Remedial dosing recommendations for delayed or missed doses of valproic acid in patients with epilepsy based on Monte Carlo simulations

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Abstract

Objective: Delayed or missed doses are unavoidable in the pharmacotherapy of epilepsy and significantly compromise the efficacy of antiepileptic drug treatment. An inappropriate remedial regimen can cause seizure relapse or serious adverse events. This study investigated the effect of delayed or missed doses on the pharmacokinetics (PK) of valproic acid (VPA) in patients with epilepsy and established remedial dosing recommendations for nonadherent patients.

Methods: Monte Carlo simulations are based on all published population pharmacokinetic models for pediatric, adult and elderly patients with epilepsy. The following four remedial strategies were investigated for each delayed dose: A) A partial dose or a regular dose is taken immediately; a regular dose is taken at the next scheduled time. B) The delayed dose was administered immediately, followed by a partial dose at the next scheduled time. C) The delayed dose and a partial dose are taken; the next scheduled time is skipped, and the regular regimen is resumed. D) Double doses are taken when one dose or two doses are missed, and the regular regimen is resumed at the subsequent scheduled time.

Results: The recommended remedial dose was related to the delay duration and daily dose. Remedial dosing strategies A and B were almost equivalent, whereas Strategy C was recommended when the delayed dose was close to the next scheduled dose. Strategy D was only suggested when two doses were missed.

Conclusion: Simulations provide quantitative insight into the remedial regimens for nonadherent patients, and clinicians should select the optimal regimen for each patient based on the individual' s status.

Full Text

Preamble

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the regular regimen is resumed thereafter. D) Double doses are taken when one or two doses are missed, with the regular regimen resumed at the subsequent scheduled time.

Results: The recommended remedial dose was related to the delay duration and daily dose. Remedial dosing strategies A and B were almost equivalent, whereas Strategy C was recommended when the delayed dose was close to the next scheduled dose. Strategy D was only suggested when two doses were missed.

Conclusion: Simulations provide quantitative insight into remedial regimens for non-adherent patients, and clinicians should select the optimal regimen for each patient based on the individual' s status.

Key words: Epilepsy; Valproic acid; Non-adherence; Monte Carlo simulation; Remedial dose; Population pharmacokinetics

1 Introduction

Epilepsy is one of the most common and disabling neurological disorders, requiring long-term, sometimes lifelong, antiepileptic drug (AED) treatment [**?**]. Adherence to the prescribed regimen is crucial for seizure control [**?**]. However, delayed or missed doses frequently occur in epilepsy treatment [**?**]. Approximately 30%–50% of patients with epilepsy are non-adherent to their prescribed AED therapies, with over 70% of respondents in one study reporting missed AED doses [**?**, **?**]. Such non-adherence can lead to sub-therapeutic drug concentrations and increase seizure risk [**?**], while excessive remedial doses may cause clinical toxicity, including somnolence, heart block, and deep coma [**?**].

Valproic acid (VPA) is a broad-spectrum AED used to treat both generalized and focal seizures [**?**] and is often combined with other AEDs in patients with multiple seizure types [**?**]. According to FDA requirements, the VPA package insert (Depakote ER®) states: "If a dose is missed, it should be taken as soon as possible, unless it is almost time for the next dose. If a dose is skipped, the patient should not double the next dose" [**?**]. However, no clear remedial dose regimen is provided for missed doses, and no comprehensive evaluation of non-adherence effects and corresponding remedial dosing regimens has been performed.

Prospective studies intentionally delaying or interrupting medications for experimental purposes raise ethical concerns [**?**, **?**], and retrospective data are difficult to collect accurately. Monte Carlo simulation based on population pharmacokinetic (PPK) models provides the most appropriate means to investigate delayed or missed dose effects [**?**] and is widely accepted for developing treatment protocols, thereby avoiding unnecessary clinical studies. This study aims to investigate the effects of delayed or missed doses on VPA pharmacokinetics and provide practical recommendations for patients through Monte Carlo simulation.

2 Methods

2.1 Typical Patients and Dose Regimens

The characteristics of typical patients and corresponding investigated dose regimens were based on the following criteria: (1) all patients were assumed to receive VPA monotherapy; (2) dose regimens were selected according to FDA-approved labeling and treatment guidelines published by the International League Against Epilepsy [**?**], including formulation, dose strength, and dosing interval; (3) pediatric patient weights were based on the World Health Organization Child Growth Standards [**?**], while adult and elderly patient weights were fixed at 70 kg.

2.2 Population Pharmacokinetic Characteristics for Monte Carlo Simulations

PPK characteristics for simulations were extracted from previous studies. A systematic review of PPK studies published before November 30, 2019, was conducted using PubMed and Embase, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [**?**].

Published studies were included if they (1) evaluated patients receiving valproate and (2) had complete PPK parameters. Studies were excluded if they (1) were reviews or focused only on methodology, (2) were published in non-English languages, or (3) contained data or cohorts overlapping with another included study. In cases of overlap, only the most recent study or the one with the largest sample size was included. Reference lists of all selected articles were also evaluated.

The following PPK parameters were collected from each identified study: apparent clearance (CL/F), apparent volume of distribution (V/F), absorption rate (ka), and corresponding between-subject variability and residual variability. The demographic characteristics of the study cohorts were also extracted.

2.3 Monte Carlo Simulation

Monte Carlo simulations with nested random effects were conducted using the $SIMULATION block in NONMEM software (Version 7.4; Icon Incorporation, PA, USA) with ONLYSIMULATION and SUBPROBLEMS options. Post-processing of the output was performed in R (version 3.4.0, www.r-project.com).

VPA time-concentration profiles were simulated for 1000 virtual patients. These fully adherent patients were assumed to have complete seizure control without undesired effects, or if that goal was not achievable, the best compromise between seizure suppression and concentration-related adverse effects [**?**]. Concentration-time profiles were generated using PPK parameters extracted from identified studies. For each scenario, PPK parameters with the longest and shortest elimination half-life (T1/2) from the identified studies were em-

ployed for further investigation. T1/2 was calculated using Eq. 1, and the time-concentration profile was calculated using Eq. 2.

$$T12/ = 0.693 \times V \quad \text{(Eq. 1)}$$

$$Cn = ka{\cdot}F{\cdot}X0V{\cdot}(ka{-}[(1{-}e{-}{\cdot}t){-}(1{-}e{-}ka{\cdot}n{\cdot}\tau 1{-}e{-}ka{\cdot}\tau{\cdot}e{-}ka{\cdot}t)] \quad \text{(Eq. 2)}$$

where ka represents the absorption rate constant, T1/2 represents elimination half-life, F represents bioavailability, X0 represents the dose amount, CL represents clearance, V represents volume of distribution, n represents the number of dose administrations, represents the dosing interval, and t represents the time after the last dose.

Regularly scheduled, adherent VPA dosing with its corresponding steady-state plasma concentrations was simulated as reference, followed by simulation of steady-state concentration perturbations occurring with various delays or non-adherence.

2.3.1 Non-adherence Scenarios and Remedial Strategies Delayed-dose scenarios for each medication regimen included 1–12 h delays for each 12 h (q12h) dosing regimen or 1–24 h delays for each 24 h (q24h) dosing regimen. Scenarios with one and two missed doses were evaluated for each medication. When a delayed dose occurred, the following four remedial strategies were investigated:

Strategy A: A partial dose or a regular dose is taken immediately, and the regular dose is taken at the next scheduled time.

Strategy B: The regular dose is taken immediately, followed by a partial dose at the next scheduled time.

Strategy C: The delayed dose and a partial dose are taken immediately, the next scheduled dose is skipped, and the regular dose is then taken at the subsequent scheduled time.

Strategy D: Double doses are taken when one or two doses are missed, and the regular dose is taken at the subsequent scheduled time.

Considering tablet size (extended-release tablet, Depakote ER®) and patient convenience, the remedial dosage was designed to change by 250 mg (half of a 500 mg tablet) for optional remedial dosing regimens. Regarding syrup, dosage could be more flexible for remedial regimens.

2.3.2 Criteria to Select the Optimal Remedial Regimen The individual therapeutic range, defined as the concentration that produced the best response in an individual patient, was considered to be the interval delineated by the 5th-percentile trough concentration and the 95th-percentile peak concentration

for each regimen based on guidelines for therapeutic drug monitoring of AEDs [?, ?, ?].

Deviation time was estimated for each scenario and remedial regimen, defined as the time outside the individual therapeutic range (the sum of sub-therapeutic and supra-therapeutic concentrations). The regimen with the shortest deviation time was considered most appropriate. If the difference in deviation time between competing regimens was less than 0.5 h, those regimens were considered equivalent.

2.4 Sensitivity Analysis

Previous studies have shown that weight significantly affects VPA clearance in pediatric, adult, and elderly patients [?]. Additionally, when monotherapy is unsuccessful, combination therapy is usually attempted to improve efficacy, tolerability, or both, with combination therapy used in 79% of adults and 75% of children [?]. Concomitant drugs in polytherapy may be inducers or inhibitors of VPA [?, ?]. Moreover, ka values in previous PPK models of VPA were fixed, and dosing intervals in our simulations were also fixed, which may not accurately reflect real clinical scenarios.

Therefore, sensitivity analysis is helpful to investigate the effects of weight, ka, dosing interval, and concomitant AED use on concentration-time profiles and dosage recommendations in non-adherence events [?]. Non-adherent patients missing one dose were assessed by sensitivity analysis. For simplicity, we changed one parameter at a time and investigated its impact on deviation time and optimal remedial regimen.

3 Results

3.1 Typical Patients and Dose Regimens

Seven typical dose regimens were employed to examine non-adherence effects on pharmacokinetic profiles and to design remedial dose regimens. We investigated extended-release tablets for pediatric, adult, and elderly patients, as well as syrup for pediatric patients. Detailed dosing regimens are listed in Table 1 .

3.2 Population Pharmacokinetic Characteristics

We identified 11 eligible PPK studies from which to extract VPA PPK characteristics [?, ?]. The screening process is presented in Supplementary Text S1. Five studies were conducted in pediatric patients [?, ?, ?, ?, ?]; 2 studies in adults [?, ?]; 1 study in elderly patients [?]; 2 studies in both adult and elderly patients [?, ?]; and 1 study in pediatric, adult, and elderly patients [?]. Five studies were conducted in East Asia (China and Japan), 3 in Europe, 2 in the US, and 1 in Mexico. Study details are summarized in Supplementary Table S1.

The longest and shortest T1/2 values in eligible studies are listed in Table 1. T1/2 ranged from 8.62 to 23.72 h for infant and pediatric patients and from 9.36 to 15.41 h for adult and elderly patients.

3.3 Effect of Delayed or Missed Doses

Monte Carlo simulation results showed that the percentage of subjects outside their individual therapeutic ranges for VPA was related to delay time, daily dose, and T1/2 [Figure 1: see original paper]. The risk of patients being in the sub-therapeutic range increased with delay time. For example, for 70-kg adult patients with the shortest T1/2 (9.23 h) receiving VPA 500 mg q12h [**?**], the percentage of subjects in the sub-therapeutic range was 12% and 22% when the dose was delayed for up to 4 and 8 h, respectively [Figure 1a: see original paper].

Patients receiving higher VPA doses had a higher risk of being outside the individual therapeutic range than those receiving lower doses. For example, in 70-kg adult patients with the shortest T1/2 (9.23 h) [**?**], the percentages of subjects in the sub-therapeutic range were 42.6%, 54%, and 65% for dosing delays of up to 24 h for the 500 mg, 750 mg, and 1000 mg q12h regimens, respectively [Figure 1b: see original paper].

Moreover, patients with longer T1/2 had a higher risk of being outside the individual therapeutic range than patients with shorter T1/2. For instance, the percentage of subjects in the sub-therapeutic range was 65% for 70-kg adult patients with T1/2 of 15.41 h who delayed 24 h for 500 mg q12h [**?**], compared to 42% for adult patients with T1/2 of 9.23 h [**?**].

3.4 Remedial Dosing Regimen

Dosing recommendations for remedial treatment after delayed and missed doses are shown in Table 2 . Results show that remedial dosing recommendations were related to delay time and daily dose. We also developed a tool to check remedy dose regimens under different scenarios (Supplementary tool). If one dose was delayed, one of four remedial strategies with the same total remedial dose could be used.

Strategies A and B for remedial dosing were almost pharmacokinetically equivalent, while Strategy C had a larger deviation time than either of the others regardless of patient age and dosing interval [Figure 2: see original paper]. For example, if a dose was delayed 8 h, a 70-kg adult patient receiving VPA 500 mg q12h could receive 250 mg immediately and 500 mg at the next scheduled dosing time (Strategy A) or 500 mg immediately and 250 mg at the next scheduled dosing (Strategy B). The deviation times were 9.2 h for Strategy A and 8.7 h for Strategy B. If the patient was administered 750 mg immediately and skipped the next scheduled dose (Strategy C), the deviation time was 12.4 h.

Strategy C was recommended only when the delayed dose was close to the next

scheduled dose (e.g., delay time > 10 h for q12h regimen or delay time > 20 h for q24h regimen).

With increasing delays from the scheduled dosing time, there was a decrease in the total remedial dose necessary to minimize deviation time from the individual therapeutic range. For example, consider a 70-kg adult patient receiving VPA 500 mg q12h with satisfactory therapeutic outcome. If a dose was delayed 2 h, the patient could be administered 500 mg immediately and 500 mg at the next scheduled dosing time (total 1000 mg). If a dose was delayed 10 h, patients should be administered 250 mg immediately and 500 mg at the next scheduled dose (or 500 mg immediately and 250 mg at the next scheduled dose), totaling 750 mg [Figure 3: see original paper]. In this situation, if a total remedial dose of 1000 mg (500 mg immediately and 500 mg at the next scheduled dose) was taken, deviation time over the upper limit of the individual therapeutic range was much longer than with a 750 mg remedial dose (7 h vs 0 h), whereas deviation times below the lower limit were similar (12.1 h vs 10.2 h).

Moreover, patients should avoid taking double doses when they miss a single dose. If two doses were missed, double doses are recommended for most scenarios.

3.5 Sensitivity Analysis

The influence of weight (2.5–50 kg for pediatric patients and 50–100 kg for adult and elderly patients) on remedial recommendations was investigated. The effect of concomitant medications on VPA time-concentration profiles was investigated by changing T1/2 ±50%. The influence of ka was studied by changing ±50% values in VPA population PK models. Dosing intervals of 10, 14, 22, and 26 hours were also assessed. Detailed sensitivity analysis settings are presented in Table 3 and Supplementary Table S2.

Results are presented in Supplementary Figure S1, showing that weight, ka, T1/2, concomitant medications, and dosing intervals could change deviation time but had no significant impact on the proper remedial regimen when patients missed one dose.

4 Discussion

For the first time, we systematically established remedial regimens for missed or delayed VPA doses using Monte Carlo simulation. Compared to previous studies using conventional PK approaches, our study fully considered the effects of between-subject variability, residual variability, and covariates on remedial dosing recommendations. Moreover, when performing Monte Carlo simulations for each scenario, we chose two sets of PPK models—those with the longest and shortest T1/2 among all previous population analyses across different countries. This approach helps determine the range of remedial doses and could improve applicability to patients with various VPA PK characteristics.

We employed the individual therapeutic range instead of a fixed reference range to investigate delayed or missed dose effects [**?**, **?**]. Previous retrospective and observational studies suggest VPA reference ranges of 50–100 mg/L. However, the reference range concept is controversial because it was initially defined based on limited data for individual AEDs, which may not adequately describe the concentration-response relationship in epilepsy patients [**?**, **?**]. The trend in epilepsy treatment is shifting from reference ranges to individual therapeutic ranges [**?**, **?**], defined as the concentration (or range) empirically found to produce optimal response in individual patients. Therefore, our study used individual therapeutic range rather than reference range, as employed in previous studies to assess missed or delayed dose effects and make remedial dose recommendations.

We proposed four treatment strategies for different clinical scenarios and conducted detailed investigations. Strategy A is most appropriate for patients with low seizure frequency because concentration returns gradually to the individual therapeutic range, and these patients might have higher breakthrough seizure risk than with other strategies. In contrast, Strategy B allows VPA concentration to return quickly to the individual therapeutic range, making it more suitable for patients with high seizure frequency. However, Strategy B may cause more concentration-related adverse effects such as headache, dizziness, nausea, and emesis than Strategy A.

Strategy C resulted in greater VPA concentration fluctuation than the other strategies and should be used only for patients unable to take the next planned dose as specified or who are near the next scheduled dosing time. Strategy D is not recommended for most non-adherent scenarios, especially when patients miss one dose, consistent with FDA-approved labeling [**?**]. Strategy D may only be applied for patients who miss two doses. Clinicians can choose the best remedial strategy based on patient condition.

Several limitations remain. The ka of extended-release tablets reported in classical PK studies is lower than that investigated in previous population PK studies (0.18 ± 0.19 versus 0.23–1.9) [**?**], and current evidence may not fully cover these scenarios [**?**, **?**]. The impact of extended-release tablets needs further investigation. Moreover, dose recommendations in this study were based on typical patients. Physicians should carefully consider toxicity risk after patients take a remedial dose, especially in pediatric, pregnant, and elderly patients.

5 Conclusions

This study systematically investigated remedial dosing recommendations for delayed or missed VPA doses in epilepsy patients using Monte Carlo simulation. We proposed four remedial strategies for patients who delayed or missed doses. The optimal strategy for non-adherent patients depends on delay time and daily dose. Based on Monte Carlo simulations, we suggest taking the delayed dose when remembered within 3 hours and resuming the regular regimen. If the dose

is remembered over 3 hours but before the next dose, we suggest taking a partial dose immediately and a regular dose at the next scheduled time, or taking a regular dose immediately followed by a partial dose at the next scheduled time. When one dose is missed, patients should avoid double dosing.

Clinicians should always evaluate patients' situations and select the optimal regimen based on clinical status.

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Declaration of Interest

None.

Supplementary Data

Supplementary Text S1. Detailed literature search process

Supplementary Figure S1. Sensitivity analysis of patients administered VPA monotherapy at steady state and missing one dose. (a) 120 mg q12h (8 months, 8 kg), (b) 240 mg q12h (5 years, 16 kg), (c) 500 mg q12h (10 years, 30 kg), (d) 500 mg q24h (6 years, 20 kg), (e) 500 mg q12h (30 years, 70 kg), (f) 750 mg q12h (70 years, 70 kg), and (g) 1000 mg q12h (50 years, 70 kg).

Supplementary Table S1. A summary of published population pharmacokinetic studies of VPA in patients with epilepsy.

Supplementary Table S2. Population pharmacokinetic characteristics of VPA for Monte Carlo simulations.

Supplementary tool: Remedial dosing recommendations for delayed or missed doses of VPA.

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Figure Legends

Fig. 1. Percentage of subjects outside their individual therapeutic ranges after the last dose. (a) Children with the longest and shortest elimination half-life (T1/2) taking 120 mg q12h (8 months, 8 kg), 240 mg q12h (5 years, 16 kg), and 500 mg q12h (10 years, 30 kg). (b) Adults with the shortest and longest T1/2 taking 500 mg q12h (30 years, 70 kg), 750 mg q12h (50 years, 70 kg), and 1000 mg q12h (70 years, 70 kg). All simulated patients have VPA monotherapy at steady state.

Fig. 2. Three remedial strategies identified for 70-kg adults taking 500 mg q12h, simulated with the longest elimination half-life (T1/2). (a) Full adherence. (b) Remedial dosing using strategies A, B (panel c), and C (panel d) when the dose was delayed up to 10 h. All simulated patients have VPA monotherapy at steady state. The dark pink shadow represents the distribution of the 5th–95th percentiles of simulated concentrations, and light pink shadows represent the distribution of simulated concentrations outside the 5th–95th percentiles in remaining virtual subjects. The solid red line represents the median of simulated concentrations, and dotted lines represent the 0.5th and 99.5th percentiles. Dotted black lines represent the individual therapeutic range of the 5th-percentile trough concentration and 95th-percentile peak concentration (48–151 mg/L). The horizontal black solid line represents deviation time.

Fig. 3. Comparison of deviation time for different strategies when a 70-kg adult patient at steady state delayed a dose from 0 h to 10 h. Adults taking VPA monotherapy at 500 mg q12h (a) or 750 mg q12h (c) were simulated using the model with the longest elimination half-life (T1/2: 15.41 h). Adults taking 500 mg q12h (b) or 750 mg q12h (d) were simulated using the model with the shortest T1/2 (9.36 h). Values in parentheses are the dose taken immediately followed by the dose taken at the next scheduled dosing time.

Tables

Table 1. Settings of patient characteristics, dosing regimens, and elimination half-life used in the simulations.

Patient Group	Age	Weight	Formulation	Dose	Dosing Interval	T1/2 (h)
						Shortest
Children	8 months	8 kg	syrup	120 mg	q12h	8.62
	5 years	16 kg	syrup	240 mg	q12h	8.62
	6 years	20 kg	ER-tablet	500 mg	q24h	8.62
	10 years	30 kg	ER-tablet	500 mg	q12h	8.62
Adults	30 years	70 kg	ER-tablet	500 mg	q12h	9.36
	50 years	70 kg	ER-tablet	1000 mg	q12h	9.36
Elderly	70 years	70 kg	ER-tablet	750 mg	q12h	9.36

All simulated patients have VPA monotherapy at steady state. ER-tablet, extended-release tablet. T1/2, elimination half-life, T1 2⁄ = 0.693× .

Table 2. Dosing recommendations after delayed or missed doses of valproic acid.

Regimen	Delay Time (h)	Remedial Strategy and Dose Recommendation (mg)
Children		
120-mg q12h (8 months, 8 kg)	1–3	A (120–120)
	4–8	A (120–120); A (80–120); B (120–80)
	9–12	A (80–120); B (120–80)
	Missed 1 dose	A (80–120); B (120–80); C (160-0)
	Missed 2 doses	C (160)
240-mg q12h (5 years, 16 kg)	1–3	A (240–240)
	4–8	A (160–240); B (240–160)
	9–12	A (160–240); B (240–160); A (120–240); B (240–120)
	Missed 1 dose	A (120–240); B (240–120); C (360–0)
	Missed 2 doses	C (360); D (480)

Regimen	Delay Time (h)	Remedial Strategy and Dose Recommendation (mg)
500-mg q12h (10 years, 30 kg)	1–3	A (500–500)
	4–8	A (500–500); A (250–500); B (500–250)
	9–12	A (250–500); B (500–250)
	Missed 1 dose	A (250–500); B (500–250); C (750-0)
	Missed 2 doses	C (750); D (1000)
500-mg q24h (6 years, 20 kg)	1–3	A (500–500)
	4–12	A (500–500); A (250–500)
	13–20	A (500–500); A (250–500); B (500–250)
	21–24	A (250–500); B (500–250); C (750–0)
	Missed 1 dose	C (750)
Adults		
500-mg q12h (70 kg)	1–3	A (500–500)
	4–8	A (500–500); A (250–500); B (500–250)
	9–12	A (250–500); B (500–250)
	Missed 1 dose	A (250–500); B (500–250); C (750–0)
	Missed 2 doses	C (750); D (1000)
1000-mg q12h (70 kg)	1–3	A (1000–1000)
	4–8	A (1000–1000); A (750–1000); B (1000–750)
	9–12	A (750–1000); B (1000–750); A (500–1000); B (1000–500)
	Missed 1 dose	A (500–1000); B (1000–500); C (1500–0)
	Missed 2 doses	C (1500); C (1750)
Elderly		
750-mg q12h (70 kg)	1–3	A (750–750)
	4–8	A (750–750); A (500–750); B (750–500)
	9–12	A (500–750); B (750–500); C (1250–0)
	Missed 1 dose	A (500–750); B (750–500); C (1250–0)
	Missed 2 doses	C (1250); D (1500)

All simulated patients have VPA monotherapy at steady state. Four remedial

strategies were evaluated:

- *Strategy A: A partial dose or a regular dose is taken immediately, and the regular dose is taken at the next scheduled time.*
- *Strategy B: The regular dose is taken immediately, followed by a partial dose at the next scheduled time.*
- *Strategy C: The delayed dose and a partial dose are taken immediately, the next scheduled dose is skipped, and the regular dose is then taken at the subsequent scheduled time.*
- *Strategy D: Double doses are taken when one or two doses are missed, and the regular dose is then taken at the subsequent scheduled time.*

Values in parentheses for delayed doses are the dose taken immediately followed by the dose taken at the next scheduled dosing time. Values in parentheses for missed doses are the dose taken immediately. The most appropriate remedial regimen has the shortest deviation time. If the difference in deviation time between competing regimens was less than 0.5 h, those regimens were considered equivalent.

Table 3. Sensitivity analysis settings.

Parameter	Setting
Weight	Children: 2.5–50 kg; Adults: 50–100 kg
T1/2 of concomitant medication	Children: 4.31–24.36 h; Adults: 4.66–23.12 h
Absorption rate (Ka)	Children: 0.67–2.6 1/h; Adults: 0.67–1.9 1/h
Dosing interval	10–14 h; 14–10 h

Patients co-administered VPA with an enzyme-inducing antiepileptic drug (e.g., carbamazepine, phenytoin, or phenobarbital) were simulated using the shortest T1/2. Those co-administered with enzyme-inhibiting antiepileptic drugs (e.g., topiramate or clobazam) were simulated using the longest T1/2. Sensitivity analysis of patients administered VPA monotherapy at steady state and missing one dose.

Note: Figure translations are in progress. See original paper for figures.