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Pharmacogenetics-based population pharmacokinetic analysis of gabapentin in patients with chronic pain: Effect of OCT2 and OCTN1 gene polymorphisms

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Abstract

Gabapentin (GAB) is eliminated unchanged in urine, and organic cation transporters (OCT2 and OCTN1) have been shown to play a role in GAB renal excretion. This prospective clinical study aimed to evaluate the genetic polymorphisms effect on GAB pharmacokinetic (PK) variability using a population pharmacokinetic approach. Data were collected from 53 patients with chronic pain receiving multiple doses of GAB. Patients were genotyped for *SLC22A2* c.808G>T and *SLC22A4* c.1507C>T polymorphisms. Both polymorphisms' distribution followed the Hardy-Weinberg equilibrium. An one-compartment model with first-order absorption and linear elimination best described the data. The absorption rate constant, volume of distribution, and clearance estimated were 0.44 h^{-1}, 86 L, and 17.3 × (estimated glomerular filtration ratio/89.58)$^{1.04}$ L/h, respectively. The genetic polymorphism *SLC22A4* c.1507C>T did not have a significant influence on GAB absorption, distribution or elimination. Due to the low minor allelic frequency of *SLC22A2* c.808G>T, further studies require higher number of participants to confirm its effect on GAB renal elimination. In conclusion, GAB clinical pharmacokinetics are strongly influenced by renal function and absorption process, but not by the OCTN1 (*SLC22A4* c.1507C>T) polymorphism.

KEYWORDS
chronic pain, gabapentin, genetic polymorphism, population pharmacokinetics

1 | INTRODUCTION

Gabapentin (GAB) is largely prescribed in clinical practice as chronic pain treatment.[1-7] Studies reported that GAB is rapidly and mainly absorbed in the small intestine, but the absorption mechanisms are not clear.[8-10] The L-amino acid transport system 2 (LAT2) activity is involved in GAB absorption and the saturation of the transporter explains the dose-dependent oral bioavailability.[8,11-14] GAB does not bind to plasma proteins, is not metabolised and is eliminated unchanged in urine.[15-17] Renal function showed a positive correlation with GAB renal clearance, since GAB is mainly eliminated by glomerular filtration.[18-20] However, studies suggested the activity of the organic cation transporters OCT2 and OCTN1 in the renal excretion of GAB.[21,22]

OCT2 and OCTN1 are coded by *SLC22A2* and *SLC22A4* genes, respectively.[23,24] These genes are polymorphic and the presence of single nucleotide polymorphisms (SNP) can alter the activity of both transporters. *SLC22A2* c.808G>T (A270S) is the most frequent SNP of OCT2 gene.[25] In vitro and clinical studies reported that this polymorphism reduces the transport of OCT2 substrates, such as metformin.[26-28] A small number of studies evaluating OCTN1 polymorphisms effects are available. The most common SNPs in OCTN1 gene are *SLC22A4* c.917C>T (T306I) and c.1507C>T (L503F).[29] These polymorphisms seem to increase or decrease the transporter activity depending on the substrate.[21,29-31] Individuals homozygous for *SLC22A4* c.1507C>T rare allele (TT) showed active tubular secretion of GAB approximately ten-fold lower when compared with individuals homozygous for the reference allele (CC). Significant difference between GAB renal clearance was also observed (CC = 141.4 ± 8.3 mL/min and TT = 109.9 ± 12.3 mL/min).[21]

As suggested in the literature, organic cation drug transporters seem to play a role in the active tubular secretion of GAB. Based on this hypothesis, a population pharmacokinetic (PopPK) model was developed to evaluate the influence of pharmacogenetic polymorphisms of OCT2 and OCTN1 on the PK parameters of GAB in patients with chronic pain.

2 | MATERIALS AND METHODS

2.1 | Subjects

The study was written in accordance with the recognised standards of the Declaration of Helsinki and was approved by the Ethics Committee of School of Pharmaceutical Sciences - São Paulo State University and the Ethics Committee of Clinical Hospital of the Ribeirão Preto Medical School (HCFMRP-USP). The study was conducted in accordance with the BCPT policy for clinical studies.[32] The clinical protocol was explained and all patients signed the free informed consent form. Participants were recruited between September 2016 and February 2018. Patients treated with GAB, for at least 7 days without change in the daily dose were investigated. No restrictions on daily dose, gender, weight, race, or dose regimen were considered. Pregnant and breastfeeding women or patients who were receiving OCT2 and/or OCTN1 inhibitors were excluded. The study is registered on ClinicalTrials.gov (identifier NCT02977208).

After steady state was reached, four blood samples (8 mL) were collected from each participant (sparse sampling): immediately before the dose of GAB, 1.5 and 4 hour after the administration and immediately before the next GAB dose. The times of fourth blood sample differs among participants since it depends on the dose interval (e.g. 6, 8, 12, 24 hours). Plasma samples were stored frozen at −70°C until analysis. Demographic (gender, age, body weight, height) and clinical data (daily dose, dose regimen, serum creatinine concentration, comorbidities, and concomitant medications) were obtained from medical charts.

2.2 | Genotyping

DNA samples were extracted from whole blood with a salting-out method. The SNPs *SLC22A2* c.808G>T (rs316019, C__3111809_20) and *SLC22A4* c.1507C>T (rs1050152, C__3170459_30) were determined using TaqMan™ Drug Metabolism SNP Genotyping Assays (Life Technologies, Tapevi, Brazil). Genotyping assays were performed at 7500 Real Time PCR System (Applied Biosystems®, Foster City, USA). RT-PCR reagents and conditions were used as the manufacturer's recommendations: 10 minutes at 95°C for enzyme activation step; 50 cycles of 95°C for 15 seconds and 60°C for 90 seconds.

A Chi square (χ^2) test was performed to evaluate Hardy-Weinberg equilibrium for each polymorphism. The genotype distribution with P-value <0.05 is not conforming with Hardy-Weinberg equilibrium.

2.3 | Gabapentin plasma analysis

Gabapentin plasma concentration was determined by liquid chromatography (LC) with UV detector. The method was based on literature and established at our laboratory with some modifications.[33] Amlodipine was used as internal standard and 1-fluoro-2,4-dinitrobenzene (FDNB) as derivatisation agent. Shortly, 100 μL of plasma was spiked with 25 μL of amlodipine (200 μg/mL) and 200 μL of acetonitrile. Samples were agitated for 5 minutes and centrifuged for 15 minutes at 15 000 ×g. Derivatisation reaction was performed

with 200 μL of the supernatant, 200 μL 0.25 M borate buffer (pH 8.2), 30 μL 0.06 M FDNB, and 1000 μL acetonitrile. The reaction was heated for 10 minutes at 65°C in a dryer block, and then kept for 5 minutes at room temperature. To stop the reaction, 25 μL of 1 M HCl was added. Samples were evaporated up to dryness and the residue was reconstituted in 200 μL of mobile phase.

Fifty microliters were analysed into LC system consisted of LC-20AT quaternary pump, DGV-20A5R degasser, and SDP-20AT UV-Vis detector (Shimadzu, Kyoto, Japan). LiChrospher C18 RP column (125 × 4.0 mm, 5 μm; Merck, Darmstadt, Germany) with LiChroCART 4-4 Purospher RP-18 capped (5 μm, Merck, Darmstadt, Germany) guard-column were used for separation. A mixture of 50 mM sodium phosphate buffer (pH 3.9) and methanol (27:73, v/v) was used as mobile phase, at the flow rate of 1.2 mL/min. Ultraviolet detection was performed at 360 nm. The method validation was performed according to the European Medicines Agency (EMA) guideline and showed linearity at the range of 200-14 000 ng/mL.

2.4 | Population pharmacokinetic analysis (PopPK analysis)

The modelling was performed with Monolix Suite 2018R1 (Lixoft®, Antony, France). Structural models evaluated included: one and two-compartments, first-order absorption, linear and Michaelis-Menten elimination. Additive and proportional error models were tested. A log-normal distribution was used to model the between-subject variability (BSV, η). The model was parameterised as clearance (Cl), volume of distribution (V), and first-order absorption rate constant (k_a). The parameters were estimated with a stochastic approximation. Object function value (OFV) represented as −2 times the log-likelihood (−2LL) and Akaike Information Criterion (AIC), were used to compare the models.

Covariate models were developed after base model was established. The covariates investigated were body weight, body mass index, estimated glomerular filtration ratio (eGFR), gender, and OCT2 and OCTN1 genotypes. The eGFR was estimated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and transformed to logarithmic normalised by the mean. Visual analysis of the plots and statistics tests (Pearson correlation and Wald test) were performed to identify which covariates could improve the model. Covariates analysis followed a stepwise inclusion/backward elimination approach and were based on changes in OFV. The covariate was considered statistically significant if its addition reduces OFV in at least 3.84 (χ^2, $P < 0.05$, $df = 1$) and AIC values should be reduced in 2. Backward elimination criterion used was an increase of OFV in 6.63 (χ^2, $P < 0.01$, $df = 1$). Model evaluation was performed with visual examination of goodness-of-fit plots, visual predictive check (VPC, n = 10 000 simulations), and a bootstrap analysis (n = 5 000 replicates) using the package Rsmlx for RStudio software (version 1.1.442, Free Software Foundation, Boston, USA).

3 | RESULTS

A total of 53 patients, who declared to follow the prescription of GAB for at least 7 days, participated in this study. Demographic and clinical characteristics of the participants

TABLE 1 Demographic and clinical characteristics of the study population (n = 53)

	Value or mean ± SD	% or range
Demographic characteristics		
Gender (men/women)	27/26	51/49
Age (years)	54 ± 12	25-75
Body weight (kg)	80.5 ± 15.6	50.0-120.0
BMI (kg/m^2)	29.14 ± 6.26	19.53-44.89
Race (White/Black/Brown)[a]	46/5/2	87/9/4
Clinical characteristics		
Daily dose (mg)	1392 ± 670	600-3600
Serum creatinine (mg/dL)	0.92 ± 0.44	0.44-3.34
eGFR (mL/min/1.73 m^2)	89.80 ± 23.94	19.50-132.00
Genetic polymorphisms		
SLC22A2 c.808G>T (GG/GT/TT)	46/7/0	87/13/0
SLC22A4 c.1507C>T (CC/CT/TT)	25/22/6	47/42/11
Indication		
Lumbar/cervical disc herniation	14	26.4
Central pain	7	13.2
Traumatic/postsurgical nerve injury pain	3	5.7
Complex regional pain syndrome	3	5.7
Diabetic neuropathic pain	3	5.7
Post-stroke pain	3	5.7
Trigeminal neuralgia	3	5.7
Other chronic pain	17	32.1

BMI, body mass index; eGFR, estimated glomerular filtration ratio; SD, standard deviation.

[a]Brazilian race/colour classification according to the official Brazilian Census.

TABLE 2 Univariate covariate analysis with best PopPK base model

Covariate	OFV	ΔOFV	AIC	ΔAIC	*P*-value	Included in the multivariate analysis
Base model	611.92		625.92			
log(eGFR/89.58) on Cl	568.18	−43.74	584.18	−41.74	<0.0001*	Yes
Gender on V	606.70	−5.22	622.70	−3.22	0.0986	Yes
Gender on k_a	607.21	−4.71	623.21	−2.71	0.0633	Yes
OCT2 genotype on Cl	609.91	−17.99	625.91	−0.01	0.652	No
OCTN1 genotype on Cl	610.29	−1.63	626.29	0.37	0.332	No

AIC, Akaike Information Criterion; Cl, clearance; eGFR, estimated glomerular filtration ratio; ka, first-order absorption rate constant; OCT2, organic cation transporter 2; OCTN1, organic cation/ergothioneine transporter; OFV, object function value; V, volume of distribution; ΔAIC, AIC difference from base model; ΔOFV, OFV difference from base model.

*P-value ≤0.05 was statistically significant (Wald test).

TABLE 3 Final population pharmacokinetic parameter estimated of gabapentin in patients with chronic pain (n = 53[a])

	Final model		Bootstrap analysis	
Parameter	Estimate	%RSE	Estimate	95% CI
ka (h^{-1})	0.44	14.5	0.44	0.22-0.62
V (L)	86.0	13.3	86.0	44.1-110-3
Cl (L/h)	12.5	4.67	12.49	11.43-13.78
log(eGFR/89.58) effects on Cl	1.04	12.8	1.04	0.73-1.25
BSV (η)		CV (%)		
η_{ka}	0.323	61.7[b]	0.323	0.156-0.606
η_V	0.546	85.2[b]	0.546	0.256-0.654
η_{Cl}	0.325	62.0[b]	0.325	0.250-0.374
Residual error				
Proportional	0.133	36.5[c]	0.133	0.087-0.184

%RSE, relative standard error; BSV, between-subject variability; CI, confidence interval; Cl, clearance; CV, coefficient of variation; eGFR, estimated glomerular filtration ratio; ka, first-order absorption rate constant; V, volume of distribution.

[a]Total number of samples = 212.

[b]Calculated by the equation: $CV = 100 \times \sqrt{\exp(BSV) - 1}$.

[c]Calculated by the equation: $CV = 100 \times \sqrt{\text{residual error}}$.

are presented in Table 1. GAB was prescribed as treatment for several chronic pain conditions, such as lumbar/cervical disc herniation and central pain. All patients were genotyped for *SLC22A2* c.808G>T and *SLC22A4* c.1507C>T (Table 1). No patients homozygous for *SLC22A2* c.808G>T variant (808TT) were found. The minor allele frequencies (MAF) were 6.6% and 32.1% for *SLC22A2* c.808G>T and *SLC22A4* c.1507C>T, respectively. Both polymorphisms distributions were in Hardy-Weinberg equilibrium (χ^2 test, $P \geq 0{,}94$). Patients were grouped as wild-type homozygous (c.808GG or c.1507CC) and heterozygous/rare homozygous (c.808GT or c.1507CT/TT) for both SNPs (*SLC22A2* c.808G>T and *SLC22A4* c.1507C>T).

Based on literature and on the structural models tested, one-compartment model was used with first-order absorption and linear elimination.[19,34,35] PopPK model was developed using a total of 212 sparse samples of GAB plasma concentration. GAB plasma concentration was higher than the limit of quantification in all samples. Proportional error model was the best to estimate the unexplained residual variability. The parameters estimated with the base model were a Cl of 12 L/h, a V of 55.4 L, and k_a of 0.266 h^{-1}.

Univariate analysis with the variables which showed correlation (continuous covariates) with PK parameters or seemed to have difference in parameters median values (categorical covariates) was performed (Table 2). During the univariate analysis, OFV and AIC values decrease when gender was associated with V and k_a (Table 2). However, the effect of gender on V and k_a was not significant ($P = 0.0986$ and 0.0633, respectively). Only eGFR influence on Cl was statistically significant ($P < 0.0001$). No difference in Cl was observed when OCT2 and OCTN1 genotypes were added as covariates. The covariates BMI and body weight were tested and did not alter any PK parameters.

A stepwise inclusion/backward elimination approach was applied with the covariates that reduces OFV significantly ($P < 0.05$, $df = 1$, Table 2). Only renal function showed to affect the clearance of GAB. The equation that describes the final model clearance is:

$$\text{Cl}(L/h) = 17.3 \times (\text{eGFR}/89.58)^{1.04}$$

The final PopPK model presented relative standard error (%RSE) of the estimated population parameter mean between 4.67%-14.5% (Table 3). The estimated parameters were similar to the median and within the 95% confidence intervals of the bootstrap replicates. The individual GAB plasma concentration predicted has good correlation with observed values and no systematic bias was observed (Figure 1).

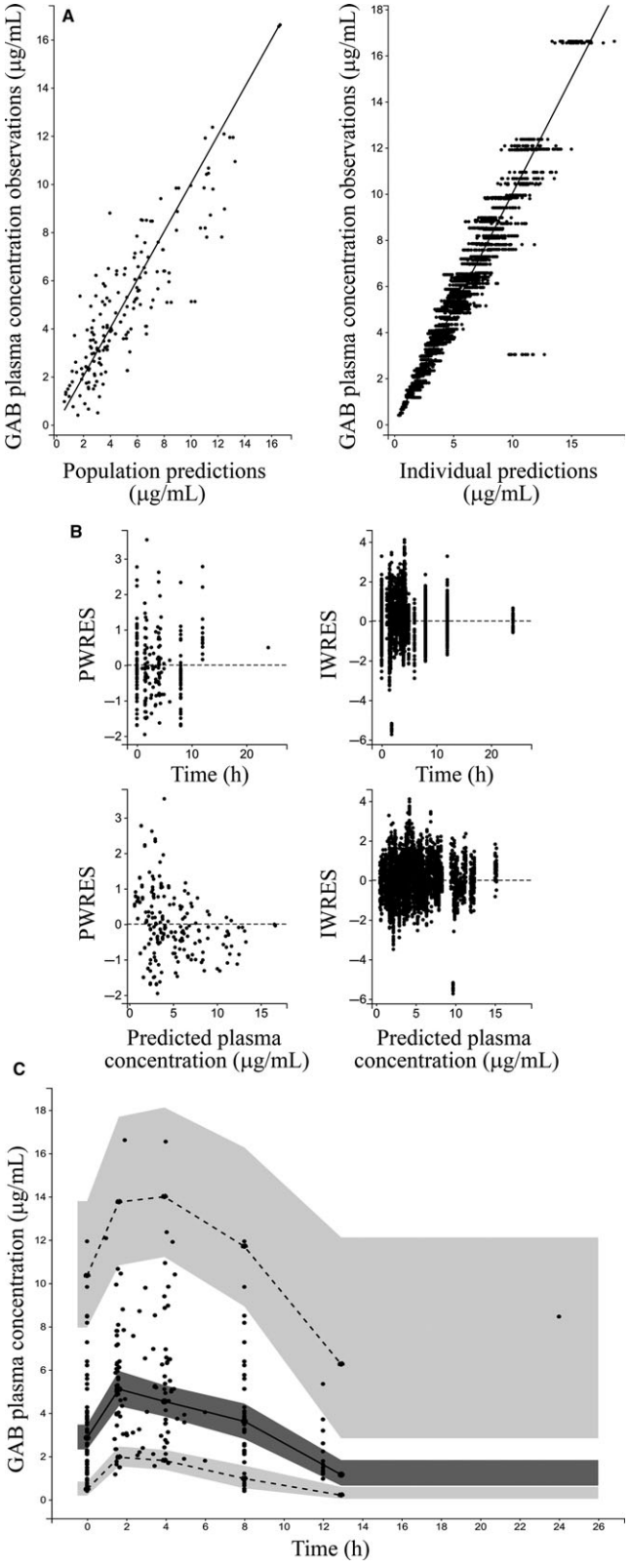

FIGURE 1 Final PopPK model evaluation. A, Goodness-of-fit plots: observed GAB plasma concentrations vs population (left) and individual (right) predicted concentrations. B, Population and individual weighted residues *versus* time and GAB plasma concentration (PWRES and IWRES, respectively). C, Visual predictive check (VPC) of GAB plasma concentration vs time. The observed data are represented as solid circles. The solid line represents the median of the predicted data. The dashed lines represent the 5th and 95th percentiles of the predicted data. The grey areas represent the 95% confidence interval of predicted percentiles

4 | DISCUSSION

There is an extensive interindividual variability on GAB pharmacokinetics. Its dose-dependent oral bioavailability and the influence of age/renal function or drug transporters activity can explain this variability.[11,19,21,22,36,37] A PopPK model was developed to correlate the pharmacogenetics of drug transporters and other covariates with PK parameters (k_a, Cl and V).

The impact of k_a values (between 0.2 and 1.6 h^{-1}) in PopPK model likelihood has been evaluated and the value of 0.44 h^{-1} showed the lowest OFV.[34] The final PopPK model for our population also presented a k_a of 0.44 h^{-1}. The mean estimated value of V was 86.0 L, which is approximated to the V reported for healthy volunteers (81.0-90.0 L) and elderly (71.2 L) populations.[19,35,38] The estimated Cl of GAB was 12.5 L/h which was similar to the value reported for healthy male volunteers (11.1 L/h).[35]

In vitro and clinical studies showed that GAB is a substrate of OCT2 and OCTN1, suggesting that drug transporters contribute to GAB clearance.[21,22,31] The OCTN1 polymorphism *SLC22A4* c.1507C>T was associated with decrease in active tubular secretion of GAB.[21] To our knowledge, this is the first clinical study which evaluated the effect of OCT2 genotype in GAB PK. Previous PopPK models for GAB did not analyse OCT2 and OCTN1 genotype data as covariates.

During the study design, sample size was calculated based on MAF for rs316019 and rs1050152 in Brazilians of 11.9% and 32.9%, respectively,[39] and considering a power of at 80%, type 1 error of 5%, and a difference of 30% between groups. However, the MAF for rs316019 observed in our study was only 6.9%, probably due to the small sample size. The lower MAF resulted in a low statistical power (49%) for the reported results for rs316019. Thus, the influence of rs316019 (SLC22A2 c.808G>T) on GAB pharmacokinetic parameters cannot be assessed in this study and further clinical trials for this SNP require higher number of participants.

The MAF of *SLC22A4* c.1507C>T observed in this study (32.1%) was similar to previously described for the Brazilian population.[39] For this SNP, the statistical power of the study was 81.6%. No effect of *SLC22A4* c.1507C>T genetic

polymorphism in GAB clearance was observed. In this study, only eGFR was considered to predict clearance. Therefore, renal function (represented by eGFR) is the major covariate described up to date to explain the variability on GAB pharmacokinetics in both healthy individuals and patients receiving GAB.[18-20] Although OCTN1 is also expressed in the intestinal epithelium, no effect of *SLC22A4* c.1507C>T polymorphism in the absorption process was observed in this study or reported in the literature.[21]

The main limitation of this study is that non-linear absorption of GAB was not taken into account during PopPK modelling, due to the lack of bioavailability data. Another limitation is that genetic polymorphisms related to absorption process were not evaluated as covariates. Few studies about the influence of *ABCB1* expression in GAB PK are available.[35,40] The polymorphism 2677G>T/A of *ABCB1* gene was recently correlated with increase in k_a of GAB. Although LAT2 transporter activity has been associated with GAB absorption, its gene (*SLC7A8*) is highly conserved and there are no studies showing that polymorphisms could change gene expression or transporter function.[11,41,42] Studies showed that LAT1 transporter plays a role in GAB distribution through the blood-brain and blood-retinal barriers.[43,44] The effect of genetic polymorphisms in LAT1 gene (*SLC7A5*) activity has been studied. The SNP rs1060250 (N230K) did not change the transport of phenylalanine.[45] On the other hand, the SNP rs4240803 was associated with melphalan toxicity and had a significant effect on melphalan distribution to the peripheral compartment.[46,47]

Although there is evidence that GAB is a substrate for OCTN1, the genotype of this transporter did not show relevant impact on the clinical practice. In summary, GAB clinical pharmacokinetics is influenced by renal function and absorption processes saturation and not by the genetic polymorphism *SLC22A4* c.1507C>T of OCTN1 transporter.

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CONFLICTS OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

REFERENCES

1. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280:1837-1842.
2. Rice AS, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain*. 2001;94:215-224.
3. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998;280:1831-1836.
4. Hahn K, Arendt G, Braun JS, et al. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. *J Neurol*. 2004;251:1260-1266.
5. Serpell MG. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. *Pain*. 2002;99:557-566.
6. Tai Q, Kirshblum S, Chen B, Millis S, Johnston M, DeLisa JA. Gabapentin in the treatment of neuropathic pain after spinal cord injury: a prospective, randomized, double-blind, crossover trial. *J Spinal Cord Med*. 2002;25:100-105.
7. Levendoglu F, Ogun CO, Ozerbil O, Ogun TC, Ugurlu H. Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine*. 2004;29:743-751.
8. Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on therapeutic strategies. *Epilepsia*. 2008;49:1239-1276.
9. Chen C, Cowles VE, Sweeney M. The intestinal absorption mechanism of gabapentin makes it appropriate for gastroretentive delivery. *Curr Clin Pharmacol*. 2013;8:67-72.
10. Krasowski MD, McMillin GA. Advances in anti-epileptic drug testing. *Clin Chim Acta*. 2014;436:224-236.
11. Stewart BH, Kugler AR, Thompson PR, Bockbrader HN. A saturable transport mechanism in the intestinal absorption of gabapentin is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma. *Pharm Res*. 1993;10:276-281.
12. Striano S, Striano P, Capone D, Pisani F. Limited place for plasma monitoring of new antiepileptic drugs in clinical practice. *Med Sci Monit*. 2008;14:RA173-RA178.
13. Yagi T, Naito T, Mino Y, Umemura K, Kawakami J. Impact of concomitant antacid administration on gabapentin plasma exposure and oral bioavailability in healthy adult subjects. *Drug Metab Pharmacokinet*. 2012;27:248-254.
14. Tjandrawinata RR, Setiawati E, Putri RS, Yunaidi DA, Amalia F, Susanto LW. Single dose pharmacokinetic equivalence study of two gabapentin preparations in healthy subjects. *Drug Des Devel Ther*. 2014;8:1249-1255.
15. Patsalos PN, Zugman M, Lake C, James A, Ratnaraj N, Sander JW. Serum protein binding of 25 antiepileptic drugs in a routine clinical setting: a comparison of free non-protein-bound concentrations. *Epilepsia*. 2017;58:1234-1243.
16. Goa KL, Sorkin EM. Gabapentin A review of its pharmacological properties and clinical potential in epilepsy. *Drugs*. 1993;46:409-427.
17. Johannessen SI, Battino D, Berry DJ, et al. Therapeutic drug monitoring of the newer antiepileptic drugs. *Ther Drug Monit*. 2003;25:347-363.

18. Galitz LA, Jayawardena S, Furey SA. Pharmacokinetic effects of simultaneous administration of single-dose gabapentin 500 mg and zolpidem tartrate 10 mg in healthy volunteers: a randomized, open-label, crossover trial. *Drugs R D*. 2015;15:71-77.
19. Ahmed GF, Bathena SP, Brundage RC, et al. Pharmacokinetics and saturable absorption of Gabapentin in nursing home elderly patients. *AAPS J*. 2017;19:551-556.
20. Blum RA, Comstock TJ, Sica DA, et al. Pharmacokinetics of gabapentin in subjects with various degrees of renal function. *Clin Pharmacol Ther*. 1994;56:154-159.
21. Urban TJ, Brown C, Castro RA, et al. Effects of genetic variation in the novel organic cation transporter, OCTN1, on the renal clearance of gabapentin. *Clin Pharmacol Ther*. 2008;83:416-421.
22. Lal R, Sukbuntherng J, Luo W, et al. Clinical pharmacokinetic drug interaction studies of gabapentin enacarbil, a novel transported prodrug of gabapentin, with naproxen and cimetidine. *Br J Clin Pharmacol*. 2010;69:498-507.
23. Koepsell H, Lips K, Volk C. Polyspecific organic cation transporters: structure, function, physiological roles, and biopharmaceutical implications. *Pharm Res*. 2007;24:1227-1251.
24. Koepsell H. The SLC22 family with transporters of organic cations, anions and zwitterions. *Mol Aspects Med*. 2013;34:413-435.
25. Leabman MK, Huang CC, Kawamoto M, et al. Polymorphisms in a human kidney xenobiotic transporter, OCT2, exhibit altered function. *Pharmacogenetics*. 2002;12:395-405.
26. Kang HJ, Song IS, Shin HJ, et al. Identification and functional characterization of genetic variants of human organic cation transporters in a Korean population. *Drug Metab Dispos*. 2007;35:667-675.
27. Song IS, Shin HJ, Shim EJ, et al. Genetic variants of the organic cation transporter 2 influence the disposition of metformin. *Clin Pharmacol Ther*. 2008;84:559-562.
28. Wang ZJ, Yin OQ, Tomlinson B, Chow MS. OCT2 polymorphisms and in-vivo renal functional consequence: studies with metformin and cimetidine. *Pharmacogenet Genomics*. 2008;18:637-645.
29. Urban TJ, Yang C, Lagpacan LL, et al. Functional effects of protein sequence polymorphisms in the organic cation/ergothioneine transporter OCTN1 (SLC22A4). *Pharmacogenet Genomics*. 2007;17:773-782.
30. Peltekova VD, Wintle RF, Rubin LA, et al. Functional variants of OCTN cation transporter genes are associated with Crohn disease. *Nat Genet*. 2004;36:471-475.
31. Futatsugi A, Masuo Y, Kawabata S, Nakamichi N, Kato Y. L503F variant of carnitine/organic cation transporter 1 efficiently transports metformin and other biguanides. *J Pharm Pharmacol*. 2016;68:1160-1169.
32. Tveden-Nyborg P, Bergmann TK, Lykkesfeldt J. Basic & clinical pharmacology & toxicology policy for experimental and clinical studies. *Basic Clin Pharmacol Toxicol*. 2018;123:233-235.
33. Jalalizadeh H, Souri E, Tehrani MB, Jahangiri A. Validated HPLC method for the determination of gabapentin in human plasma using pre-column derivatization with 1-fluoro-2,4-dinitrobenzene and its application to a pharmacokinetic study. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2007;854:43-47.
34. Carlsson KC, van de Schootbrugge M, Eriksen HO, Moberg ER, Karlsson MO, Hoem NO. A population pharmacokinetic model of gabapentin developed in nonparametric adaptive grid and nonlinear mixed effects modeling. *Ther Drug Monit*. 2009;31:86-94.
35. Tran P, Yoo HD, Ngo L, Cho HY, Lee YB. Population pharmacokinetics of gabapentin in healthy Korean subjects with influence of genetic polymorphisms of ABCB1. *J Pharmacokinet Pharmacodyn*. 2017;44:567-579.
36. Gidal BE, DeCerce J, Bockbrader HN, et al. Gabapentin bioavailability: effect of dose and frequency of administration in adult patients with epilepsy. *Epilepsy Res*. 1998;31:91-99.
37. Boyd RA, Türck D, Abel RB, Sedman AJ, Bockbrader HN. Effects of age and gender on single-dose pharmacokinetics of gabapentin. *Epilepsia*. 1999;40:474-479.
38. Glerum PJ, Yu Y, Yamada WM, et al. Interchangeability of generic drugs: a nonparametric pharmacokinetic model of gabapentin generic drugs. *Clin Pharmacol Ther*. 2018;. https://doi.org/10.1002/cpt.1023.
39. Bonifaz-Peña V, Contreras AV, Struchiner CJ, et al. Exploring the distribution of genetic markers of pharmacogenomics relevance in Brazilian and Mexican populations. *PLoS ONE*. 2014;9:e112640.
40. Kang HA, Cho HY, Lee YB. The effect of MDR1 G2677T/A polymorphism on pharmacokinetics of gabapentin in healthy Korean subjects. *Arch Pharm Res*. 2007;30:96-101.
41. Kühne A, Kaiser R, Schirmer M, et al. Genetic polymorphisms in the amino acid transporters LAT1 and LAT2 in relation to the pharmacokinetics and side effects of melphalan. *Pharmacogenet Genomics*. 2007;17:505-517.
42. Nguyen TV, Smith DE, Fleisher D. PEPT1 enhances the uptake of gabapentin via trans-stimulation of $b^{0,+}$ exchange. *Pham Res*. 2007;24:353-360.
43. Dickens D, Webb SD, Antonyuk S, et al. Transport of gabapentin by LAT1 (SLC7A5). *Biochem Pharmacol*. 2013;85:1672-1683.
44. Akanuma SI, Yamakoshi A, Sugouchi T, et al. Role of l-type amino acid transporter 1 at the inner blood-retinal barrier in the blood-to-retina transport of Gabapentin. *Mol Pharm*. 2018 Jun;4(15):2327-2337.
45. Boado RJ, Li JY, Wise P, Pardridge WM. Human LAT1 single nucleotide polymorphism N230K does not alter phenylalanine transport. *Mol Genet Metab*. 2004;83:306-311.
46. Giglia JL, White MJ, Hart AJ, et al. A single nucleotide polymorphism in SLC7A5 is associated with gastrointestinal toxicity after high-dose melphalan and autologous stem cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. 2014;20:1014-1020.
47. Cho YK, Sborov DW, Lamprecht M, et al. Associations of high-dose melphalan pharmacokinetics and outcomes in the setting of a randomized cryotherapy trial. *Clin Pharmacol Ther*. 2017;102:511-519.

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