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Remedial dosing recommendations for delayed or missed doses of lamotrigine in pediatric patients with epilepsy using Monte Carlo simulations

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ABSTRACT

Objective: This study investigated the effect of delayed or missed doses on the pharmacokinetics (PK) of lamotrigine (LTG) in children with epilepsy and established remedial dosing recommendations for nonadherent patients.

Methods: The Monte Carlo simulation based on a published LTG population PK model was used to assess the effect of different scenarios of nonadherence and the subsequently administered remedial regimens. The following three remedial approaches were investigated for each delayed dose: A) A partial dose was administered immediately, and the regular dose was administered 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 and partial doses were coadministered immediately, the next scheduled dose was skipped, and the regular dosing was resumed at the subsequent scheduled time. The most appropriate remedial regimen was that with the shortest deviation time from the individual therapeutic window.

Results: The effect of nonadherence on PK was dependent on the delay duration and daily dose, and the recommended remedial dose was related to the delay duration and concomitant antiepileptic drugs. Remedial dosing strategies A and B were almost equivalent, whereas C showed a larger PK deviation time. If one dose was missed, double doses were not recommended for the next scheduled time.

Conclusions: Simulations provide quantitative insight into the remedial regimens for nonadherent patients, and clinicians should select the optimal regimen based on the status of patients.

1. Introduction

Lamotrigine (LTG) is a second-generation oral antiepileptic drug (AED), widely used as monotherapy and adjunctive treatment for partial-onset, primary generalized tonic–clonic, and generalized seizures of Lennox–Gastaut syndrome. It is well-tolerated and has fewer related adverse effects and drug interactions than traditional first-line AEDs do [1,2].

Lamotrigine is rapidly and completely absorbed following oral administration with negligible first-pass metabolism [1]. It is extensively metabolized by glucuronic acid conjugation to an inactive metabolite [3]. In addition, following unsuccessful monotherapy, LTG is commonly coadministered with other AEDs such as carbamazepine, phenytoin, phenobarbital, and primidone, which induce its metabolism, or valproate (VPA), which has the opposite effect [4,5].

Epilepsy requires long-term AED treatment. Maintaining plasma concentrations within the therapeutic concentration is critical for retaining efficacy and minimizing the adverse effects. However, nonadherence is a common problem in managing epilepsy, even for the most willing patients. It has been reported that 33%–58% of children with epilepsy did not take AEDs as prescribed [6–9]. Moreover, patients with epilepsy who were nonadherent had a significantly increased incidence of visiting emergency rooms, being hospitalized , increased mortality rates and costs, and decreased health-related quality of life [10–13].

It is also worth noting that an inappropriate remedial dose may result in toxicity or breakthrough seizures. The US Food and Drug Administration (FDA) package insert of LTG recommends that "if a dose is missed it should be taken as soon as possible, unless it is almost time

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for the next dose. If a dose is skipped, the patient should not double the next dose" [14]. Chen et al. [15] investigated the impact of irregular doses on LTG pharmacokinetics (PK) for patients aged 13 years or older and suggested remedial doses for one missed dose. However, pediatric patients who are nonadherent and their subsequently administered remedial doses have not been assessed.

It is well-known that it is unethical to examine the effect of irregular dosing in patients with epilepsy, as it would require prospectively withholding doses from patients. Moreover, it is difficult to obtain accurate adherence data from retrospective studies. Therefore, computer simulation is an appropriate method of evaluating the effect of irregular dosing on drug PK [16,17]. In addition, the suggested reference range for LTG is 2.5–15 mg/L [18]. However, there is a substantial overlap in LTG concentrations between responders and nonresponders as well as between patients with or without adverse effects [19–22]. Thus, it is appropriate to use the individual therapeutic range for specific patients.

The purpose of this analysis was to investigate the influence of delayed or missed doses on the PK profile of LTG and provide dosing recommendations for patients to minimize the risk of uncontrolled seizures or drug-related toxicity based on Monte Carlo simulation and individual therapeutic range.

2. Materials and methods

2.1. Patients and dosing regimen

Virtual pediatric patients ranging from 2 to 18 years old were simulated according to the FDA drug label [14], a previous study [23], and The World Health Organization (WHO) maturation-body weight charts [24]. Patients were grouped as follows according to the concomitant AEDs:

(1) Neutral group: patients coadministered LTG with a noninduced or noninhibited AED or as a monotherapy.
(2) Induced group: patients coadministered LTG with an enzyme-inducing AED (e.g., carbamazepine, phenytoin, phenobarbital, and primidone) with or without a neutral AED.
(3) Inhibited group: patients coadministered LTG and VPA with or without a neutral AED.

The dosing regimens of LTG were based on the FDA drug label [14] and guidance for epilepsy treatment (ILAE) [25]. Nine dosing regimens each for the neutral and induced groups, and 13 for the inhibited group were designed to investigate the effect of nonadherence on the PK profile. The dosing intervals were fixed to every 12 (q12h) or 24 (q24h) h. The detailed dosing regimens are listed in Table 1.

2.2. Simulated population PK (PPK) characteristics

The population PK (PPK) model of LTG from a PPK study that had the largest study cohort to date was used to generate virtual concentration–time data [23]. In this study, 388 patients with epilepsy aged between 0.6 and 17.6 years were enrolled. These patients received LTG as a monotherapy or adjunctive treatment remaining on a consistent regimen for at least 7 days. The steady-state serum concentrations (n = 539) were collected and described using a one-compartment model with first-order absorption and elimination, which included three PK parameters: the absorption rate constant (k_a), apparent clearance (CL/F), and the apparent volume of distribution (V/F). The interindividual variability of the V/F and k_a were set to 0 according to the published study, which only collected trough data. The intraindividual variabilities were ranged from 0.86 to 1.79 mg/L for patients with different age. The inter-individual variability of CL/F and the intra-individual variability followed a normal distribution. The final model adequately described the data without systematic bias and had satisfactory predictive performance. The final model consisted of three age groups for LTG and is listed in Table 2.

Table 1
Simulated dosage regimens for delayed or missed doses of lamotrigine (LTG) for every 12 h (q12h) and 24 h (q24h) regimens.

Age (years)	Weight (kg)	Regimen (mg)			Dosing interval (h)
		Neutral group[a]	Induced group[b]	Inhibited group[c]	
2	12	37.5	75	12.5	12
4	16	50	100	12.5	12
6	20	50	125	25	12
8	25	75	150	25	12
10	30	100	150	37.5	12
12	40	125	200	50	12
14	50	125	200	50	12
16	60	150	250	75	12
18	70	175	250	100	12
8	25	–	–	50	24
12	40	–	–	100	24
16	60	–	–	150	24
18	70	–	–	200	24

[a] Neutral group, patients coadministered LTG with a noninduced or noninhibited antiepileptic drug (AED) or as a monotherapy;
[b] Induced group, patients coadministered LTG with an enzyme-inducing AED (e.g., carbamazepine, phenytoin, phenobarbital, and primidone) with or without a neutral AED;
[c] Inhibited group, patients coadministered LTG and valproate with or without a neutral AED.

2.3. Simulation

NONlinear Mixed Effects Modelling (NONMEM) (version 7.4; Icon Inc., PA, USA) was used to generate all model-based simulations, and the output was obtained using the R package (version 3.5.0, https://www.r-project.org/). The LTG concentration–time profiles were simulated based on 5000 virtual patients using Eq. (1) shown below, and the PPK parameters used in the simulations are summarized in Table 2. The virtual patients were administered multiple doses of LTG to reach steady-state and were hypothesized to have become seizure-free without undesired drug-related adverse effects.

$$C_n = \frac{k_a \cdot F \cdot X_0}{V \cdot \left(k_a - \frac{CL}{V}\right)} \cdot \left[\left(\frac{1-e^{-\frac{CL}{V}\cdot n\cdot\tau}}{1-e^{-\frac{CL}{V}\cdot\tau}} \cdot e^{-\frac{CL}{V}\cdot t}\right) - \left(\frac{1-e^{-n\cdot k_a\cdot\tau}}{1-e^{-k_a\cdot\tau}} \cdot e^{k_a\cdot t}\right)\right] \quad (1)$$

where the k_a represents the absorption rate constant; F represents the bioavailability; X_0 represents the dose amount; CL represents the clearance; V represents the volume of distribution; n represents the number of times the doses were administered; τ represents the dosing interval, and t represents the time after the last doses.

2.3.1. Scenarios

For the q12h regimens (8:00 and 20:00), the patients were administered LTG 2, 4, 6, 8, and 10 h later than the scheduled time or missed one or two doses. For the q24h regimens (8:00), the patients were dosed 4, 8, 12, 16, and 20 h later than the expected time or missed one dose. Plasma LTG concentration–time profiles were simulated for nonadherence and the following remedial regimens. When a delayed dose occurred, one of three remedial strategies could be used.

Strategy A: a partial dose was administered immediately, and the regular dose was administered at the next scheduled time.
Strategy B: the delayed dose was administered immediately, followed by a partial dose at the next scheduled time.
Strategy C: the delayed and partial doses were coadministered immediately; the next scheduled time was skipped, and the regular dose was then administered at the subsequent scheduled time. Moreover, administration of double doses after a dose was missed, were also investigated.

Table 2
Population pharmacokinetic characteristics of lamotrigine (LTG) in pediatric patients with epilepsy [23].

Population (years)	Group	Formula of pharmacokinetic (PK) parameters	Interindividual variability (%)	Intraindividual variability (mg/L)
0.6–6	Neutral group[a]	$CL/F = 0.715 \times (WT/16.25)^{0.655}$	30.2	1.79
	Induced group[b]	$= 1.42 \times (WT/16.25)^{0.655}$	30.2	
	Inhibited group[c]	$= 0.327 \times (WT/16.25)^{0.655}$	30.2	
	All group	$V/F = 10.4$	/	
	All group	$k_a = 1.3$	/	
6–12	Neutral group	$CL/F = 1.01 \times (WT/30)^{0.399}$	24.3	1.65
	Induced group	$= 2.00 \times (WT/30)^{0.399}$	24.3	
	Inhibited group	$= 0.47 \times (WT/30)^{0.399}$	24.3	
	All group	$V/F = 17.7$	/	
	All group	$k_a = 1.3$	/	
12–18	Neutral group	$CL/F = 1.49 \times (WT/51.5)^{0.509}$	31.1	0.86
	Induced group	$= 2.53 \times (WT/51.5)^{0.509}$	31.1	
	Inhibited group	$= 0.724 \times (WT/51.5)^{0.509}$	31.1	
	All group	$V/F = 23.1$	/	
	All group	$k_a = 1.3$	/	

CL/F, the apparent clearance (L/h); *V/F*, the apparent volume of distribution (L); k_a, the absorption rate constant (/h); *WT*, body weight (kg).
[a] Neutral group, patients coadministered LTG with a noninduced or noninhibited antiepileptic drug (AED) or as a monotherapy;
[b] Induced group, patients coadministered LTG with an enzyme-inducing AED (e.g., carbamazepine, phenytoin, phenobarbital, and primidone) with or without a neutral AED;
[c] Inhibited group, patients coadministered LTG and valproate with or without a neutral AED.

2.3.2. Criteria to select optimal remedial regimen

The individual therapeutic range, defined as the concentration that produced the best response in an individual patient, was considered as the 5th–95th percentiles of the simulated data for each regimen based on the guidelines for therapeutic drug monitoring of antiepileptic drugs [18,21].

The effect of nonadherence was estimated as the percentage of subjects that were out of the individual therapeutic range at a specified time. For each scenario and remedial regimen, deviation time, which is defined as the duration time out of the individual therapeutic range, was also estimated. The most appropriate remedial regimen was considered that with the smallest deviation time. If the difference in deviation time among the different regimens was <0.5 h, these regimens were considered equivalent.

2.4. Sensitivity analysis

Previous studies have shown that weight has a significant effect on the clearance of LTG in pediatric patients [23,26–30]. Therefore, the influence of weight range on the corresponding maximum and minimum weight for the WHO maturation-body weight charts was investigated [24]. In addition, the fixed dosing interval may not represent real clinical settings. Dosing intervals of 10–14 (8:00 and 18:00) and 14–10 h (8:00 and 22:00) for q12h regimens and 22–26 (8:00 and 6:00) and 26–22 h (8:00 and 10:00) for q24h regimens on the remedial recommendations were also assessed.

The interindividual variability of the k_a and V/F was set at 0 in the established model [23], and the effect of k_a on the concentration–time profile of LTG was investigated by changing the value ±50% to 0.65 and 1.95/h accordingly. In addition, the influence of V/F on the remedial recommendations were also studied by changing the V/F values of ±20%, for instance, 10.4 L to 8.32 and 12.48 L for patients aged 2–6 years, 17.7 L to 14.16 and 21.24 L, for 6–12 years, and 23.1 L to 18.48 and 27.72 L, for 12–18 years.

3. Results

3.1. Effect of nonadherence

The simulation results showed that the percentage of subjects out of the individual therapeutic ranges of LTG depended on the duration of the delay. The risk of patients falling outside the therapeutic range

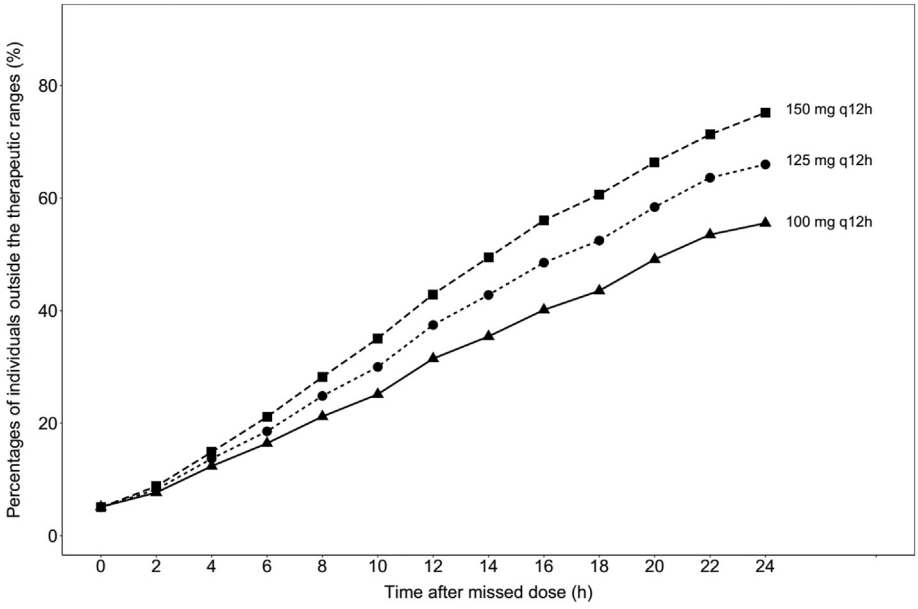

Fig. 1. Percentage of subjects falling outside individual therapeutic ranges at different times after last dose (8:00) for 12-year-old and 40-kg patients administered lamotrigine (LTG) as neutral group.

Table 3
Dosing recommendations for delayed or missed doses in neutral group.

Regimen	Scenarios	Dosing recommendations		
		Dose (mg)	Percentage (%)[a]	Remedial strategy
37.5 mg q12h	Delayed 0–2 h	75	200	A/B
	Delayed 2–10 h	62.5	167	A/B
	Delayed 10–12 h	62.5	167	A/B/C
	Missing one dose	62.5	167	C
	Missing two doses	75	200	C
50 mg q12h	Delayed 0–6 h	87.5	175	A/B
	Delayed 6–10 h	75	150	A/B
	Delayed 10–12 h	75	150	A/B/C
	Missing one dose	75	150	C
	Missing two doses	87.5	175	C
75 mg q12h	Dose delayed 0–4 h	137.5	183	A/B
	Dose delayed 4–10 h	125	167	A/B
	Dose delayed 10–12 h	112.5	150	A/B/C
	Missing one dose	112.5	150	C
	Missing two doses	150	200	C
100 mg q12h	Delayed 0–6 h	175	175	A/B
	Delayed 6–10 h	162.5	163	A/B
	Delayed 10–12 h	162.5	163	A/B/C
	Missing one dose	150	150	C
	Missing two doses	200	200	C
125 mg q12h	Delayed 0–4 h	225	180	A/B
	Delayed 4–10 h	200	160	A/B
	Delayed 10–12 h	175	140	A/B/C
	Missing one dose	175	140	C
	Missing two doses	200	160	C
150 mg q12h	Delayed 0–2 h	275	183	A/B
	Delayed 2–8 h	250	167	A/B
	Delayed 8–10 h	225	150	A/B
	Delayed 10–12 h	200	133	A/B/C
	Missing one dose	200	133	C
	Missing two doses	200	133	C
175 mg q12h	Delayed 0–2 h	325	186	A/B
	Delayed 2–4 h	300	171	A/B
	Delayed 4–10 h	275	157	A/B
	Delayed 10–12 h	250	143	A/B/C
	Missing one dose	250	143	C
	Missing two doses	250	143	C

A, a partial dose was administered immediately, followed by the delayed dose 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 the partial dose were coadministered immediately until the second next scheduled time.
[a] The LTG dose to be given remedially compared to the original LTG dose.

Table 4
Dosing recommendations for delayed or missed doses in induced group.

Regimen	Scenarios	Dosing recommendations		
		Dose (mg)	Percentage (%)[a]	Remedial strategy
75 mg q12h	Delayed 0–2 h	137.5	183	A/B
	Delayed 2–4 h	125	167	A/B
	Delayed 4–8 h	112.5	150	A/B
	Delayed 8–10 h	100	133	A/B
	Delayed 10–12 h	100	133	A/B/C
	Missing one dose	100	133	C
	Missing two doses	100	133	C
100 mg q12h	Delayed 0–2 h	175	175	A/B
	Delayed 2–8 h	150	150	A/B
	Delayed 8–10 h	125	125	A/B
	Delayed 10–12 h	125	125	A/B/C
	Missing one dose	125	125	C
	Missing two doses	125	125	C
125 mg q12h	Delayed 0–2 h	225	180	A/B
	Delayed 2–4 h	200	160	A/B
	Delayed 4–8 h	175	140	A/B
	Delayed 8–10 h	150	120	A/B
	Delayed 10–12 h	150	120	A/B/C
	Missing one dose	150	120	C
	Missing two doses	150	120	C
150 mg q12h	Delayed 0–2 h	275	183	A/B
	Delayed 2–4 h	250	167	A/B
	Delayed 4–8 h	225	150	A/B
	Delayed 8–10 h	200	133	A/B
	Delayed 10–12 h	200	133	A/B/C
	Missing one dose	200	133	C
	Missing two doses	200	133	C
200 mg q12h	Delayed 0–2 h	350	175	A/B
	Delayed 2–6 h	300	150	A/B
	Delayed 6–10 h	275	138	A/B
	Delayed 10–12 h	250	125	A/B/C
	Missing one dose	250	125	C
	Missing two doses	250	125	C
250 mg q12h	Delayed 0–2 h	450	180	A/B
	Delayed 2–4 h	400	160	A/B
	Delayed 4–10 h	350	140	A/B
	Delayed 10–12 h	300	120	A/B/C
	Missing one dose	300	120	C
	Missing two doses	300	120	C

A, a partial dose was administered immediately, followed by the delayed dose 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 the partial dose were coadministered immediately until the second next scheduled time.
[a] The LTG dose to be given remedially compared to the original LTG dose.

increased with increasing delay. For example, for 12-year-old and 40-kg patients administered LTG 125 mg q12h regimen in the neutral group, the percentage of subjects outside the therapeutic range were from 5% (full adherence) to 13.70% and 24.84% when the dose was delayed for up to 4 and 8 h, respectively (Fig. 1).

The percentage of subjects outside the therapeutic range was related with the daily dose. Regimens with a higher daily dose increased the risk of patients falling outside the therapeutic range. The percentage of 12-year-old and 40-kg patients administered LTG 100, 125, and 150 mg as the neutral group every 12 h who were outside the therapeutic range was 21.18%, 24.84%, and 28.20%, respectively when the dose was delayed by up to 8 h (Fig. 1).

3.2. Remedial dosing recommendations

The remedial dosing recommendations following delayed and missed LTG doses are summarized in Tables 3–5. concentration–time profile of full adherence in neutral group is shown in Fig. 2a, and those of induced and inhibited group are shown in Fig. S1. If one dose was delayed, one of three remedial strategies with the same total remedial dose could be used. The results suggested that strategies A and B for remedial dosing were almost equivalent, whereas strategy C caused a larger deviation time than the others did (Fig. 2). For example, if a dose was delayed 4 h, a 12-year-old and 40-kg patient administered LTG at 125 mg on the q12h regimen as the neutral group could be administered 100 mg immediately and 125 mg at the next scheduled dose (strategy A) or 125 mg immediately and 100 mg at the next scheduled dose (strategy B). The deviation time was 4.1 and 4.2 h for strategies A and B, respectively. If a patient was administered 225 mg immediately until the second next scheduled time (strategy C), the deviation time could be 15.8 h. It is noteworthy that strategy C was recommended only when the delayed dose was close to the next scheduled dose such as the delayed time >10 h for the q12h regimen. For example, for the same patient, if a dose was delayed 10 h, the deviation time was 10.7 h, 10.2 h, and 12 h for strategies A, B, and C, respectively (Fig. 2).

The recommended remedial dose depended on how long the dose was delayed. For instance, if the delay was up to 4 h, for a 12-year-old and 40-kg patient administered the LTG 125 mg q12h regimen as the neutral group, 225 mg was the recommended dose using strategy A or B. However, if the delay was >4 h until the next dose, 200 mg was recommended.

Table 5
Dosing recommendations for delayed or missed doses in inhibited group.

Regimen	Scenarios	Dosing recommendations		
		Dose (mg)	Percentage (%)[a]	Remedial strategy
12.5 mg q12h	Delayed 0–10 h	25	200	A/B
	Delayed 10–12 h	25	200	A/B/C
	Missing one dose	25	200	C
	Missing two doses	25	200	C
25 mg q12h	Delayed 0–8 h	50	200	A/B
	Delayed 8–10 h	37.5	150	A/B
	Delayed 10–12 h	37.5	150	A/B/C
	Missing one dose	37.5	150	C
	Missing two doses	50 or 62.5	200 or 250	C
37.5 mg q12h	Delayed 0–4 h	75	200	A/B
	Delayed 4–10 h	62.5	167	A/B
	Delayed 10–12 h	62.5	167	A/B/C
	Missing one dose	62.5	167	C
	Missing two doses	87.5	233	C
50 mg q12h	Delayed 0–2 h	100	200	A/B
	Delayed 2–10 h	87.5	175	A/B
	Delayed 10–12 h	87.5	175	A/B/C
	Missing one dose	87.5	175	C
	Missing two doses	100	200	C
75 mg q12h	Delayed 0–2 h	150	200	A/B
	Delayed 2–6 h	137.5	183	A/B
	Delayed 6–10 h	125	167	A/B
	Delayed 10–12 h	125	167	A/B/C
	Missing one dose	125	167	C
	Missing two doses	150	200	C
100 mg q12h	Delayed 0–4 h	187.5	188	A/B
	Delayed 4–10 h	175	175	A/B
	Delayed 10–12 h	150	150	A/B/C
	Missing one dose	150	150	C
	Missing two doses	200	200	C
50 mg q24h	Delayed 0–20 h	87.5	175	A/B
	Delayed 20–24 h	75	150	A/B/C
	Missing one dose	75	150	C
100 mg q24h	Delayed 0–16 h	175	175	A/B
	Delayed 16–20 h	150	150	A/B
	Delayed 20–24 h	150	150	A/B/C
	Missing one dose	150	150	C
150 mg q24h	Delayed 0–8 h	275	183	A/B
	Delayed 8–16 h	250	167	A/B
	Delayed 16–20 h	225	150	A/B
	Delayed 20–24 h	200	133	A/B/C
	Missing one dose	200	133	C
200 mg q24h	Delayed 0–4 h	375	188	A/B
	Delayed 4–12 h	350	175	A/B
	Delayed 12–20 h	300	150	A/B
	Delayed 20–24 h	300	150	A/B/C
	Missing one dose	300	150	C

A, a partial dose was administered immediately, followed by the delayed dose 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 the partial dose were coadministered immediately until the second next scheduled time.
[a] The LTG dose to be given remedially compared to the original LTG dose.

The recommended remedial dose was also related to the concomitant AEDs. If a 12-year-old and 40-kg patient missed one dose, 175 mg (140% of the missed dose) was recommended to be administered immediately on the regimen of 125 mg q12h as the neutral group; 250 mg (125% of the missed dose) was recommended on the 200 mg q12h regimen as the induced group, and 87.5 mg (175% of the missed dose) was appropriate for patients administered the LTG 50 mg q12h regimen as the inhibited group.

3.3. Sensitivity analysis

Patients who missed one dose were chosen for the sensitivity analysis. Typical patients investigated were 4 years old, weighing 16 kg; 8 years old, weighing 25 kg; 12 years old, weighing 40 kg; and 16 years old, weighing 60 kg. The results are shown in Fig. 3 and Fig. S 2–4. The results suggested that the weight, dosing intervals, and k_a and V/F had no significant effect on the dosing recommendations.

4. Discussion

This is the first study to investigate the effect of nonadherence on PK of LTG and make corresponding remedial dose recommendations in pediatric patients with epilepsy. Chen et al. [15] previously investigated the effect of nonadherence on patients aged 13 years or older. However, little is known about the effect of nonadherence on pediatrics and it is inappropriate to extrapolate from adults to children because of their different PK characteristics.

Moreover, compared to previous studies [15,31–36], we used the therapeutic range and not the fixed reference range to investigate the effect of delayed or missed doses. The reference range is unsuitable because of the individual variation. Some patients can achieve therapeutic benefits with LTG concentrations outside the reference range. However, the therapeutic range is defined as the range of concentrations associated with the optimal response in a particular patient [18,21]. Consequently, the therapeutic range has been more widely used in epilepsy management recently and was used in this analysis.

In addition, the deviation time was used to assess the optimal remedial dose in the present study, which more comprehensively describes the risks of patients outside the therapeutic range than the trough and peak concentrations do. Furthermore, our study incorporated the intra- and interindividual variabilities in the simulation, which could describe the variations of nonadherent patients more accurately.

The effect of delayed or missed doses on the concentration–time profile of LTG is determined by considering the duration of delay and the daily dose. Our results were consistent with the results of the study by Ding et al. [17]. Based on the definition of therapeutic range, a higher dose raised the lower and upper limit of the therapeutic range, and the concentration decrease per unit time was also larger when one dose was delayed (Fig. S5). For instance, for 12-year-old and 40-kg patients, the individual therapeutic range was 1.5–13.8 mg/L when the LTG 100 mg q12h regimen was administered. Furthermore, it was 2.4–16.8 mg/L and 3.3–19.9 mg/L for the 125 mg and 150 mg doses, respectively. If the dose was delayed by 8 h, the 5th percentiles of the simulated concentrations were decreased by 1.5 mg/L for 100 mg, 2.11 mg/L for 125 mg, and 2.48 mg/L for 150 mg q12h regimens. The results indicated that compared to the fixed reference range, for regimens with a higher daily dose, the risk of patients falling outside the therapeutic range was increased.

Our investigation proposed and assessed three remedial strategies for different delayed scenarios. Strategy A was more appropriate for patients whose seizures were well-controlled because the concentration gradually returned to the therapeutic range, and these patients might have a higher risk of breakthrough seizures. However, it may have caused less concentration-related adverse effects such as headache, dizziness, nausea, and emesis. Moreover, strategy B rapidly returned the LTG concentration to the therapeutic range, which was more suitable for patients with epilepsy who have high seizure frequency. However, it was likely to result in more concentration-related adverse effects. Strategy C caused the LTG concentration to fluctuate more than the other two strategies did and was only appropriate for patients who could not take the next scheduled dose as prescribed and whose time delay considerably shortened the time to the next scheduled dose. Patients who missed doses needed to take at least one regular dose to achieve the therapeutic range, therefore, strategy C was the only choice. Clinicians can choose the optimal remedial strategy according to the status of patients.

Our study suggests that if a dose is missed, double doses are not recommended at the next schedule time, which is consistent with the FDA label. However, it differs from the results of previous study by Chen et al. [15] who reported that doubling the dose would be more appropriate,

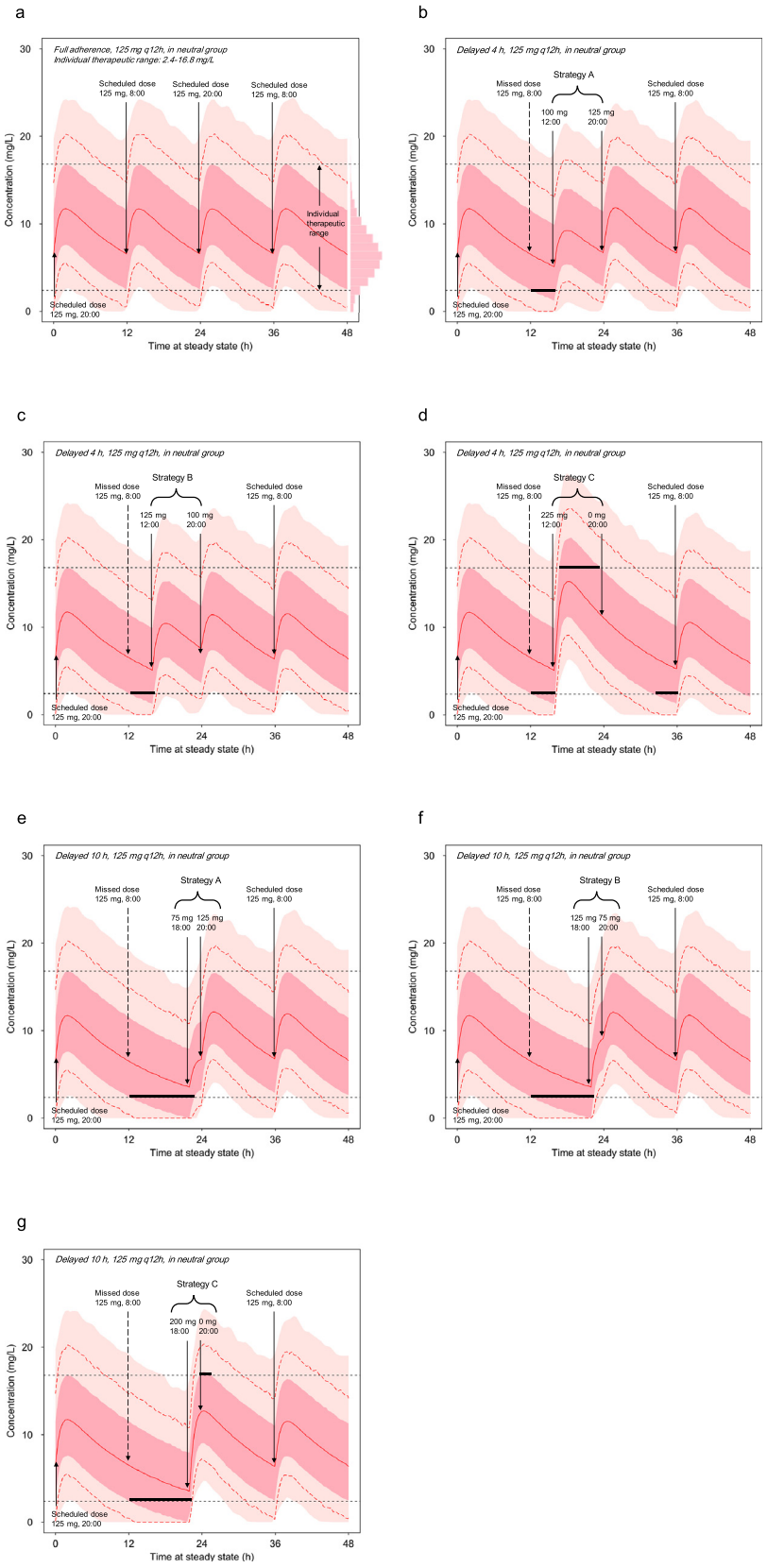

Fig. 2. Three remedial strategies identified for different scenarios for 12-year-old and 40-kg patients administered lamotrigine (LTG) on 125 mg every 12 h (q12h) regimen as neutral group. (a) Full adherence and (b) remedial dosing using strategies A, (c) B, and (d) C when dose was delayed by up to 4 h. (e) Remedial dosing using strategies A, (f) B, and (g) C when dose was delayed by up to 10 h. The dark pink shadow represents the distribution of the 5th–95th percentiles of the simulated concentrations in 90% of the virtual subjects and the light pink shadows represent the distribution of the simulated concentrations outside the 5th–95th percentiles in the remaining 10% virtual subjects. Red solid line represents median of the simulated concentrations and dotted lines represent 0.5th and 99.5th percentiles of the simulated concentrations, respectively. Black dotted lines represent the individual therapeutic range. Black solid line represents the deviation time. The histogram on the right represents the probability density of the simulated concentrations.

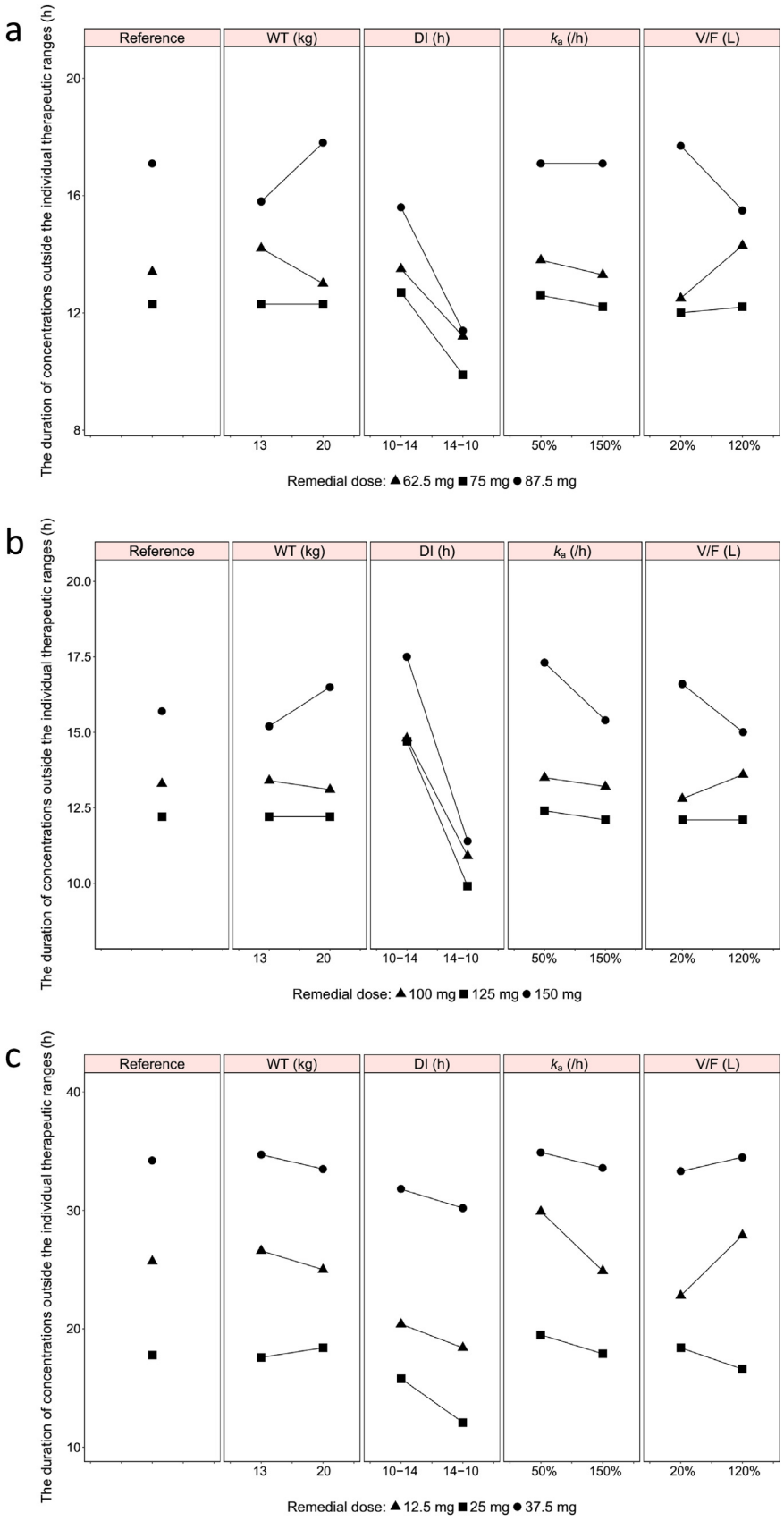

Fig. 3. Impact of weight (WT), dosing interval (DI), absorption rate constant (k_a), and apparent volume of distribution (V/F) on the remedial dosing recommendation for one missed dose. Four-year-old and 16-kg patients in (a) neutral, (b) induced, and (c) inhibited groups. Reference represents scenarios based on 16-kg patients administered lamotrigine (LTG) every 12 h whose k_a were 1.3/h and V/F were 10.4 L. $WT_{13\ kg}$ and $WT_{20\ kg}$ represent the WT of patients who were 13 and 20 kg, respectively. $DI_{10–14\ h}$ represents patients administered LTG at 8:00 and 18:00, and $DI_{14–10\ h}$ represents patients administered LTG at 8:00 and 22:00. $k_{a\ 50\%}$ and $k_{a\ 150\%}$ represent the k_a of patients decreased and increased by 50%, respectively. $V/F_{20\%}$ and $V/F_{120\%}$ represent the V/F of patients decreased and increased by 20%, respectively.

because it returned the concentration of LTG to the therapeutic range quickly without any major concentration-related adverse effects. The discrepancy may be attributable to a much higher V/F in the study by Chen et al. [15] than in the current study (91.1 L vs 10.4–23.1 L).

We performed a sensitivity analysis to investigate the applicability of the dosing recommendations. The wide range of body weight, various dosing intervals, and different k_a and V/F levels were assessed, and the results showed that they did not affect the dosing recommendations significantly. In addition, the CL/F values of the sensitivity analysis covered those previously reported [0.014–0.088 L/(h·kg)] in different epilepsy centers, which indicated that those results may apply to more general populations [26–30,37].

Most previous studies used one-compartment models to describe the PPK of LTG in both adult and pediatric patients [23,26–30,38–46]. However, one recent study by Polepally et al. [47] indicated that LTG followed a two-compartment model. This may lead to a bias in estimation of CL/F and apparent steady-state volume of distribution (Vss/F) using different compartmental models. However, Kowalski and Hutmacher [48] found that the bias of estimation of CL/F and Vss/F was <5% when they fitted a one-compartment model based on the data simulated using a two-compartment model. Consequently, the two-compartment model simplified to a one-compartment model may have little influence on the estimation of pharmacokinetic parameters.

There are some limitations in this study. First, our results only applied to the LTG immediate-release formulation, the extended-release formulation was not assessed because of lack of information. Second, the dosing recommendations in this study were based on 90% prediction interval of virtual patients, and clinicians should also pay attention to the remaining 10% to avoid toxicity after a remedial dose.

5. Conclusions

Based on our PK simulation data, double dosing was not recommended when one dose is missed because of a large deviation time, potentially resulting in toxicity. Moreover, we proposed three remedial strategies for delayed or missed dose: Strategy A: a partial LTG dose administered immediately with a regular dose at the next schedule time; Strategy B: the delayed LTG dose was administered immediately with a partial dose at the next schedule time; Strategy C: the delayed and partial doses were coadministered immediately; the next scheduled time was skipped, and regular dose was administered at the subsequent scheduled time. Strategy A and B were pharmacokinetically equivalent when the dose was delayed, whereas strategy C was only appropriate when the dose was skipped. Therefore, the varying status of patients requires clinicians to select the optimal remedial strategy for nonadherent patients.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.04.007.

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