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Factors influencing topiramate clearance in adult patients with epilepsy: A population pharmacokinetic analysis

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ABSTRACT

Purpose: To identify the factors influencing topiramate pharmacokinetics (PK) in a large population of adult patients with epilepsy using population PK analysis.
Methods: Clinical data and blood samples were collected from 550 adult patients with epilepsy treated using topiramate. Nonlinear mixed effects modeling software (NONMEM, version 7.2) was used to fit the plasma concentration to a one-compartment PK model. Demographic and clinical variables tested as potential covariates were age, sex, body weight, height, serum creatinine, creatinine clearance (CLcr), total bilirubin, prothrombin time, albumin, aspartate transaminase (AST), alanine transaminase (ALT), daily dose (DOSE), and concomitant medications (phenytoin [PHT], clobazam, carbamazepine [CBZ], valproic acid, lamotrigine, levetiracetam, oxcarbazepine [OXC], pregabalin, clonazepam, and phenobarbital [PB]).
Results: The final PK model was $CL/F\ (L/h) = (1.16 + 1.36 \times PHT + 1.01 \times CBZ + 0.643 \times OXC + 0.476 \times PB) \times (CLcr/90)^{0.310} \times (DOSE/100)^{0.0929}$ (1 in patients co-medicated with each drug, 0 in otherwise) and $V/F\ (L) = 109 \times (WT/62)$. For a typical patient with CLcr of 90 mL/min and DOSE of 100 mg, co–medication with PHT, CBZ, OXC, and PB increased the CL/F to 2.52 (1.16 + 1.36) L/h, 2.17 (1.16 + 1.01) L/h, 1.803 (1.16 + 0.643) L/h, and 1.636 (1.16 + 0.476) L/h, respectively, which was 117, 87, 55, and 41% higher, respectively, than in patients without co-medication.
Conclusion: The apparent clearance of topiramate increased with co-medication of PHT, CBZ, OXC, and PB. This population PK model can be applied for optimizing topiramate dosage regimens in actual clinical practice.

1. Introduction

Topiramate is a second-generation broad-spectrum antiepileptic drug (AED) with multiple mechanisms of action that is approved as monotherapy or adjunctive therapy in the treatment of adult and pediatric patients with generalized tonic–clonic seizures, partial seizures with or without generalized seizures, and seizures associated with Lennox–Gastaut syndrome [1–3]. The pharmacokinetic (PK) profile of topiramate is characterized by a linear PK within the recommended dosing range, low oral clearance, which, in monotherapy, is predominantly through renal excretion, and a long half-life [1]. The clearance of topiramate is known to be affected by various factors, including age, renal function, and concomitant medication. To begin with age, the oral clearance of topiramate is highest in young children and decreases progressively with age until puberty, presumably because of age-dependent changes in the rate of drug metabolism [4]. In addition, because topiramate is primarily excreted by the kidney, the mean topiramate exposure increases with increasing degree of renal impairment. Therefore, dose adjustment is necessary in patients with moderate to severe renal impairment [5]. Lastly, concurrent medication, especially enzyme (cytochrome P450)-inducing AEDs, can alter the clearance of topiramate in the patients on polytherapy. Although approximately 20–30% of topiramate is metabolized when it is administered as monotherapy, the

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metabolized proportion of the dose increases to 50–70% in patients receiving enzyme-inducing AEDs (e.g. carbamazepine and phenytoin) [6]. Therefore, during concomitant treatment with topiramate and carbamazepine or phenytoin, topiramate clearance increases 2-fold and its half-life becomes shorter by up to 50%. This PK change may require topiramate dose adjustment when phenytoin or carbamazepine are added or discontinued [1]. However, these factors have not been thoroughly quantified, and remain controversial for non-enzyme-inducing or second-generation AEDs [7,8]. Since topiramate is more commonly used for epilepsy treatment in polytherapy rather than in monotherapy, more information about the influence of co-medication on the PK properties of topiramate is needed. Therefore, the main objective of the present study was to identify the factors influencing topiramate PK in a large population of adult patients with epilepsy using population PK analysis.

2. Materials and methods

2.1. Patients

We collected 670 blood samples of 550 adult patients treated with topiramate with or without concomitant AEDs for epilepsy from February 2011 to May 2013 at the epilepsy center, Seoul National University Hospital, Seoul, Korea. Blood samples were drawn from each patient in a steady state. Data, including demographic characteristics, weight, height, age, and sex; results of biochemical analysis, serum creatinine, creatinine clearance, serum transaminases (aspartate transaminase [AST] and alanine transaminase [ALT]), total bilirubin, albumin and prothrombin time; concomitant drug therapy, dosing regimen, and times of blood sampling were collected from electronic medical charts. Written informed consent was obtained from all patients. The study was approved by the institutional review board of Seoul National University Hospital.

2.2. Determination of topiramate concentration

Plasma concentrations of topiramate were determined using positive ion liquid chromatography (LC) (Agilent 1100 series; Agilent Technologies, Wilmington, DE, USA)–tandem mass spectrometry (MS/MS) (API 4000TM instrument; Applied Biosystems/MDS Sciex, Toronto, Canada). Chromatographic separation was performed at 30 °C using a Luna® C18 column (50 × 2.0 mm, 5 μm Phenomenex, Torrance, CA, USA) operated under reverse-phase conditions with a mobile phase A (10 mmol/L ammonium acetate:acetonitrile = 90:10, v/v) with 0.1% formic acid and mobile phase B (10 mmol/L ammonium acetate:methanol:acetonitrile = 10:45:45, v/v) with 0.1% formic acid. The standard curve for topiramate was linear in the range of 20–2,000 ng/mL. Intra-batch and inter-batch accuracy ranged from 89.11 to 99.48%, while the precision ranged from 2.70 to 6.54% at concentrations of 50, 500, and 1600 ng/mL.

2.3. Population PK model

A population PK analysis was conducted using the first-order conditional estimation method in NONMEM version 7.2 (Icon Development Solutions, Ellicott City, MD, USA) with the G77 Fortran compiler. The structural model of topiramate was assumed to follow a one-compartment model with first-order absorption and elimination (ADVAN2, TRANS2). Absorption rate constant (k_a) was fixed at 2 h^{-1} as the same method used in a previous report [8]. Apparent clearance (CL/F) and apparent volume of distribution (V/F) were estimated in the model development process.

Inter-individual variability (IIV) of PK parameters was evaluated using an exponential error model, and the PK parameters of the ith subject (P_i) were described as the following equation:

$$P_i = \theta \times \exp(\eta_i)$$

where θ is the typical value of the PK parameters, and η_i is a random variable of the *ith* subject. Additive, proportional, and combined (additive and proportional) error models were compared with assess residual variability. Model selection was based on the likelihood-ratio test, Akaike information criterion, and goodness-of-fit including the distribution of conditional weighted residuals vs. time after dose. A decrease in the objective function value (OFV) greater than 3.84 (α = 0.05, df = 1) between two nested models was considered significant.

Demographic and clinical variables tested as potential covariates were age, sex, body weight (WT), height, serum creatinine, creatinine clearance (CLcr), total bilirubin, prothrombin time, albumin, AST, ALT, daily dose (DOSE), and concomitant medications (phenytoin [PHT], clobazam, carbamazepine [CBZ], valproic acid, lamotrigine, levetiracetam, oxcarbazepine [OXC], pregabalin, clonazepam, phenobarbital [PB], and alprazolam). CLcr was estimated by the modification of diet in renal disease (MDRD) formula [9] and prothrombin time was expressed as an international normalized ratio. When a variable was missing in a patient, this value was replaced by the population median value. The covariate model was built in a stepwise fashion with forward selection and backward deletion. Each covariate was included to the base model one at a time in the forward selection based on previously described model selection criteria. The full covariate model was developed by incorporating all significant covariates. At the backward deletion step, covariates that did not increase the minimized OFV by more than 6.63 (α = 0.01, df = 1) were deleted from the full model.

2.4. Model evaluation

A bootstrap resampling method and visual predictive checks (VPCs) were used to evaluate the stability and robustness of the final PK model. The final PK model was fitted repeatedly to the 1,000 bootstrap-resampled data sets from the original data set. The median and 95% confidence intervals (CIs) of PK parameters obtained from the bootstrap process were compared with the final parameter estimates. VPCs were performed by simulating 1,000 data sets from the final model. The 5th, 50th, and 95th percentile curves of the simulated concentrations at each time were overlaid with observed concentrations classified by significant covariates.

3. Results

3.1.1. Characteristics of the patients

Baseline characteristics of the patients are summarized in Table 1. All 550 patients (222 male) were included in the analysis. The mean age was 39.0 years (range 18-75 years) and the mean weight was 63.9 kg (range 27−128 kg). Median daily dose and plasma concentration of topiramate were 100 mg (range 25−1000 mg) and 3.2 mg/L (range 0.4−19.7 mg/L), respectively. Topiramate was used as monotherapy in 55 patients (10%). Otherwise, it was mostly used in polytherapy with multiple AEDs. The numbers of concomitant AEDs were one in 172 patients (31.3%), two in 145 (26.4%), three in 114 (20.7%), and four or more in 64 patients (11.6%). The five most frequently used concomitant AEDs were levetiracetam, CBZ, valproic acid, OXC, and lamotrigine, in that order.