Population Pharmacokinetics of Valproic Acid in Patients with Mania: Implication for Individualized Dosing Regimens

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ABSTRACT

Purpose: This study characterized the population pharmacokinetic properties of valproic acid in patients with mania and determined potential factors that affect the pharmacokinetic properties of valproic acid in this population.

Methods: Routine therapeutic drug monitoring of valproic acid concentrations, demographic data, and concomitant medications from 206 hospitalized patients with mania were retrospectively collected from Somdet Chaopraya Institute of Psychiatry and Srithanya Hospital, Thailand. Nonlinear mixed-effect modeling was used for data analysis. Covariate model building was conducted using stepwise forward addition and stepwise backward elimination. The final model was evaluated using bootstrap analysis and normalized prediction distribution error. The results were compared with those previously reported in patients with epilepsy given that there is an evidence of a difference in valproic acid clearance between patients with mania and those with epilepsy.

Findings: Valproic acid data were adequately described by a 1-compartment model. Significant predictors for valproic acid clearance included valproic acid dose and weight. The population estimates for valproic acid CL/F and V/F were 0.464 L/h and 23.3 L, respectively. Valproic acid clearance obtained from this study did not seem to be significantly different from that of patients with epilepsy.

Implications: A qualified population pharmacokinetic model for valproic acid in patients with mania was developed. This model could be used to optimize valproic acid therapy in patients with mania. Valproic acid clearance could be predicted from valproic acid dose and weight of patients. This predicted clearance can subsequently be used for individualization of optimum valproic acid maintenance dose. (*Clin Ther.* 2017;39:1171–1181) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: bipolar disorder, mania, pharmacokinetic properties, population pharmacokinetic model, valproate, valproic acid.

INTRODUCTION

Although valproic acid (VPA) is widely used as an antiepileptic drug in the treatment of generalized and partial seizures, it also exerts activity for treatment of bipolar disorder and prevention of migraine attacks.[1,2] The drug is characterized as having a narrow therapeutic window and large intersubject pharmacokinetic variability. The initial VPA dose of 750 mg/d is generally recommended for the treatment of bipolar disorder. The dose is subsequently titrated upward as tolerated to a maximum dose of 1000 to 2000 mg/d.[3] The accepted therapeutic range of VPA for seizure control is 50 to 100 mg/L. However, Hiemke et al[4] reported that VPA levels above 120 mg/L are tolerated in acute mania. The therapeutic range of 50 to 125 mg/L is usually suggested for the treatment of bipolar disorder.[1,3,5] Most of the drug (95%) is eliminated through hepatic metabolism. There is a high variability of volume of distribution (V_d) of VPA, ranging from 0.1 to 0.5 L/kg.[1] Given its narrow therapeutic window and large intersubject pharmacokinetic variability, therapeutic drug

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monitoring (TDM) and individualized dosing regimens are important. In clinical settings where only one blood sample per patient is usually obtained, it is difficult to determine individual pharmacokinetic parameters, and the mean parameters from the reference population will be used for dosing. However, these mean parameters were conducted in white populations, which might be different from Asian populations.[6]

Several studies have proposed that a population pharmacokinetic model with Bayesian prediction offers benefits in guiding dosage adjustment. Even though several population pharmacokinetic modeling studies of VPA have been reported, all of them were conducted in patients with epilepsy. However, there is an evidence that VPA clearances in patients with acute mania are significantly higher than those in patients with epilepsy (10.35 vs 7.70 mL/kg/h), which may be accounted for by membrane transport system abnormalities that affect cellular uptake of the drug and its V_d.[7] Moreover, most population pharmacokinetic modeling studies of VPA conducted using routine TDM data did not address the differences in absorption rate constant (K_a) between extended-release and controlled-release dosage forms. On the basis of these considerations with the lack of pharmacokinetic studies describing factors that affect pharmacokinetic characteristics of VPA in patients with mania, the objectives of this study were to conduct a population pharmacokinetic modeling study of VPA in patients with mania using routine TDM data and to identify potential covariates that affect pharmacokinetic properties of VPA in this population. The results of this study can help guiding clinicians in VPA dosage adjustment in patients with mania.

METHODS

Patient Data

Data on steady-state serum concentrations of VPA were collected retrospectively from Thai patients with mania exposed to routine monitoring of VPA at Somdet Chaopraya Institute of Psychiatry and Srithanya Hospital, Thailand during January 2009 to December 2016. Patients with mania were identified and recorded in medical records by physicians according to the *International Classification of Diseases, Tenth Revision* (ICD-10) criteria. Patients of all ages were eligible to be recruited in this study. The protocol of this study was approved by ethics committee of Naresuan University, Somdet Chaopraya Institute of Psychiatry and Srithanya Hospital. All patients received VPA orally as enteric coated or controlled-release dosage forms 1 to 3 times a day with the dose range of 250 to 2000 mg/d. According to a routine policy of drug sampling in the hospitals, data on trough concentrations at the end of the dosing interval, before the morning dose, were collected for analysis to minimize diurnal variations in plasma protein binding. All patients had normal kidney and liver functions as well as normal serum albumin levels, which are defined as serum creatinine <1.5 mg/dL, alanine aminotransferase <45 U/L, aspartate aminotransferase <45 U/L, and serum albumin levels within the range of 3.5 to 5.0 g/dL.

Drug Analysis

Serum VPA concentrations were measured using the Homogeneous Enzyme Immunoassay Technique (Cobas Mira; Roche Diagnostics, Basel, Switzerland) with a lower limit of quantitation of 1 mg/L. The inter-assay and intra-assay %CV was $<10\%$.

Population Pharmacokinetic Analysis

Population pharmacokinetic modeling of VPA was conducted using a nonlinear mixed-effect modeling approach via NONMEM software version 7.3 (ICON Development Solutions, San Antonio, Texas). PDx-Pop version 5.1 (ICON Development Solutions) and Xpose version 4.3.0 (Uppsala University, Uppsala, Sweden) were used to generate NONMEM output. Graphical plots were performed using R 2.10.1 (The R Foundation for Statistical Computing, Vienna, Austria). VPA pharmacokinetic models were built using a first-order conditional estimation method with interaction. Criteria for model selection included (1) minimum objective function value (MOFV), equivalent to minus twice the log likelihood function; (2) Akaike information criteria, equivalent to MOFV plus 2 times the number of parameters; (3) a condition number, defined as the ratio of the largest Eigen value to the smallest Eigen value; (4) goodness-of-fit plots; and (5) plausibility and precision of parameter estimates.

Given the sparse sampling strategy of VPA concentrations, basic model development was conducted using a 1-compartment pharmacokinetic model with first-order absorption and elimination in PREDPP subroutines ADVAN2, TRANS2. Parameterization of the model was used with K_a, CL/F, and V/F.