individual pharmacokinetic parameter estimates were first explored by graphical analysis. The individual estimates for eta (deviation of the individual estimate from the population mean) of the respective pharmacokinetic parameters were plotted against the individual values of the covariate (eta-plots). Several body size descriptors such as total body weight, body mass index (BMI), and fat-free mass (FFM) [20] were tested. The effect of body size on the pharmacokinetic parameters was predicated on allometric scaling based on FFM as follows:

$$V_i = V_{pop} \cdot \frac{FFM_i}{FFM_{std}}$$

$$CL_i = CL_{pop} \left(\frac{FFM_i}{FFM_{std}} \right)^{0.75}$$

where V_i and V_{pop} are the group and populaton estimates of volume of distribution for all subjects with the same FFM, FFM_i is the individual FFM, and FFM_{std} is a standard FFM chosen at 53 kg to enable comparisons with adult subjects. The CL_i and CL_{pop} are the group and population estimates of clearance for all subjects with the same FFM. Similar equations were used for allometric scaling based on a standard body weight of 70 kg.

After accounting for body size and body composition, the potential effect of other covariates was assessed. Covariates were introduced into the model in a stepwise fashion. Inclusion of a specific covariate in the final model was based on visual analysis of eta-plots, change in NONMEM's objective function, and the reduction in BSV.

Computation

The Laplacian estimation method with the interaction estimation option in NONMEM version VI level 1.1 (NONMEM Project Group, University of California, San Francisco, CA, USA) was used for population PK modeling and simulation. The Beal M3 method [21] was implemented with the F-FLAG option in NONMEM in order to consider concentrations below the quantification limit. The individual limits of quantification for each site were included.

RESULTS

Demographics

Thirty-nine subjects were enrolled into treatment arms I and II across seven study sites and received the single dose of study medication. No subjects who received study medication

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