A Nonlinear Mixed Effects Modelling Analysis of Topiramate Pharmacokinetics in Patients with Epilepsy

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Topiramate pharmacokinetics is influenced by individual factors such as patient age, renal function and co-treatment. The aim of this study was to develop a population pharmacokinetic model of topiramate to assist dosage adjustments in individual patients. Steady-state topiramate plasma concentrations in patients with epilepsy were determined by HPLC using fluorescent labelling. Demographic, biochemical data and dosing history including concomitant drug therapy were collected from patients' charts. Nonlinear mixed effects modelling was used to fit a one-compartment pharmacokinetic model. The influence of patient weight and gender, body surface area, age, creatinine clearance, serum transaminases, topiramate daily dose and co-treatment with carbamazepine, valproic acid, benzodiazepines, and risperidone on topiramate pharmacokinetics was evaluated. Additionally, the relationship between topiramate plasma concentration and clinical response was investigated. Volume of distribution of topiramate was 0.518 l/kg. For a typical patient oral clearance was estimated at 1.47 l/h, with interindividual variability of 39.2%. Clearance was 70% higher in patients co-treated with carbamazepine and was found to increase with patient age. Somnolence was the most frequently observed adverse event. Incidence of headache was associated with topiramate plasma concentration. Somnolence, ataxia, tremor, speech disorders and fatigue were associated with adjunctive therapy with carbamazepine, valproic acid, benzodiazepines, risperidone, and clozapine. No association of topiramate plasma concentration with frequency of seizures or patient quality of life was observed. The developed model can be used for Bayesian estimation of pharmacokinetic parameters based on sparse plasma samples and for selection of optimum dosing in routine patient care.

Key words topiramate; epilepsy; population pharmacokinetics; therapeutic drug monitoring; NONMEM

Topiramate belongs to the second generation of antiepileptic drugs (AEDs) and has been approved for treatment of adults and children with different kinds of epilepsy as mono or as adjunctive therapy.[1,2] The exact mechanism of topiramate action is unknown; however, it is considered that antiepileptic effects are exerted by modulation of voltage-dependent sodium channels, enhancement of γ-aminobutyrate (GABA)ergic inhibition on the $GABA_A$ receptor, inhibition of carbonic anhydrase isoenzymes, and possibly, through the activity at non-*N*-methyl-D-aspartate receptors.[1,3,4] The effectiveness of topiramate in adults and children with partial onset and primary generalized seizures was established as initial monotherapy as well as adjunctive treatment.[5]

Following oral administration of topiramate, absorption is rapid and almost complete with bioavailability ranging from 81 to 95%.[4,6] Peak plasma concentrations of the drug are reached within 1—4 h after administration.[4,6] Food delays topiramate absorption by approximately 2 h, but the extent of absorption remains unaffected.[4] Plasma protein-bound fraction of topiramate varies from 9 to 17%.[4,6] In the dose range 100 to 1200 mg the mean apparent volume of distribution is between 0.6 and 1.0 l/kg.[4,6] In women the volume of distribution is about 50% less than in men, which is attributed to a higher percentage of body fat in women.[6] This difference is not considered to be clinically relevant. Over 80% of topiramate is eliminated *via* the kidneys, predominantly as unchanged drug.[6] To date, six trace metabolites formed by glucuronidation, hydroxylation and hydrolysis have been identified in humans. In animal seizure models the metabolites have little or no anticonvulsant activity.[4,6] At steady-state the renal clearance of topiramate is 1.02 l/h[6] and its elimination half-life ($t_{1/2}$) varies from 20 to 30 h.[1,4] Consequently, the steady-state is being reached in 4 to 8 d.[2] Over the dose range 100—800 mg the relationship between topiramate dose and serum concentration is linear in both adults and children.[3,7,8]

With the commonly used dosage regimen, serum topiramate concentrations in the range between 16 and 60 μmol/l have been reported.[3] A wide range of doses and serum concentrations have been associated with optimal clinical response.[3] Topiramate serum concentration was found to correlate with the time to the first seizure,[9] while in the majority of studies no clear relationship between average plasma concentration of topiramate and seizure reduction was found.[6,8,10] Based on these findings, clinical response, rather than blood concentrations is used to guide topiramate dosage adjustments.[1,6]

Topiramate pharmacokinetic data mostly come from single dose studies with frequent blood sampling in healthy volunteers as well as from studies with sparse sampling in epileptic patients. However, both types of studies provide little information on inter- and intraindividual variability in pharmacokinetics of topiramate. So far there is no published study with a population pharmacokinetic model of topiramate. Pharmacokinetic variability can be addressed using a nonlinear mixed effects modelling approach. A population pharmacokinetic model is a prerequisite for optimal therapeutic drug monitoring and individual dose adjustments as it allows estimation of an individual patient's pharmacokinetic parameters based on sparse concentration measurements, and

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in the end, effective control of dosing. Nonlinear mixed effects modelling has been successfully applied to pharmacokinetic analysis of other AEDs based on routine therapeutic drug monitoring data.[11—14)]

The aim of the present study was to develop a population pharmacokinetic model to evaluate the influence of various factors on pharmacokinetics of topiramate. Moreover, we tried to estimate the relationship between the topiramate average steady-state plasma concentration (C_{ss}) and clinical response, to provide a basis for improvement in the clinical use of the drug.

MATERIALS AND METHODS

Patients The study population included 26 patients treated with topiramate for partial or generalised tonic–clonic seizures, juvenile myoclonic or benign childhood epilepsy at the University clinical centre Kragujevac, Serbia. Patients were of both genders and various age groups. They were on mono anticonvulsive therapy with topiramate, or in combination with other AEDs, for at least two weeks prior to inclusion in the study. Some patients were additionally treated with other psychoactive drugs, including benzodiazepines, risperidone and clozapine. Topiramate was administered one to three times per day in the form of 25, 50 or 100 mg tablets (Topamax, Janssen Pharmaceutica N.V., Beerse, Belgium). Compliance was assessed by an interview with the attending physician and all patients suspected of poor compliance were excluded from the study. Before coming to the clinic for the medical check-up, all patients were instructed to record the time when the last dose was taken.

All data, including demographic characteristics, weight (WT), height, age, and gender; results of biochemical analysis, serum creatinine, serum transaminases (aspartate aminotransferase (AST) and alanine transaminase (ALT)); concomitant drug therapy, dosing regimen and times of blood sampling were collected from patients' charts. Seizure control was assessed from patients' seizure diaries for three consecutive months. Additionally, patients were asked to fill in the standard questionnaire on the quality of life with epilepsy (QOLIE-31 or QOLIE-48) in the beginning and at the end of the three month follow-up period. Adverse event data were retrieved from patient interviews.

Written informed consent was obtained from all patients. The study was approved by the Ethics Committee of the University Clinical Centre Kragujevac and was carried out according to the Declaration of Helsinki.

Blood Sampling and Assay Two blood samples were drawn from each patient in the steady-state. The first sample was taken immediately before drug application (trough concentration) and the second was taken around 2 h after the topiramate dosing (approximating peak concentration). Exact blood sampling times were recorded by the laboratory personnel. Immediately after blood draws plasma samples were prepared by centrifugation and stored at $-20\,^{\circ}C$ until assayed.

For quantification of topiramate in plasma the HPLC method with fluorescent labelling was adapted from Bahrami *et al.*[15)] In brief, 250 μl topiramate plasma samples were extracted with dichloromethane, centrifuged and the organic phase was evaporated to dryness. Dry residues were derivatised with 9-fluorenylmethyl chloroformate in the presence of borate buffer. The derivatised samples were separated using gradient elution method on phenyl–hexyl column and a mobile phase composed of 0.6% acetic acid and 0.1% of triethylamine in methanol/acetonitrile/water. The method was linear over the range of 0.1—15 mg/l of topiramate in plasma. The intra- and inter-day precision (RSD) were from 2.8 to 6.1% and 5.4 to 9.7%, respectively. The accuracy of the method was 94.5—104.5% and the lower limit of quantification was 0.1 mg/l.

Data Analysis Pharmacokinetic analysis was performed by a population pharmacokinetic modelling approach using NONMEM (Version 6, level 2, Icon Development Solutions, Ellicott City, MD, U.S.A.). Model building steps were managed using Perl speaks NONMEM (Version 2.3.0, http://psn.sourceforge.net) and Xpose (version 4, http://xpose.sourceforge.net). All concentration measurements of topiramate were assumed to be obtained in the steady-state. The structural model used was a one-compartment model with first-order absorption and elimination as implemented in ADVAN2/TRANS2 PREDPP subroutine. The first-order conditional method with interaction was used for estimation of oral clearance (CL/F) and volume of distribution (V/F). Due to insufficient data in the absorption phase, absorption rate could not be estimated. Therefore, the absorption rate constant k_a was fixed at $2\,h^{-1}$ as estimated using the following relationship: $t_{max}=\ln(k_a/k_e)/(k_a-k_e)$, based on a literature value of plasma elimination half-life of 21 h (single and multiple doses), corresponding to the elimination rate constant (k_e) of $0.033\,h^{-1}$, and t_{max} of 2 h.[16)]

An exponential error model was used to describe interindividual variability of pharmacokinetic parameters (ω^2), while additive, proportional and combination error models were evaluated to describe residual intraindividual variability of topiramate concentration (σ^2). The model adequacy was evaluated by standard diagnostic plots, including the agreement between the observed and predicted plasma concentrations and uniformity of the distribution of conditional weighted residuals (CWRES) *vs.* the predicted concentrations. CWRES were computed with Perl speaks NONMEM as the first-order conditional estimation approximated difference between the observed concentrations and the individual model predictions of that data divided by the root of the covariance of the data given the model. Additional criteria were convergence of minimization, number of significant digits more than 3, successful covariance step, gradients in the final iteration in the range 10^{-3}—10^{2} and absence of substantial η- and ε-shrinkage. Alternative models were compared by the likelihood ratio test. Criterion for selection of a model was a change in minimum value of objective function (ΔOFV) of at least 3.84 per one additional parameter, corresponding to $p<0.05$.

In the first step the base model was derived, while in the second step covariates were included stepwise into the base model one at a time. Effects of continuous covariates, WT, body surface area (BSA), age, daily topiramate dose (DTD), Cockroft–Gault estimate of creatinine clearance (CL_{Cr}), AST and ALT levels were centred to the population mean covariate values and were investigated using a power model. Among categorical covariates considered for inclusion were patient gender and co-treatment with carbamazepine (CBZ),

valproic acid (VPA), benzodiazepines (BDZ) and risperidone (RIS). Covariates were introduced sequentially into the population models to develop a full model. In each step of the covariate model building the covariate with the highest drop in OFV was included in the model and in the following step all the remaining covariates were tested against the model developed in the preceding cycle. When the effects of all the remaining covariates were insignificant, the full model was achieved. The final model was determined by testing each covariate against the full model using a likelihood ratio test to see if it should remain in the model. Additional criterion for the retention of a covariate in the model was reduction in the unexplained interindividual variability. A bootstrap sampling method with replacement using 1000 replications was applied to calculate 95% confidence intervals (95% CI) of the final model parameter values.

Bayesian estimate of topiramate clearance and its daily dose were used to calculate average steady-state topiramate concentration in an individual patient. Average steady-state concentration was logarithmically transformed for the statistical analysis. Independent samples *t*-test and Fisher's exact test were used to test the association of the occurrence of adverse events with steady-state topiramate concentration and concomitant treatment with other psychoactive drugs (CBZ, VPA, BZD, RIS, and clozapine), respectively. Linear regression was used to evaluate the relationship between steady-state concentration and quality of life with epilepsy score. Significance level was set at $p<0.05$. Statistical analysis was performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, U.S.A.).

RESULTS

Characteristics of the Patients Data from 26 patients, including adults and children were included in the study. They were on mono anticonvulsive therapy with topiramate ($n=13$), or on adjunctive therapy with carbamazepine ($n=3$), valproic acid ($n=5$), lamotrigine ($n=1$), clonazepam ($n=1$) and phenobarbital ($n=1$); or in combination with carbamazepine and valproic acid ($n=1$) and carbamazepine and clonazepam ($n=1$). Of the 26 patients on therapy with topiramate, 16 patients were co-treated with other psychoactive drugs, including carbamazepine, valproic acid, benzodiazepines (diazepam, clonazepam, bromazepam, and lorazepam), risperidone and clozapine. Chronic or occasional concomitant treatment with beclomethasone, clozapine, lamotrigine, allopurinol, vitamin B, labetalol, amoxicillin, diclofenac, captopril, and nifedipine, were considered not to influence topiramate pharmacokinetics.[17,18] The characteristics of the patients are summarised in Table 1.

Model-Building Process Topiramate plasma concentration profiles were modelled with a one-compartment model and an exponential model for interindividual variability of CL/F ($\omega_{CL/F}$). Due to sparse data, estimation of interindividual variability of V/F ($\omega_{V/F}$) resulted in large ε-shrinkage of over 70%; consequently, $\omega_{V/F}$ had to be fixed to zero. Residual intraindividual variability of topiramate concentration was most adequately described by the proportional error model. With the base model, mean population CL/F (95% CI) was estimated at 1.48 (1.19—1.77) l/h with an interindividual variability of 48.9 (30.6—62.0) %, shrinkage −0.3%; and V/F was estimated at 0.526 (0.425—0.627) l/kg. Residual variability was approximated at 13.7 (9.0—18.4) % with 26.5% shrinkage.

Table 1. Patient Data

Number of patients	26
Male/female	11 (42%)/15 (58%)
Children/adults	9 (35%)/17 (65%)
TPM dose (mg/d)	200 (25—400)
Average steady-state TPM concentration (mg/l)	5.67±3.70
WT (kg)	71 (27—98)
Age (years)	26.5 (8—54)
BSA (m^2)	1.85 (0.97—2.22)
Scr (μmol/l)	74 (41—105)
CL_{Cr} (ml/min)	103 (75—189)
AST (U/l)	20 (11—155)
ALT (U/l)	21 (10—106)
QOLIE-31	53.4 (17.4—90.6)
QOLIE-AD-48	46.1 (36.6—74.1)
Seizure episodes in the last 6 months	1 (0—432)
Concomitant therapy	
CBZ	5 (19%)
VPA	6 (23%)
BZD	7 (27%)
RIS	5 (19%)

Values are median (range) or count (%). TPM, topiramate; WT, weight; BSA, body surface area; Scr, serum creatinine; CL_{Cr}, Cockroft–Gault estimate of creatinine clearance; AST, serum aspartate aminotransferase; ALT, serum alanine aminotransferase; QOLIE-31, a survey of health-related quality of life for adult patients with epilepsy; QOLIE-AD-48, a survey of health-related quality of life for adolescents (11—18 years) with epilepsy; CBZ, carbamazepine; VPA, valproic acid; BZD; benzodiazepines; RIS, risperidone.

Table 2. Summary of the Covariate Model Building

Effect on CL/F	*p*-Value[a]		
	Base model	One-covariate model	Two-covariate model
Age	0.028*		
Gender	0.229	0.532	0.306
WT	0.446	0.522	0.899
BSA	0.444	0.566	0.924
AST	0.847	0.867	0.634
ALT	0.514	0.618	0.769
CL_{Cr}	0.162	0.296	0.477
DTD	0.768	0.173	0.480
BZD	0.303	0.552	0.745
CBZ	0.100	0.015*	
RIS	0.852	0.806	0.797
VPA	0.524	0.765	0.890

a) Likelihood ratio test; $*p<0.05$. WT, weight; BSA, body surface area; AST, serum aspartate aminotransferase; ALT, serum alanine aminotransferase; CL_{Cr}, creatinine clearance, DTD, daily topiramate dose; BZD, co-treatment with benzodiazepines; CBZ, co-treatment with carbamazepine; RIS, co-treatment with risperidone; VPA, co-treatment with valproic acid.

Analysis of the plots of Bayesian estimates of an individual patient's CL/F obtained with the base model *versus* various covariates indicated an increase of CL/F with patient age. Additionally, mean topiramate CL/F in patients not co-treated with enzyme inducing AEDs (1.61 l/h) was lower compared to patients co-treated with CBZ (2.08 l/h), while in one patient co-treated with phenobarbital CL/F was 1.06 l/h.

Details of the covariate model building are summarised in Table 2. Inclusion of the influence of age on CL/F into the base model decreased OFV by 4.823 ($p=0.028$) and reduced unexplained interindividual variability of CL/F to 44.3%. Additionally, the influence of co-treatment with CBZ

Table 3. Estimates of the Final Population Pharmacokinetic Model of Topiramate

Parameter		Estimate	95% CI[a)]
$\theta_{CL/F}$	Coefficient of the final model (l/h)	1.47	1.18—1.86
$\theta_{CL/F,age}$	Effect of age on CL/F	0.421	0.177—0.755
$\theta_{CL/F,CBZ}$	Effect of carbamazepine on CL/F	1.70	1.31—2.23
$\theta_{V/F}$	Coefficient of the final model (l/kg)	0.518	0.419—0.633
$\omega_{CL/F}$	Interindividual variability of CL/F (%)	39.2	22.5—49.1
σ	Residual variability of topiramate conc. (%)	13.8	8.7—18.0

a) 2.5 and 97.5 percentile of the parameter estimates over 1000 bootstrap samples.

(ΔOBJ$=-5.930$, $p=0.015$) on topiramate CL/F was found significant and was introduced into the full model. Since the mean age of patients co-treated with CBZ was lower, we presume that the effect of CBZ co-treatment on topiramate CL/F was confounded with the patients' age when tested against the base model.

In the backward elimination step no covariate effect was removed from the full model. The final model is described by the following equations:

$$\text{CL/F (l/h)} = 1.47 \cdot 1.70^{\text{CBZ}} \cdot \left(\frac{\text{age (years)}}{30}\right)^{0.421}$$

$$\text{V/F (l)} = 0.518 \cdot \text{WT (kg)}$$

where CBZ is 1 in patients co-treated with carbamazepine, or 0 otherwise. Parameters of the final model are presented in Table 3.

With the final model, for a typical patient (30 years) topiramate CL/F (95% CI) was estimated at 1.47 (1.18—1.86) l/h. CL/F was found to increase with patient age and co-treatment with carbamazepine. The interindividual variability of CL/F was 39.2 (22.5—49.1) %, while the residual variability was 13.8 (8.7—18.0) %. In comparison to the base model, interindividual variability of CL/F decreased, while the residual variability remained unchanged. The diagnostic plots of population predicted *vs.* observed topiramate concentrations, and CWRES *vs.* population predicted topiramate concentrations of the final covariate model (Fig. 1) indicate no bias and demonstrate an improved fit compared to the base model.

Incidence of Adverse Events The adverse events that occurred in at least 5 patients of the total 26 are presented in Table 4. Less frequent were blurred vision, unpleasant abdominal sensations, and increased appetite reported by 4 (15%) patients, 3 (12%) patients gained weight, in 2 (8%) patients syncope, skin rashes, uncontrolled glycaemia and renal calculi occurred and in 1 (4%) patient alopecia, haematoma and hallucinations were present. Of the adverse effects observed in this study only headache was found to be associated with plasma concentration of topiramate. Plasma concentration of topiramate was lower in patients who reported headache (3.15 mg/l) compared to the group of patients without headache (6.17 mg/l, $p=0.026$).

Incidence of somnolence, ataxia, tremor (hands and lips), speech disorders and fatigue was higher in patients co-treated with other psychoactive drugs including carbamazepine, valproic acid, benzodiazepines, risperidone, and clozapine (81, 56, 69, 63, 69%, respectively), compared to patients on monotherapy with topiramate (30, 10, 20, 10, 20%, respectively; Fisher's exact test, $p< 0.05$). No association of topiramate plasma concentration with frequency of seizures and patient quality of life was observed.

DISCUSSION

Introduction of the second generation of AEDs led to improvements in treatment of focal and generalized epilepsies.[1)] Their main advantage is the more predictable pharmacokinetics compared to older AEDs, which have a pronounced interindividual pharmacokinetic variability and a narrow therapeutic range.[3)] However, in a substantial number of difficult-to-treat patients the second generation of AEDs still fail to achieve complete seizure control.[1)] Individual factors such as age and renal function, as well as concurrent use of other medications can contribute to the pharmacokinetic variability of topiramate.[3)]

The present study systematically explored the influence of various covariates on topiramate pharmacokinetics by a nonlinear mixed effects modelling approach. Moreover, it aimed at the establishment of the relationship between topiramate steady-state concentrations and occurrence of adverse events. Due to the relatively low number of patients included in the analysis and sparse sampling data with two plasma samples per subject, it was not possible to estimate all the parameters of the pharmacokinetic model. Therefore, the absorption rate constant k_a was fixed, which enabled other parameters (CL/F and V/F) to be adequately predicted.[19)]

In our study V/F of topiramate was estimated at 0.518 l/kg, in accordance with the results of the previous studies.[4,6)] Topiramate CL/F of a typical patient (30 years) was estimated at 1.47 l/h. This is comparable with the findings of previous studies,[16)] where oral plasma clearance of topiramate was reported to be approximately 1.2 to 1.8 l/h. Under the conditions of our study topiramate CL/F was found to increase with a patient's age and co-therapy with carbamazepine (Fig. 2). Topiramate oral clearance was 70% higher in patients co-treated with carbamazepine compared to patients on topiramate monotherapy.

Previous studies demonstrate that co-treatment with enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital, primidone) enhances the hepatic metabolism of topiramate.[4,7,10,20—24)] Carbamazepine significantly reduces topiramate concentration-to-dose ratio compared to topiramate monotherapy in both children and adults.[21,23)] Enzyme induction by carbamazepine is associated with an approximately 2 to 3-fold increase in topiramate metabolic clearance.[7,10,22,24)] It is interesting to note that in some studies in patients taking carbamazepine, topiramate renal clearance was also found to be significantly increased.[10,22)] In contrast to carbamazepine, drug interaction with phenobarbital is considered as

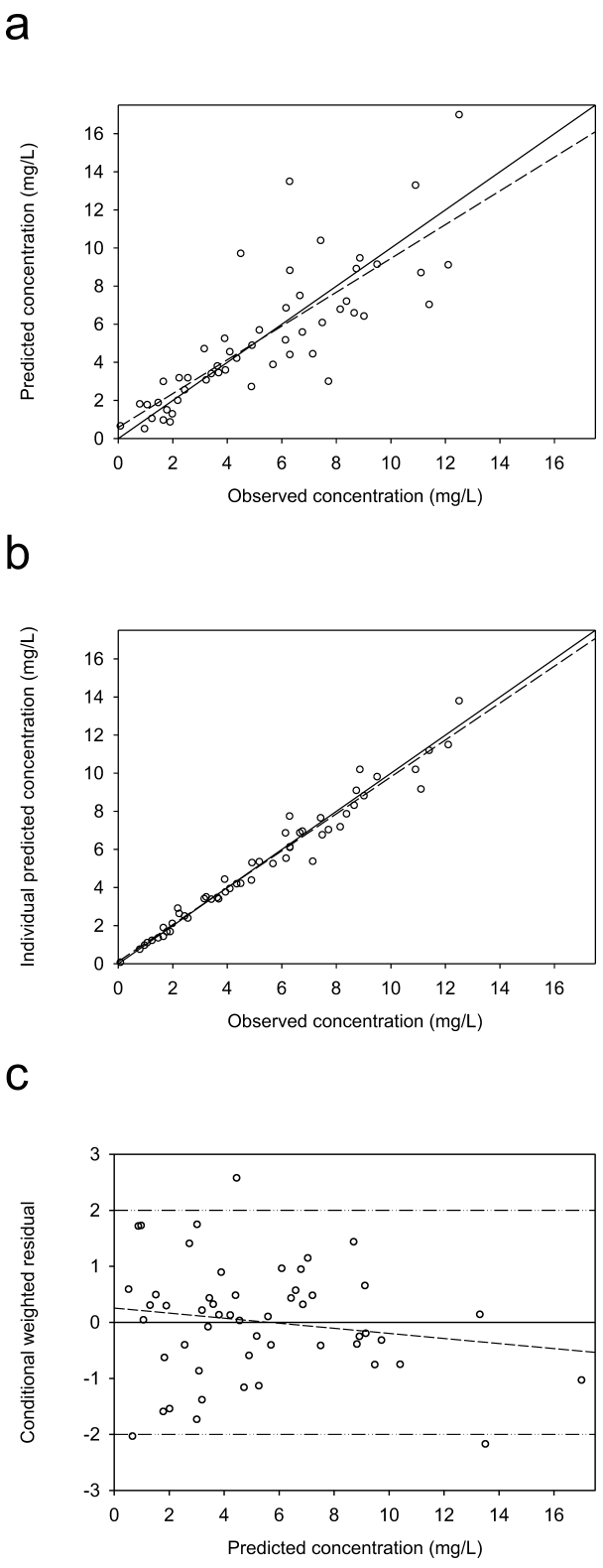

Fig. 1. Diagnostic Plots of the Final Topiramate Pharmacokinetic Model

Population predicted *vs.* observed topiramate concentrations (a), individual predicted *vs.* observed topiramate concentrations (b) and conditional weighted residuals (CWRES) *vs.* population predicted topiramate concentrations (c) with line of identity (solid line) and regression line (dashed).

minor.[17,18] In our study, Bayesian estimate of topiramate clearance in the patient co-treated with phenobarbital was comparable to the clearance in patients not co-treated with enzyme inducing AEDs. Consequently, phenobarbital was assumed not to interact with topiramate pharmacokinetics.

Table 4. Topiramate Average Steady-State Concentration in Patients Reporting Adverse Event (AE Present) and Patients Not Reporting Adverse Event (AE Absent)

Adverse event (AE)	Incidence *n* (%)	C_{ss} (mg/l)		*p*-Value[a)]
		AE present	AE absent	
Somnolence	16 (62%)	5.47±4.10	5.78±2.70	0.488
Difficulty with memory	14 (54%)	6.18±3.64	4.89±3.50	0.213
Fatigue	13 (50%)	5.44±3.25	5.73±3.99	0.905
Tremor (hands and lips)	13 (50%)	5.43±3.37	5.75±3.89	0.909
Speech disorder	11 (42%)	5.45±3.38	5.69±3.81	0.869
Ataxia	10 (39%)	5.36±3.59	5.73±3.66	0.666
Confusion	8 (31%)	5.71±3.04	5.53±3.86	0.567
Dizziness	8 (31%)	4.61±4.68	6.02±3.00	0.141
Insomnia	8 (31%)	4.74±3.23	5.96±3.73	0.443
Nausea	8 (31%)	6.29±4.23	5.28±3.32	0.473
Weight loss	8 (31%)	4.91±2.70	5.89±3.92	0.911
Depression	7 (27%)	4.25±2.59	6.08±3.81	0.261
Nervousness	7 (27%)	7.36±3.39	4.93±3.49	0.116
Muscle tonus decrease	6 (23%)	6.58±5.36	5.29±2.96	0.924
Headache	5 (19%)	3.15±2.73	6.17±3.55	0.026*

Values are mean±S.D.; *n* (%), number and percentage of patients reporting a given adverse event. *a*) Independent samples *t*-test after logarithmic transformation; $*p<0.05$.

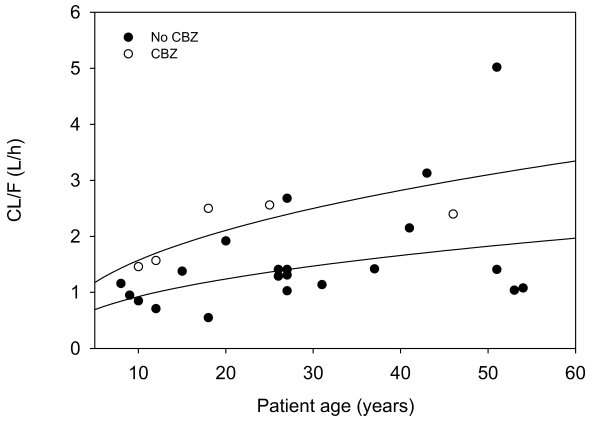

Fig. 2. Relationship between Individual Estimates of Topiramate Clearance, Patient Age and Co-treatment with Carbamazepine (CBZ)

Lines are model predictions.

Benzodiazepines, valproic acid and risperidone co-therapy did not exert a significant influence on topiramate pharmacokinetics. This is in accordance with the results of the previous studies where valproic acid did not have any clinically significant influence on topiramate pharmacokinetics.[10,23,25] In contrast, a decrease in plasma levels of topiramate up to 17% with co-treatment with valproic acid was also observed.[4] Development of severe typical valproate side effects upon initiation of adjunctive topiramate treatment in three children with severe therapy-refractory epilepsy, who tolerated well valproate treatment in various combinations with other antiepileptic drugs,[26] is presumably related to decrease in valproic acid glucuronidation rate and consequent increase in plasma levels of valproic acid. In our previous study we have demonstrated a 23% decrease in valproic acid clearance in patients co-treated with topiramate.[14]

In this study pooled data from children and adults with epilepsy were analysed and a positive correlation between age and topiramate CL/F was found as in a previous study in

a pooled population of adults and children.[20] However, when corrected for patient weight, topiramate CL/F is approximately 50% higher in children compared to adults, and as a result, children require larger doses of topiramate (in mg per body weight) to achieve plasma drug levels comparable with those in adults.[25,27] Moreover, within a more homogenous paediatric population a negative correlation between the oral clearance corrected for body weight and age was demonstrated.[20,23] Similar results were obtained in adults, where topiramate concentration-to-dose ratio was found to increase with age and an increase in concentration-to-dose ratio in the range between 8 and 19% per 10 years of life was reported.[22] In the present study however, due to correlation between patient age and weight, the effects of the two covariates could not be separated.

Topiramate is predominantly eliminated unchanged in urine.[2] In comparison with normal renal function, topiramate clearance in patients with moderate and severe renal impairment is reduced by 42 and 54%, respectively.[1] In our study of patients with normal renal function, no influence of creatinine clearance (CL_{Cr}) on topiramate pharmacokinetics was observed. Additionally, no association of the liver transaminases levels with topiramate pharmacokinetics was observed. Although topiramate is not extensively metabolized, it was previously demonstrated that moderate-to-severe liver impairment can decrease its oral clearance by 26%.[6]

Within the dose range studied (25—400 mg/d) no effect of topiramate daily dose on CL/F was found and consequently linearity in topiramate pharmacokinetics can be claimed. This is in accordance with the majority of the previous studies. However, in a study by Battino *et al.*[20] topiramate dose was found to exert a significant effect on CL/F in both a pooled population of adults and children as well as in a subpopulation of children only. This unexpected positive correlation is often observed with the therapeutic drug monitoring data and can be explained as an artefact due to the fact that patients with higher CL/F are more likely prescribed higher doses.[20]

Treatment with topiramate is commonly associated with central nervous system (CNS) side effects, including loss of concentration, psychomotor retardation, speech disorders, dizziness, somnolence, fatigue, confusion and ataxia. Moreover, dose dependent weight loss, paraesthesia, calcium phosphate renal calculi, obstructive glaucoma symptoms and metabolic acidosis may occur in some patients.

Most of the adverse events reported in our study are in accordance with those revealed in other studies.[1,2,28] Topiramate treatment has been associated with a dose-dependent weight loss[1,28] and was effective in reducing the frequency of binge eating.[28] However, unexpectedly in our study 3 out of 26 patients reported weight-gain, presumably unrelated to topiramate treatment.

Although a relationship between plasma topiramate concentrations and occurrence of adverse events related to CNS was demonstrated previously,[8] in the present study only incidence of headache was associated with the average steady-state plasma concentration of topiramate. Lower plasma concentration of topiramate was observed in patients experiencing headaches compared to patients not experiencing this adverse event. This could be attributed to the antimigraine action of topiramate.[28] On the other hand, somnolence, ataxia, tremor, speech disorders and fatigue were associated with adjunctive therapy with carbamazepine, valproic acid, benzodiazepines, and risperidone.

In some controlled clinical trials with topiramate a pharmacokinetic–pharmacodynamic relationship has been established. Longer time to first seizure was observed in patients with higher topiramate plasma concentration. However, this finding is not consistent, as there are many published studies where no clear relationship between plasma concentration of topiramate and seizure reduction was found.[6,8,21] Our results indicate no association of topiramate plasma concentration with treatment efficacy evaluated by number of seizures in a 6-month period and health-related quality of life assessed with standardised questionnaires.

Clinical practice has demonstrated that incidence and severity of adverse events may be reduced by slow titration to effective and well tolerated doses of topiramate.[1,2,28] Since epilepsy is an episodic disease, it is difficult to determine if a patient is responding to drug therapy or is just free of abnormal central nervous system discharges. Therapeutic drug monitoring of topiramate is useful to provide a reference concentration in an individual patient, despite the very weak relationship between topiramate plasma concentration and therapeutic effect. The population pharmacokinetic model can be used for Bayesian estimation of an individual patient's pharmacokinetic parameters based on sparse plasma samples and for selection of an optimum dosing regimen in routine patient care.

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