의학박사 학위논문

성인 뇌전증 환자에서 Topiramate 약동학에 영향을 미치는 ‘ 인자에 관한 연구: 집단 약동학적 분석

Factors Influencing Topiramate Pharmacokinetics in Adult Patients with Epilepsy: A Population Pharmacokinetic Analysis

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Abstract

Background: Topiramate is widely used as an antiepileptic drug (AED) in the treatment of epilepsy. The pharmacokinetics (PK) of topiramate are known to be influenced by various factors such as age, renal function, and concomitant medication. However, these factors have not been thoroughly quantified and remain controversial. The 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.

Materials and Methods: Clinical data and blood samples were collected from 553 adult patients with epilepsy treated using topiramate with or without concomitant AEDs. Plasma concentrations of topiramate in a steady state were determined by liquid chromatography-tandem mass spectrometry. 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]). In addition, the efficacy and adverse events of topiramate were analyzed according to the level of daily dose per body weight and plasma concentration.

Results: The final PK model was CL/F (L/h) = $(1.17 + 1.36\times PHT + 1.02\times CBZ + 0.621\times OXC + 0.488\times PB) \times (CLcr/90)^{0.289} \times (DOSE/100)^{0.0894}$ (1 in patients co−medicated with each drug, 0 in otherwise) and V/F (L) = 108 × (WT/62). For a typical patient with CLcr of 90 mL/min and DOSE of 100 mg, the CL/F was expected to be 1.17 L/h. Co−medication with PHT, CBZ, OXC, and PB increased the CL/F to 2.53 (1.17+1.36) L/h, 2.19 (1.17 + 1.02) L/h, 1.791 (1.17+0.621) L/h, and 1.658 (1.17+0.488) L/h, respectively, which was 116%, 87%, 53%, and 42% higher, respectively, than in patients without co-medication. Two hundred sixty-four patients (48%) were seizure free, 236 (43%) had at least 50% seizure reduction, and 52 (9%) had less than 50% seizure reduction. One hundred thirty-eight patients

(25%) reported adverse events, including memory impairment, dizziness, anomia, weight loss, paresthesia, and appetite loss. The efficacy and adverse events of topiramate did not show any clinically relevant relationship with the daily dose per body weight or plasma concentration.

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, especially for the patients on polytherapy with PHT, CBZ, OXC, and PB. Individualization of therapeutic dose and plasma concentration is needed for epilepsy patients treated with topiramate.

Keywords

Topiramate; epilepsy; population pharmacokinetics; NONMEM

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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 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. Especially in actual clinical practice, topiramate is more commonly used for epilepsy in combination, 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. In addition, we investigated the clinical response (efficacy and adverse events) of topiramate

according to the level of daily dose per body weight and steady-state plasma concentrations.

Materials and Methods

Patients

We collected 673 blood samples of 553 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. The efficacy (seizure control) and adverse events of topiramate were assessed by an attending epileptologist based on the interview and chart record for at least three consecutive months. Written informed consent was obtained from all patients. The study was approved by the institutional review board of Seoul National University Hospital.

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.

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). Because the available concentration data contained little information about the absorption phase, absorption rate constant (k_a) could not be estimated properly and was fixed at 2 h^{-1} as the same method used in a previous report.[7] 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 i^{th} 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 i^{th} subject. Additive, proportional, and combined (additive and proportional) error models were compared to 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 ($\alpha = 0.05$, 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 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 ($\alpha = 0.01$, df = 1) were deleted from the full model.

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.

Statistical analysis of clinical response

To evaluate the efficacy and adverse events of topiramate according to the daily dose per body weight and plasma concentration, we divided patients into tertiles because these independent variables did not distribute normally. The proportions of patients with seizure-free outcomes or adverse events according to tertiles were compared using a chi-square test. For comparisons of the mean daily dose per body weight and plasma concentration according to the clinical response, an analysis of variance (ANOVA) followed by a Bonferroni correction was applied. '*P*' values of < 0.05 were considered significant. Statistical analyses were performed using SPSS version 19.0 (IBM Corp, Armonk, NY, USA).

Results

Characteristics of the patients

Baseline characteristics of the patients are summarized in Table 1. All 553 patients (223 male) were included in the analysis. The mean age was 38.9 years (range 14-75 years) and the mean weight was 63.9 kg (range 27-128 kg). Mean daily dose and plasma concentration of topiramate were 152.6 mg (range 25-1000 mg) and 3.6 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 174 patients (31.5%), two in 145 (26.2%), three in 115 (20.8%), 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.

Population PK model

A one−compartmental model with combined residual errors most adequately described the topiramate concentration−time profiles. The final model was CL/F (L/h) = (1.17 + 1.36×PHT + 1.02×CBZ + 0.621×OXC + 0.488×PB) × $(CLcr/90)^{0.289}$ × $(DOSE/100)^{0.0894}$ (1 in patients co−medicated with each drug, 0 in otherwise) and V/F (L) = 108 × (WT/62). Because of sparse data, IIV was included only for CL/F and estimated as 13.9% in the final model. Covariate analysis showed that CLcr, DOSE, and concomitant medications with CBZ, OXC, PHT, and PB were included as significant covariates on the CL/F. For a typical patient with CLcr of 90 mL/min and DOSE of 100 mg, the CL/F was expected to be 1.17 L/h. With co−medication of PHT, CBZ, OXC, and PB, the CL/F was increased to 2.53 (1.17 + 1.36) L/h, 2.19 (1.17 + 1.02) L/h, 1.791 (1.17 + 0.621) L/h, and 1.658 (1.17 + 0.488) L/h, respectively. The basic goodness-of-fit plots of the final PK model are shown in Figure 1 and indicate that individual predicted topiramate concentrations were consistent with the observed data without systemic bias. The parameter estimates of the final PK model and bootstrap results (bootstrap medians and 95% CIs) are summarized in Table 2. The median parameter estimates obtained from the bootstrap process were reasonably similar to the estimates obtained previously with the original data set. VPCs of the final PK

model are presented in Figures 2 and 3 (topiramate 200 mg and topiramate 100 mg, respectively) and stratified by concomitant medications.

Clinical response

Two hundred sixty-five patients (48%) were seizure free, 236 (43%) had at least 50% seizure reduction, and 52 (9%) had less than 50% seizure reduction (Figure 4). When subjects were grouped based on tertiles of daily dose per body weight, patients tended to be more seizure free in the lower tertiles than in the highest tertile ($p < 0.001$). Plasma concentration did not show any significant association with the efficacy. Seizure-free patients had a lower mean daily dose per body weight than patients with $\geq 50\%$ seizure reduction (Figure 5). Although the mean plasma topiramate concentration of seizure-free patients was also lower, this trend was not significant (Figure 6). One hundred thirty-eight patients (25%) reported adverse events, including memory impairment (52 patients), dizziness(18), anomia(18), weight loss (14), paresthesia (11), appetite loss (10), ataxia (6), depression (6), somnolence (5), diplopia (5), nausea (3), hair loss (3), bradykinesia (2), anhidrosis (1), dysarthria (1), and indigestion (1) (Figure 7). The daily dose per body weight and plasma concentration divided into tertiles were not related the occurrence of adverse events. The mean daily dose per body weight and plasma concentration were not significantly different between the patients with and without any adverse events (Figures 8 and 9).

Discussion

This study systematically analyzed the influence of various covariates on topiramate PK by a nonlinear mixed effects modeling approach in the largest group of patients ever reported to our knowledge. Moreover, we explored the clinical significance of topiramate in the treatment of epilepsy, studying the relationship between topiramate daily dose/plasma concentrations and the clinical response. The covariate analysis showed that CLcr, DOSE, and co-medication with PHT, CBZ, OXC, and PB were included as significant covariates on the CL/F.

Population PK studies of topiramate use in epilepsy to guide the dosing regimen are limited.

Population PK models can be important extensions of therapeutic drug monitoring because they allow estimation of individual PK parameters from a large number of patients, but based on a small number of sparsely measured drug concentrations in each patient.[8] In the present study, topiramate CL/F of a typical patient with CLcr of 90 mL/min and dose of 100 mg, was expected to be 1.17 L/h. This is a little lower, but comparable with the findings of previous studies that reported topiramate CL/F to be between approximately 1.2 and 1.8 L/h.[7, 9, 10] Our study population, which included patients with greater age, lower body weight, and lower daily doses compared with previous studies [7, 9] might have influenced the lower clearance. Topiramate CL/F was found to increase with co-treatment with PHT, CBZ, OXC, and PB. Topiramate CL/F was 116%, 87%, 53%, and 42% higher in patients co-treated with PHT, CBZ, OXC, and PB, respectively, compared to patients on topiramate monotherapy. Co-medication is one of important contributors to PK variability. Drug interactions must be carefully considered when multiple drugs are prescribed.[11] Topiramate is more often given as an add-on therapy than as a monotherapy, therefore this PK interaction has particular significance for treatment with topiramate. Previous studies demonstrate that co-treatment with enzyme-inducing AEDs (CBZ, PHT, PB, and primidone) enhances hepatic metabolism of topiramate.[1, 7, 9, 11, 12] Although the specific cytochrome P450 isoenzymes for the metabolism of topiramate have not yet been identified, it seems evident that isoenzymes induced by carbamazepine and phenytoin play a major role.[13] Our results with CBZ, PHT, and PB are consistent with those of previous studies. Furthermore, our findings regarding OXC are worthy of notice. Although a few studies suggested that OXC induces the metabolism of and decreases the serum levels of topiramate,[13] the impact of OXC on topiramate PK is less known and controversial. Our study showed that OXC is the only second-generation AED among the frequently used concomitant AEDs that can influence the clearance of topiramate. The impact of OXC on topiramate was greater than that of PB. On the other hand, valproic acid, lamotrigine, and levetiracetam have no significant effect on topiramate CL/F. This is consistent with the findings of some previous studies where valproic acid, lamotrigine, and levetiracetam were not found to have any clinically significant influence on topiramate PK.[1, 14, 15] There have been some controversial reports about the impact of valproic acid on topiramate clearance.[11, 16, 17] However, we could not confirm

those findings, and their clinical significance is uncertain. Nevertheless, careful precaution against adverse events is needed when topiramate is used with valproic acid, because topiramate can enhance the risk of valproic acid-induced adverse events, such as encephalopathy, [18] and other typical side effects.[19]

Renal function (CLcr calculated by MDRD) demonstrated significant influence on topiramate CL/F in this study. This was expected, because topiramate is excreted predominantly unchanged through the kidneys.[3] Mean topiramate CL/F in patients with mild to moderate and severe renal impairment was reduced by 58% and 46%, respectively, compared with matching healthy participants.[5] Meanwhile, hepatic function (AST, ALT, total bilirubin, prothrombin time, and albumin) did not exert significant influence on topiramate CL/F in our study. Although topiramate is also eliminated by hepatic clearance via hydroxylation and hydrolysis metabolic pathways,[20] the clinical significance of hepatic function on topiramate clearance in monotherapy is low as compared with renal function.

There is a correlation between age and topiramate CL/F in populations of children and adults with epilepsy.[4, 7, 12, 21] However, we did not find a significant influence of age on topiramate CL/F. This is in part because our study population was composed of mainly adult patients. Previous studies showed a relationship between age and CL/F in children; however, the relationship was absent in patients older than 17 years.[4, 15] In addition, we used CLcr calculated by the MDRD formula, including a factor for age. Accordingly age could probably influence topiramate CL/F via CLcr in an inverse correlation. Even so, we could not estimate the independent impact of age.

Topiramate showed a favorable efficacy for seizure control in most of our patients; 91% of the patients had over 50% seizure reduction, and 48% were seizure free. Seizure-free patients tended to be in the lower tertiles of daily dose per body weight, and had a lower mean daily dose per body weight than patients with $\geq 50\%$ seizure reduction. Patients with $\geq 50\%$ seizure reduction tended to have the highest daily dose per body weight and plasma concentration among the groups categorized by efficacy. This seems to be natural because physicians do not have a reason to increase the dose if the patient is seizure free or nearly intractable. This result showed that there was a tendency to increase the dose when the

drug has a favorable effect (≥50% reduction). Although the range of daily doses in seizure-free patients was wide, from 25 mg/day to 1000 mg/day, the majority of seizure-free patients (73.6%) were prescribed less than 150 mg/day. This suggests that we can achieve a seizure-free outcome with a relatively lower dose of topiramate than expected. The profile of adverse events in our study was consistent with previous reports.[6, 22-24] The daily dose per body weight and plasma concentration were not related to the occurrence of adverse events. Although some previous studies reported a relationship between plasma concentration and the occurrence of adverse events,[25, 26] we could not find any relationship in the daily dose range of between 25 mg and 1000 mg in this study. Therefore, individualization of therapeutic dose and plasma concentration is particularly needed for epilepsy patients treated by topiramate.

A limitation of our study is the sparse sampling, especially in the absorption phase. However, population PK analysis helped to overcome this limitation because it does not require "rich" data (many observations/subject), as required for analysis of single-subject data, nor is there a need for structured sampling time schedules.[27]

In conclusion, the population PK analysis successfully described the PK of topiramate in the adult patients with epilepsy in our study. This indicated that topiramate CL/F increased with co-medication with PHT, CBZ, OXC, and PB. This population PK model can be helpful for individualizing the topiramate dosage regimen in a real clinical practice, especially for patients on polytherapy with PHT, CBZ, OXC, and PB.

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Table 1. Characteristics of the patients and concomitant medication

Characteristic	Number of patients	Mean ± SD	Median (Range)
Sex			
Male	223		
Female	330		
Age (years)	553[a]	38.9 ± 12.0	38 (14−75)
Body weight (kg)	489[a]	63.9 ± 12.9	62 (27−128)
Height (cm)	482[a]	164 ± 8.31	164(137−189)
Serum creatinine (mg/dL)	541[a]	0.83 ± 0.18	0.81 (0.27−1.91)
Creatinine clearance[b] (mL/min)	541[a]	92.0 ± 20.9	90.0(9.45−287.6)
Total bilirubin (mg/dL)	541[a]	0.52 ± 0.34	0.50 (0.20−6.7)
Prothrombin time[C]	262[a]	1.06 ± 0.23	1.04(0.88−4.33)
Albumin (g/dL)	541[a]	4.38 ± 0.32	4.4 (2.6−5.2)
AST (U/L)	542[a]	21.1 ± 27.0	18 (6−580)
ALT (U/L)	542[a]	19.8 ± 22.1	15(1−319)
Daily dose of topiramate (mg)	553[a]	152.8 ± 130.9	100 (25-1000)
Plasma concentration of topiramate (mg/L)	553[a]	3.6 ± 2.7	3.2 (0.4-19.7)
Concomitant medication			
Phenytoin	20 (3.62%)		
Clobazam	67 (12.1%)		
Carbamazepine	173 (31.3%)		
Valproic acid	152 (27.5%)		
Lamotrigine	110 (19.9%)		
Levetiracetam	194 (35.1%)		
Oxcarbazepine	143 (25.9%)		
Pregabalin	72 (13.0%)		
Clonazepam	46 (8.32%)		
Phenobarbital	69 (12.5%)		

[a]The number of patients who could be identified by their demographic and biochemical data

[b]Creatinine clearance estimated by the modification of diet in renal disease (MDRD) formula

[C]Expressed as the international normalized ratio (INR)

Table 2. The final parameter estimates and bootstrap results

Parameter	Description (units)	Estimation results Estimate (% RSE)	Bootstrap results Median (95% CI)
Structural model			
$CL/F = (\theta_1 + \theta_4 \times CBZ + \theta_5 \times OXC + \theta_6 \times PHT + \theta_7 \times PB) \times (CLcr/90)\ \hat{}\ \theta_8 \times (DOSE/100)\ \hat{}\ \theta_9$			
θ_1	Typical value of apparent clearance (L/h)	1.17 (6.67%)	1.17 (0.999 − 1.31)
θ_4	Effect of carbamazepine on CL/F (L/h)	1.02 (8.85%)	1.02 (0.842 − 1.19)
θ_5	Effect of oxcarbazepine on CL/F (L/h)	0.621 (11.9%)	0.615 (0.471 − 0.764)
θ_6	Effect of phenytoin on CL/F (L/h)	1.36 (13.6%)	1.35 (0.984 − 1.75)
θ_7	Effect of phenobarbital on CL/F (L/h)	0.488 (20.5%)	0.491 (0.301 − 0.705)
θ_8	Exponent for CLcr (normalized by 90 mL/min)	0.289 (39.1%)	0.287 (0.056 − 0.489)
θ_9	Exponent for DOSE (normalized by 100 mg)	0.0894(30.1%)	0.087 (0.035 − 0.141)
$V/F = \theta_2 \times (WT/62)$			
θ_2	Apparent volume of distribution (L)	108 (11.1%)	108 (83.0 − 132)
Ka	Absorption rate constant (h^{-1})	fixed at 2	−
Inter-individual variability (% CV)			
$\omega_{CL/F}$	Inter-individual variability for CL/F	13.9 (17.2%)	13.0 (7.09 − 17.8)
Residual error			
σ_{add}	Additive error (mg/mL)	113 (58.0%)	105 (0.005 − 241)
σ_{prop}	Proportional error (%)	32.4 (4.60%)	32.2 (29.3 − 35.0)

RSE, relative standard error; CBZ, carbamazepine; OXC, oxcarbazepine; PHT, phenytoin; PB, phenobarbital; CL_{cr}, creatinine clearance; WT, body weight

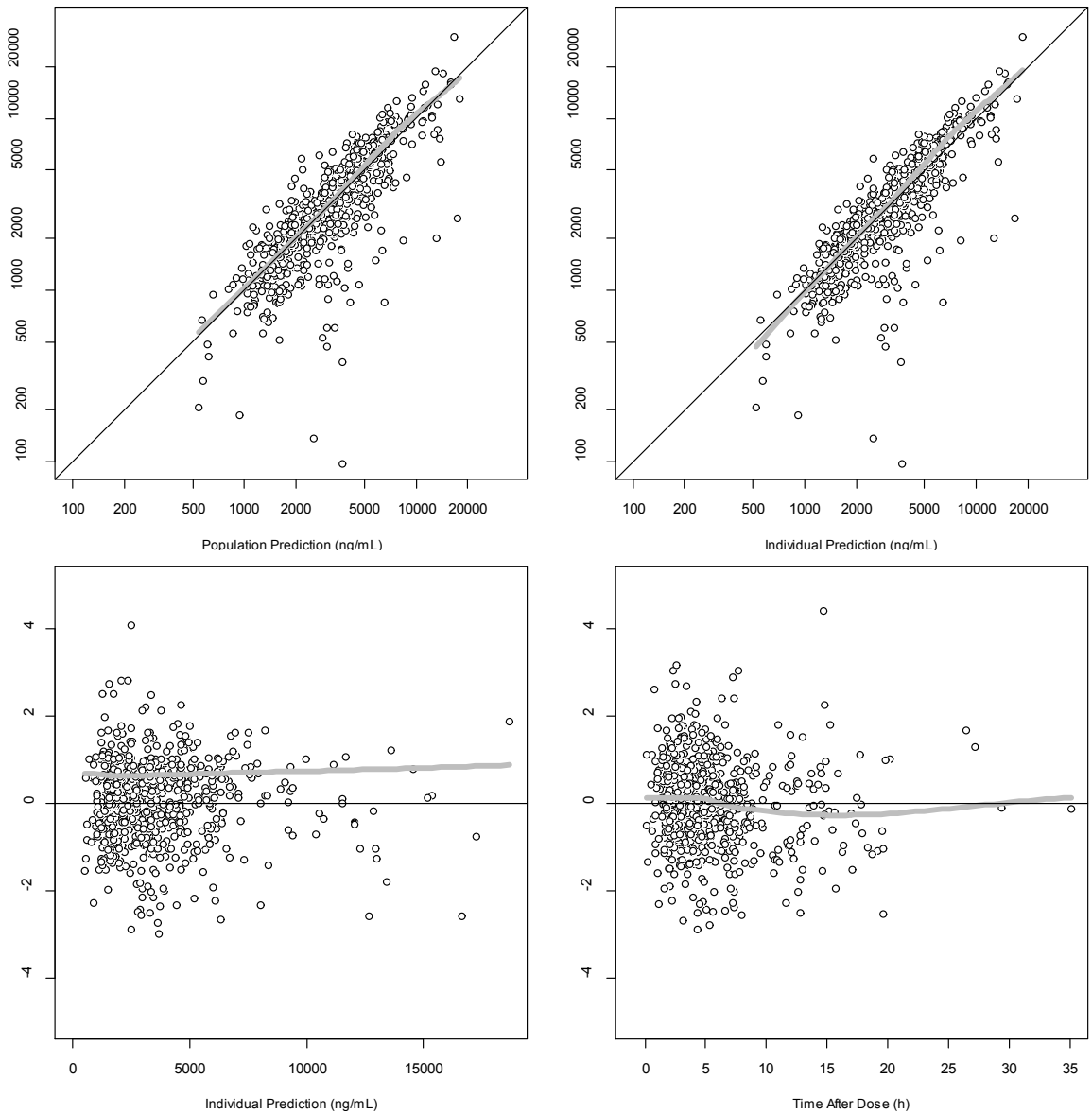
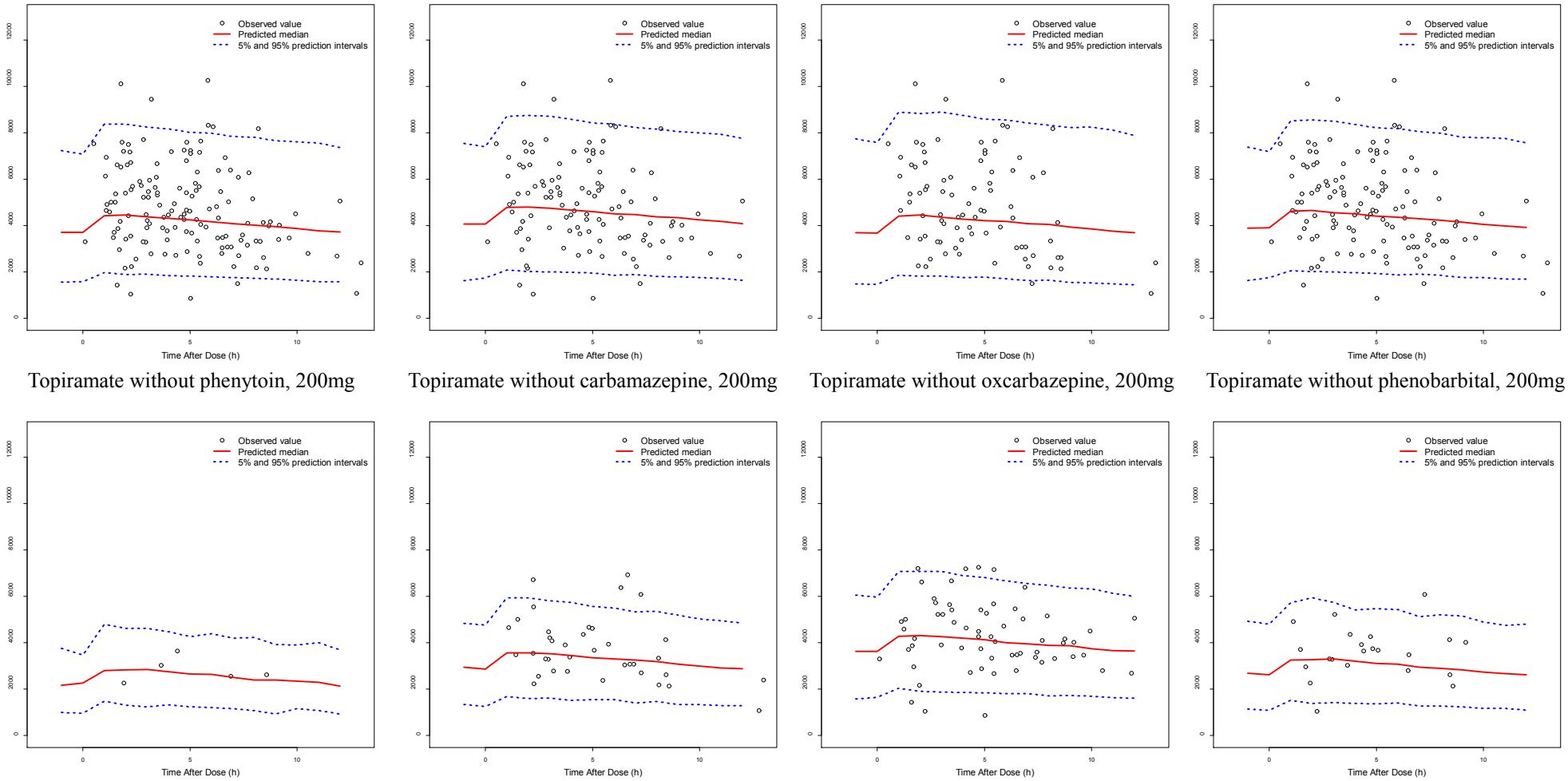


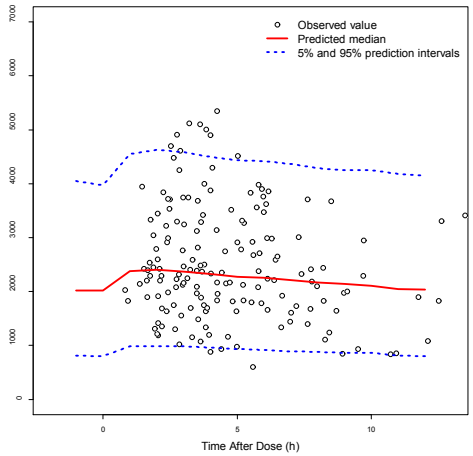
Figure 1. The basic goodness-of-fit plots of the final pharmacokinetic model



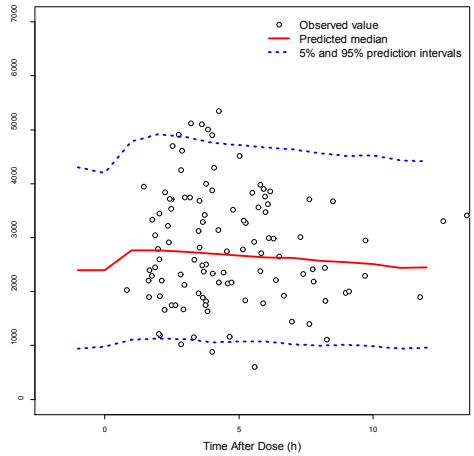
Topiramate without phenytoin, 200mg | Topiramate without carbamazepine, 200mg | Topiramate without oxcarbazepine, 200mg | Topiramate without phenobarbital, 200mg

Topiramate with phenytoin, 200mg | Topiramate with carbamazepine, 200mg | Topiramate with oxcarbazepine, 200mg | Topiramate with phenobarbital, 200mg

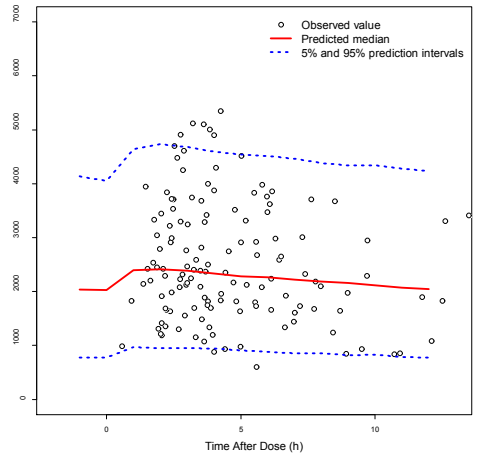
Figure 2. Visual predictive checks of topiramate 200 mg/day stratified by the concomitant drugs.



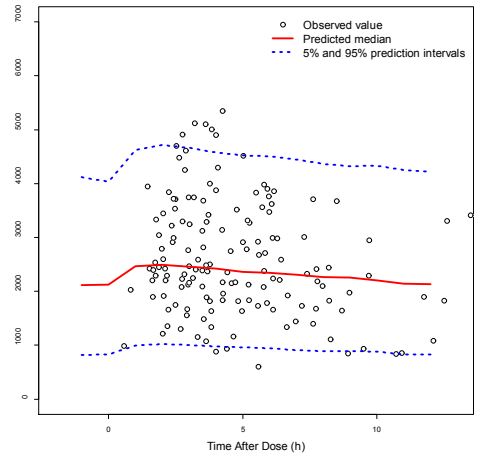
Topiramate without phenytoin, 100mg



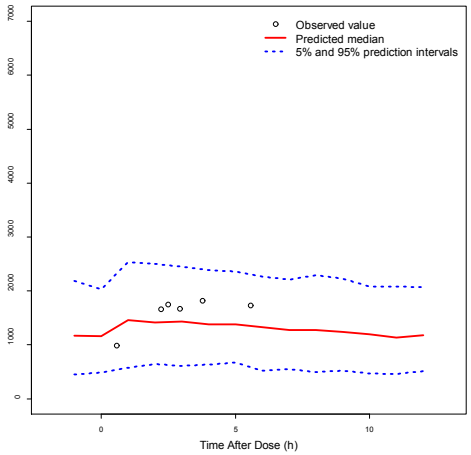
Topiramate without carbamazepine, 100mg



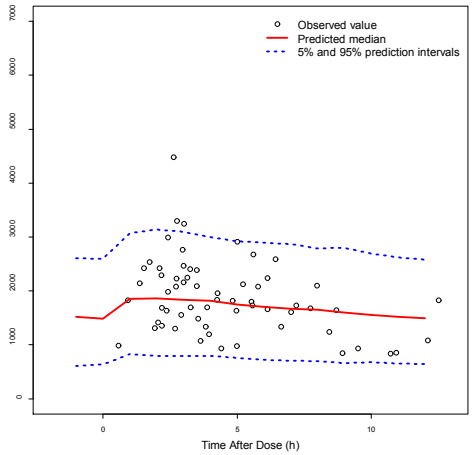
Topiramate without oxcarbazepine, 100mg



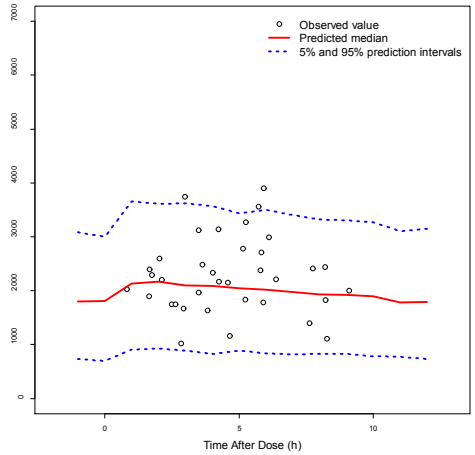
Topiramate without phenobarbital, 100mg



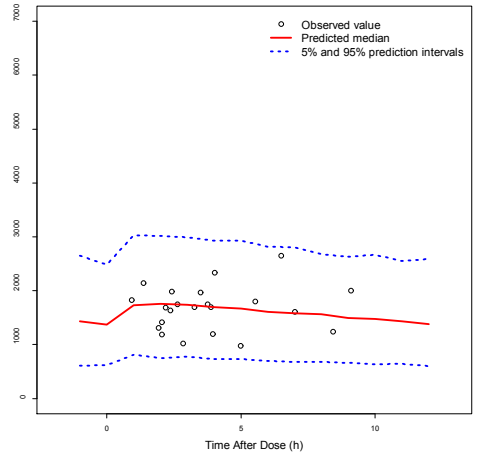
Topiramate with phenytoin, 100mg



Topiramate with carbamazepine, 100mg



Topiramate with oxcarbazepine, 100mg



Topiramate with phenobarbital, 100mg

Figure 3. Visual predictive checks of topiramate 100 mg/day stratified by the concomitant drugs.

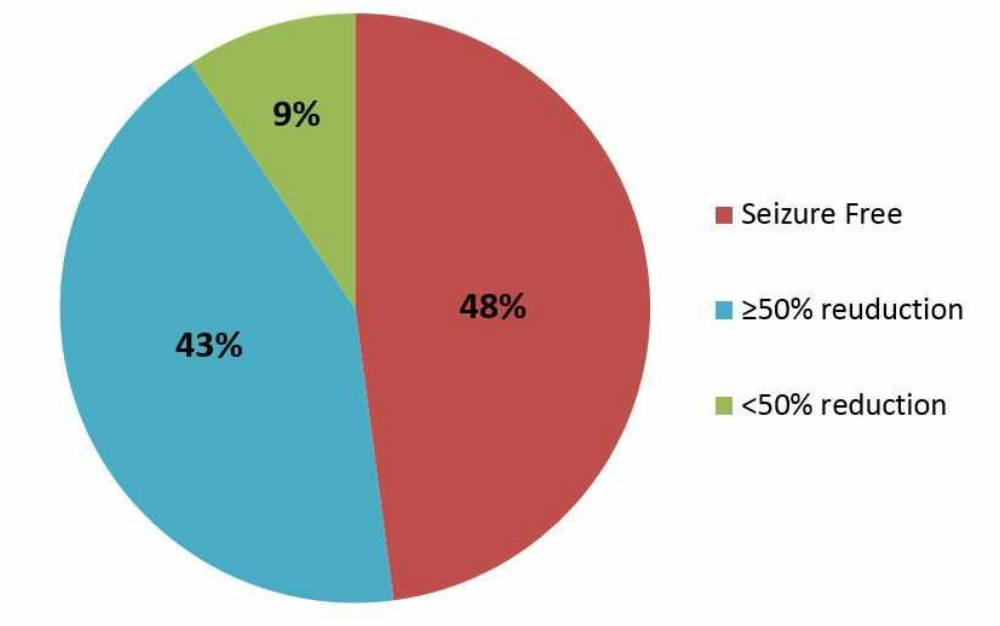


Figure 4. Clinical efficacy of topiramate

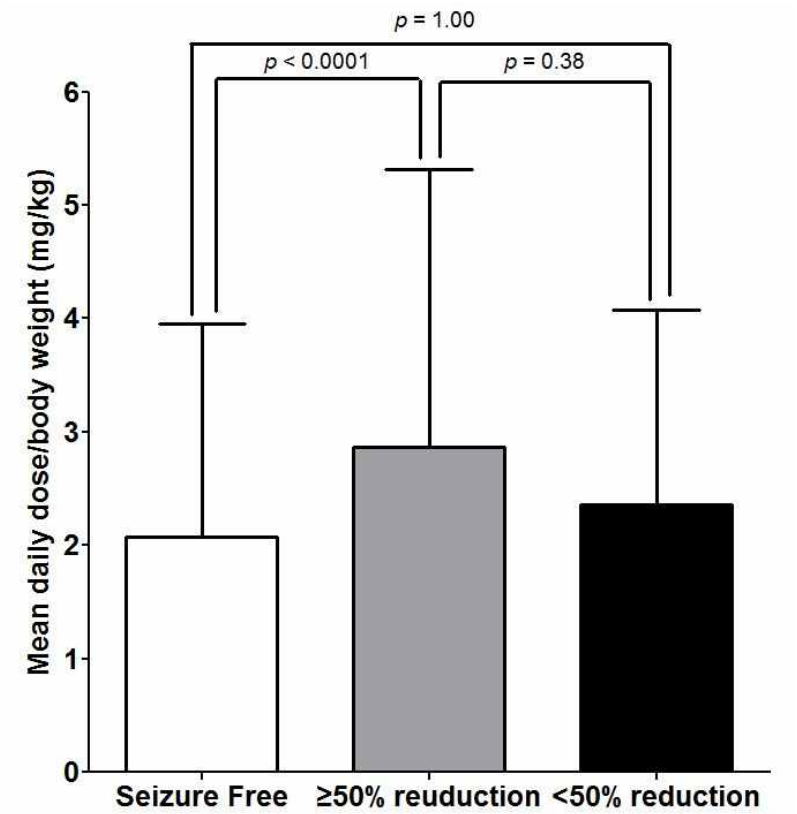


Figure 5. Mean daily dose per body weight of topiramate according to the clinical efficacy

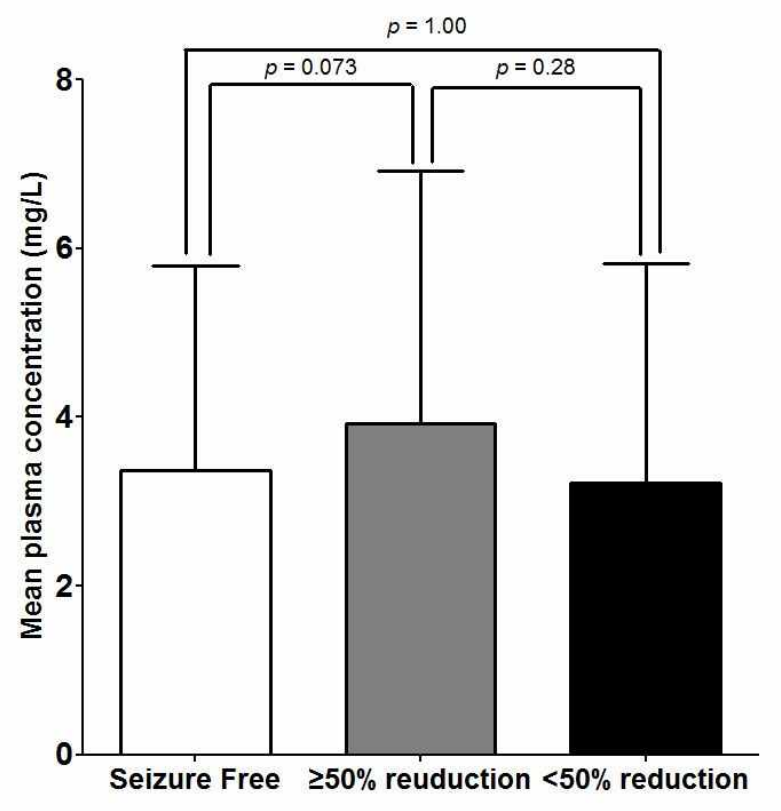
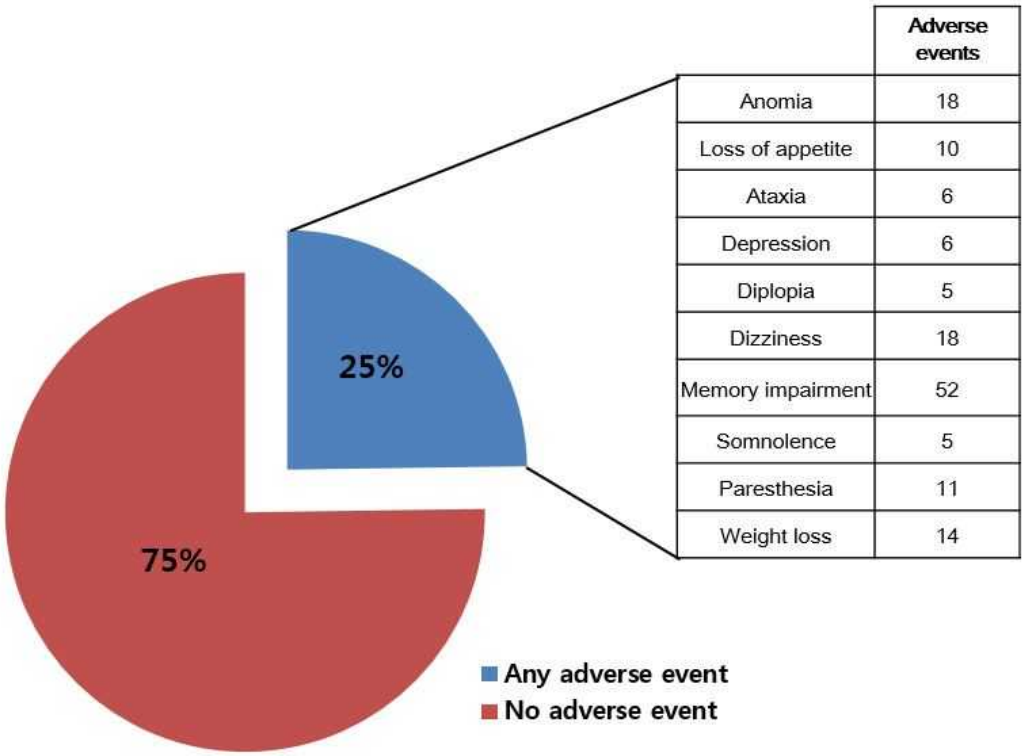


Figure 6. Mean plasma concentration of topiramate according to the clinical efficacy



	Adverse events
Anomia	18
Loss of appetite	10
Ataxia	6
Depression	6
Diplopia	5
Dizziness	18
Memory impairment	52
Somnolence	5
Paresthesia	11
Weight loss	14

Figure 7. Adverse events of topiramate

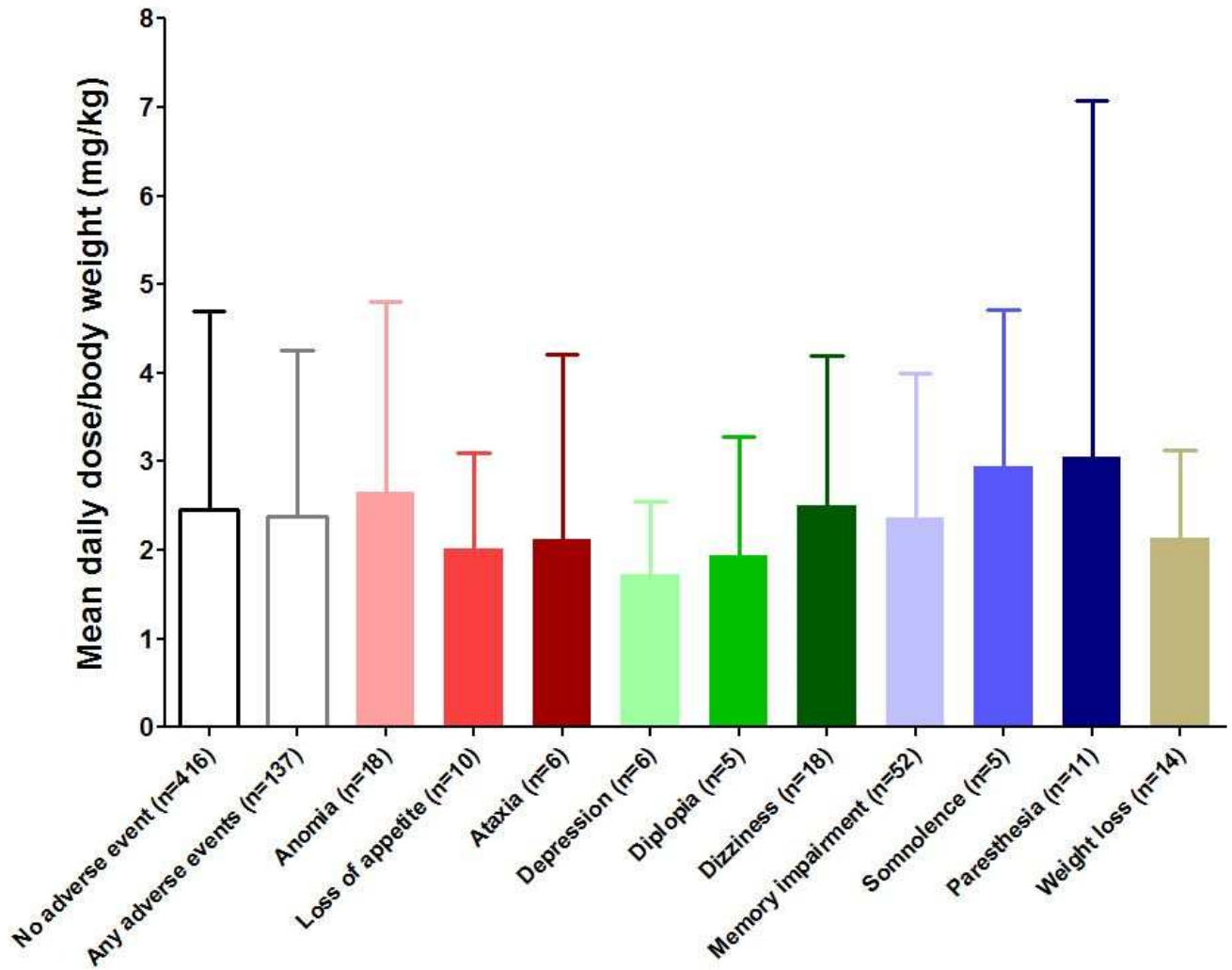


Figure 8. Mean daily dose per body weight of topiramate according to the adverse events

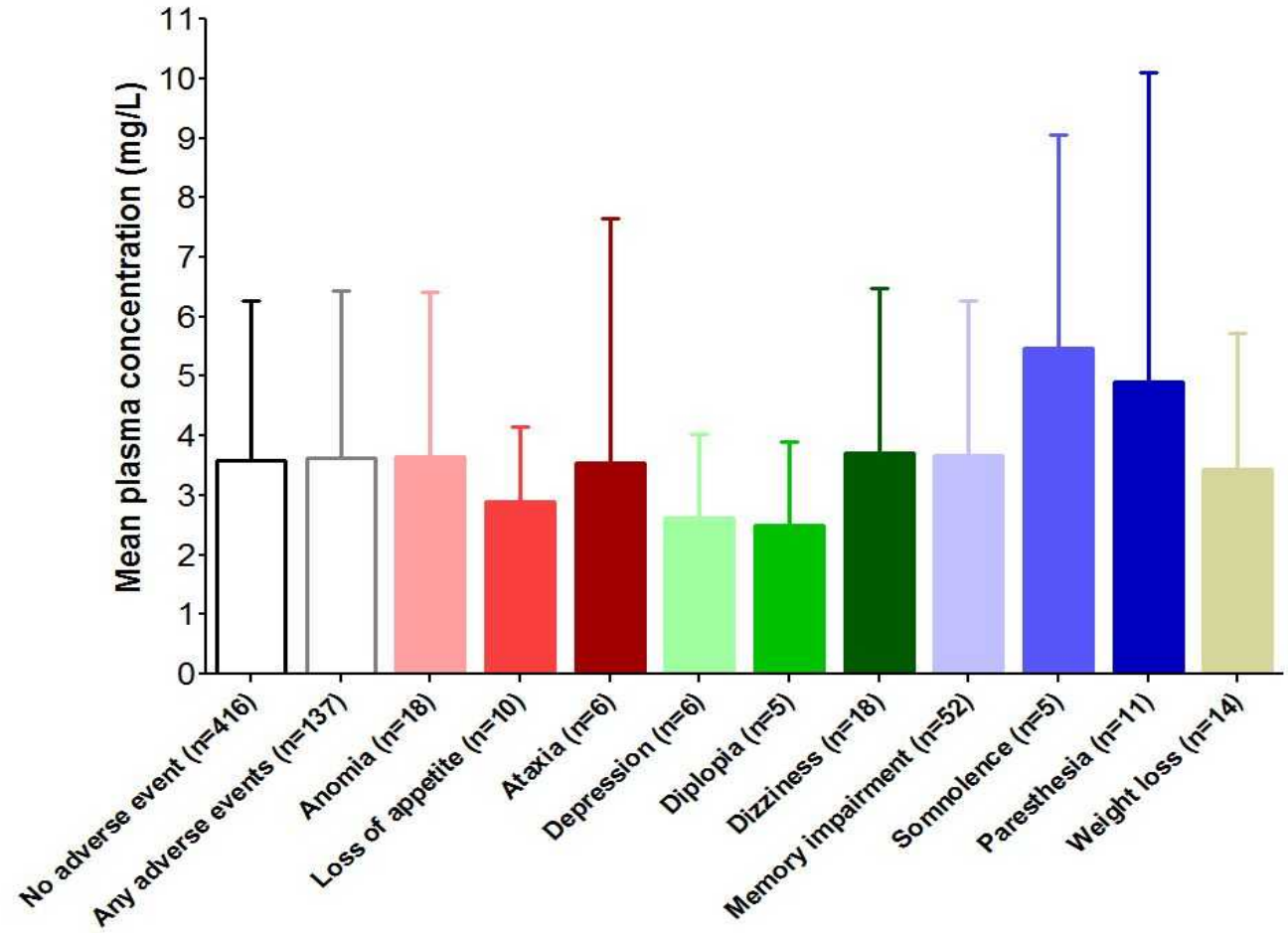


Figure 9. Mean plasma concentration of topiramate according to the adverse events

국문 초록

배경: Topiramate는 뇌전증의 치료에 널리 쓰이고 있는 항뇌전증약이다. Topiramate의 약동학은 나이, 신장 기능, 병용 약물과 같은 다양한 인자에 의해 영향을 받는 것으로 알려져 있다. 그러나 이러한 영향 인자들이 철저히 정립되어 있지 않고 논란이 있는 실정이다. 이에 본 연구에서는 집단 약동학 분석 기법을 이용하여 대규모 성인 뇌전증 환자군에서 topiramate의 약동학에 영향을 미치는 인자들은 알아보고자 한다.

대상 및 방법: 임상 정보 및 혈액 검체는 topiramate로 뇌전증 치료를 받고 있는 553 명의 성인 환자들에서 수집하였다. 항정 상태의 topiramate 혈장 농도는 액체 크로마토그래피 직렬 질량 분광계 (liquid chromatography-tandem mass spectrometry)를 이용하여 측정하였다. 측정된 혈장 농도를 일구획 약동학 모형에 적합시키도록 비선형 혼합효과 모델 (NONMEM, version 7.2) 사용하였다. 가능한 공변량으로 포함된 인구학적 및 임상적 인자들은 나이, 성, 체중, 키, 혈장 크레아티닌, 크레아티닌 청소율 (CLcr), 총 빌리루빈, 프로트롬빈 시간, 알부민, 아스파르테이트 트랜스아미나제 (AST), 알라닌 트랜스아미나제 (ALT), 하루 용량 (DOSE), 병용 약물 (phenytoin [PHT], clobazam, carbamazepine [CBZ], valproic acid, lamotrigine, levetiracetam, oxcarbazepine [OXC], pregabalin, clonazepam, phenobarbital [PB])이었다. 이외, 용량 및 혈장 농도에 따른 topiramate의 효과 및 부작용도 분석하였다.

결과: 최종 약동학 모델은 다음과 같았다.

$$CL/F\ (L/h) = (1.17 + 1.36\times PHT + 1.02\times CBZ + 0.621\times OXC + 0.488\times PB) \times (CLcr/90)^{0.289} \times (DOSE/100)^{0.0894}$$

(1 in patients co−medicated with each drug, 0 in otherwise)

$$V/F\ (L) = 108 \times (WT/62).$$

따라서, CLcr이 90 mL/min이고, DOSE가 100mg인 환자에서 겉보기 청소율 (CL/F)은 1.17 L/h로 예측되었다. PHT, CBZ, OXC, PB를 병용시 CL/F는 각각 2.53 (1.17+1.36) L/h, 2.19 (1.17 + 1.02) L/h, 1.791 (1.17+0.621) L/h, 1.658 (1.17+0.488) L/h으로 증가되었고, 이는 병용 약물이 없는 환자와 비교하였을 때 각각 116%, 87%, 53%, 42% 높은 것이다. 264명 (48%)의 환자들이 발작이 전혀 없었고, 236명 (43%)은 적어도 50% 이상 발작이 감소하였으며, 나머지 52명 (9%)은 50% 미만의 발작 감소를 보였다. 138명 (25%)에서 부작용이 발생하였고, 그 증상으로는 기억력 저하, 어지럼증, 이름대기장애, 체중 감소, 이상 감각, 식욕 저하 등이 포함되었다. Topiramate의 효과와 부작용은 체중 당 하루 용량이나 혈장 농도와는 임상적으로 유의한 관련성을 보이지 않았다.

결론: Topiramate의 겉보기 청소율은 PHT, CBZ, OXC, PB를 병용시 증가했다. 이러한 집단 약동학 모델은 실제 임상 진료에서, 특히 PHT, CBZ, OXC, PB를 병용하고 있는 환자들에게, topiramate 사용시 용량 처방을 적절히 조절하기 위해 적용할 수 있을 것이다. Topiramate로 치료를 받고 있는 뇌전증 환자에서는 치료 용량과 혈장 농도를 환자마다 개별화하는 것이 꼭 필요하다.