Remedial dosing recommendations for valproic acid in nonadherence patients with epilepsy

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Key words: Epilepsy, Antiepileptic drugs, Adherence, Population pharmacokinetcs, Monte Carlo simulation

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Summary

Objective: 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 nonadherence patients.

Methods: The Monte Carlo simulations based on all previous population pharmacokinetic models for pediatric, adult and elder patients with epilepsy receiving valproic acid, which is the most commonly used first-line AED. 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.

Results: The most appropriate remedial regimen was that with the shortest deviation time from the therapeutic window. 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.

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

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1. INTRODUCTION

Epilepsy is one of the most common and disabling neurological disorders and requires long-term and even life-long antiepileptic drug (AED) treatment[1]. Adherence to the regimen is an important issue in the control of seizures[2; 3]. Delayed or missed doses often occur in the treatment of patients with epilepsy[4]. It has been reported that approximately 30%–50% of patients with epilepsy are non-adherent to their prescribed AED therapies and more than 70% of respondents reported AED dose omissions[5-7]. This nonadherence can lead to sub-therapeutic drug concentrations and increase the risk of seizures[5]. Inappropriate over-remedial doses may lead to clinical toxicity, with effects including change or loss of consciousness and fainting[8](8).

Valproic acid (VPA) is a broad spectrum AED used in the treatment of both generalized and focal seizures [9-11]. It is also used in combination with other AEDs in patients with multiple seizure types. As required by the US Food and Drug Administration (FDA), the package insert of VPA recommends that “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”[8](8). However, no clear remedial dose regimen is provided for the missed dose. Moreover, no comprehensive evaluation of the effect of nonadherence and the corresponding remedial dosing regimens has been performed.

Monte Carlo simulation based on population pharmacokinetic (PPK) models provides the most appropriate means to investigate the effect of delayed or missed doses[12-14]. This method is widely accepted for the development of treatment protocols, avoiding unnecessary clinical studies. Prospective studies in patients whose

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47 medications are intentionally delayed or interrupted for experimental purposes may
48 not be acceptable for ethical reasons[15]. In addition, retrospective data is difficult to
49 collect, accurately.

50 To date, the perturbative effect of delayed or missed doses, along with
51 subsequent remedial of the missed dose(s), on the VPA has not been examined. This
52 study aims to investigate the effects of delayed or missed doses on pharmacokinetics
53 of VPA and to provide practical recommendations for patients by Monte Carlo
54 simulation.

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2. MATERIALS AND METHODS

2.1 Typical patients and dose regimens

Typical patients and the investigated corresponding dose regimen were based on the following criteria: (1) the weight of paediatric patients was based on the World Health Organization (WHO) Child Growth Standards, and the weight of adult and elderly patients was fixed at 70 kg; (2) all patients were assumed to receive VPA monotherapy; (3) the dose regimen was selected according to the FDA's label and treatment guidelines published by international league against epilepsy (ILAE), which includes formulation, dose strength and dosing interval.

2.2 PPK characteristics for simulations

The PPK characteristics for the simulations and further investigations were extracted from previous studies. A systematic review of PPK studies published before 31 Dec. 2018 was conducted with PubMed and Web of Science. The relevant identification, screening and assessment steps followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Published studies were included if they (1) evaluated patients with epilepsy receiving valproate and (2) had complete PPK parameters. The studies were excluded if they (1) didn't include syrup or tablet forms and (2) were studies with overlapping data or cohorts. Only the most recent or the one with the largest sample size was included. The reference lists of all selected articles were also evaluated (Table S1).

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

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demographic characteristics of the study cohorts were also extracted.

2.3 Simulation

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

Each simulation included 1000 virtual subjects. These patients with full adherence were assumed to have expected seizure control with undesired adverse drug reactions for each investigated scenario. Concentration-time profiles of VPA were generated using the PPK parameters extracted from the identified studies for each scenario.

The therapeutic range of VPA for each scenario was defined as the 5th–95th percentile of the simulated data and was employed in the further analysis, according to guidelines for therapeutic drug monitoring of AEDs[16; 17]. The effect of nonadherence was estimated as the percentage of subjects outside their individual therapeutic ranges at a specified time.

For each scenario and remedial regimen, deviation time, which is defined as the time outside the individual therapeutic range, was estimated. The regimen that has the lowest deviation time is the most appropriate remedial regimen. If the difference in deviation time was less than 0.5 h among competitive regimens, those regimens could be considered equivalent.

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2.4 Sensitivity analysis

When monotherapy is unsuccessful, combination therapy is usually tried in an attempt to improve efficacy, tolerability or both. Combination therapy was used in 79% of adults and 75% of children. [18] In multiple treatments, the combined drugs may be inducers of valproic acid (such as carbamazepine) or inhibitors (such as topiramate)[19; 20]. These will affect the Ke value of valproic acid.

Moreover, the Ka values in the previous PPK models of VPA were fixed, and the between subject variability was set to zero, which may not represent the real clinical setting. Therefore, it is very helpful to investigate the effect of Ka and the combination with other AEDs on the dosage recommendation in the event of nonadherence. The scenarios in which patients with different Ka values and in which VPA was combined with other AEDs were chosen for the sensitivity analysis. Therefore, this “noise” was added to the simulation scenario as a sensitivity analysis to investigate its effect on the concentration-time profile of VPA (Table 1).

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3. RESULTS

3.1 Typical patients and dose regimens

Seven typical dose regimens were employed to examine the effects of nonadherence on the pharmacokinetic profile and to calculate the remedial dose regimen: 1 regimen for infants aged <1 year (120 mg q12h), 3 regimens for children or adolescents aged 1-18 years (240 mg q12h, 500 mg q12h and 500 mg q24h), 2 regimens for adults aged 18-65 years (500 mg q12h and 1000 mg q12h) and 1 regimen for elderly individuals aged > 65 years (750 mg q12h). Only syrup was investigated for paediatric patients taking less than 500 mg per dose. These patients were assumed to have expected seizure control with undesired adverse drug reactions. The detailed dosing regimens are listed in Table 2.

The delayed dose scenarios for each medication regimen were 1~12 h of delay for the every 12 h (q12h) dosing regimen or 1~24 h of delay for the every 24 h (q24h) dosing regimen. Missed dose scenarios for each medication included one and two missed doses.

3.2 Simulated population pharmacokinetics (PPK) characteristics

Eleven PPK studies were selected to extract PPK characteristics of VPA[15; 19-28]. The screening process is presented in Figure S1. Five studies were conducted in paediatric patients[15; 20; 23; 24; 26], 2 studies in adults[19; 28], 1 study in elderly patients[22], 2 studies in both adult and elderly patients[21; 27] and 1 study in children, adults and elderly patients[25]. Moreover, five studies were conducted in East Asia (China and Japan), 3 in Europe, 2 in the US and 1 in Mexico. The detailed information for each study is summarized in Table S1.

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For each scenario, two sets of PPK parameters with the highest and lowest elimination rate (Ke) values in the identified studies were employed for further investigation and are listed in Table 2. The Ke ranged from 0.027 to 0.081 h^{-1} for infant and paediatric patients and 0.029 to 0.074 h^{-1} for adult and elderly patients.

3.3 Effect of nonadherence

The Monte Carlo simulation results show that the percentage of subjects outside their individual therapeutic ranges for VPA is related to the delayed time, dosing interval and Ke (Figure 1). The risk of patients in the sub-therapeutic range increased with delay time. For example, for 70-kg adult patients administered the VPA 500 mg every 12 hours (q12h) regimen in the highest Ke group (0.074 h^{-1})[19], 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 1b).

The patients who received higher doses of VPA had a higher risk of being outside the therapeutic range than the patients who received lower doses. For example, in 70-kg adult patients with highest Ke (0.074 h^{-1})[19] who were administered VPA, the percentages of subjects in the sub-therapeutic range were 42.6%, 54% and 65% for a scheduled dosing delay up to 24 h from the scheduled time for the 500 mg, 750 mg and 1000 mg q12h regimens, respectively (Figure 1b).

Moreover, patients with higher Ke have a lower risk of reaching the sub-therapeutic range than patients with lower Ke. For instance, the percentage of 70-kg adult patients taking 500 mg q12h who were in the sub-therapeutic range (42.6% vs 91%) was lower for the patients with the highest Ke of 0.074 h^{-1} than for those with the lowest Ke of 0.029 h^{-1}.

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3.4 Remedial dosing regimen

The dosing recommendations for resuming treatment after delayed and missed doses are shown in Table 3. We have also developed a tool which can be used to check remedy dose regimens under different scenarios. (Appendix e-1). If one dose was delayed, one of three 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 the other two strategies regardless of the patients' age and dosing interval (Figure 2). For example, if a dose was delayed 8 h, a 70-kg adult patient administered VPA at 500 mg on the q12h regimen could receive 250 mg immediately and 500 mg at the next scheduled dose (strategy A) or 500 mg immediately and 250 mg at the next scheduled dose (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 until the next scheduled time (strategy C), the deviation time could be 12.4 h. Strategy C was recommended only when the delayed dose was close to the next scheduled dose (e.g. > 10 h for the q12h regimen or > 20 h for the q24h regimen).

With increases in delay time from the scheduled dosing time, the total resumed dose decreased to keep the least deviation time from the individual therapeutic range. For example, a 70-kg adult patient was administered with VPA at 500 mg on the q12h regimen and achieved a satisfactory therapeutic outcome. If a dose was delayed 2 h, patients could be administered 500 mg immediately and 500 mg at the next scheduled dose, i.e., a total of 1000 mg would be administered. If a dose was delayed for 10 h,

chinaXiv:201907.00014v2

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patients could 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), i.e., a total of 750 mg would be administered (Figure 3).

The recommended remedial dose was also dependent on the Ke of the patient. With the same dose delay time, Patients with higher Ke need a higher remedial dose than those with lower Ke. For example, for a 70-kg adult patient administered VPA at 750 mg on the q12h regimen, when the delay was 4 h from the scheduled time, 750 mg and 500 mg were recommended for immediate administration to the highest Ke group (0.074 h^{-1})[19] and the lowest Ke group (0.043 h^{-1})[28], respectively.

3.5 Sensitivity analysis

The scenario of remedial doses administered at the next scheduled time after missing one dose in VPA regimen of 500 mg q12h was chosen for the sensitivity analysis. The results are presented in Figure S2. Body weight, absorption rate (Ka) and co-therapy with other AEDs had no significant effect on the dose recommendation when a dose was delayed or missed. The best recommended dose remained unchanged. Dosing intervals of 10–14 and 14–10 h for q12h regimens and 22–26 and 26–22 h for q24h regimens had no significant effect on the remedial recommendations.

4. DISCUSSION

For the first time, we systematically established remedial regimens for no adherent patients with AEDs by Monte Carlo simulation based on all previous PPK studies. The effects of delayed and missed doses on AED concentrations were previously studied using basic pharmacokinetic methods[29-34]. However, these studies

chinaXiv:201907.00014v2

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did not fully consider the effects of between subject variabilities and residual variabilities of pharmacokinetics in the patients. Moreover, the effects of covariates, such as body weight, dose, and performance were not investigated either. Monte Carlo simulation based on the PPK is much closer to the real clinical settings, which are helpful features for individualized medication research on patients with nonadherence[15].

In our study, we employed the therapeutic range instead of a fixed reference range to investigate the effect of delayed or missed doses[34; 35]. Previous retrospective or observational studies suggest that the reference ranges for VPA are 50-100 mg/L. However, the reference range has been a controversial concept, because it was initially defined on the basis of limited data for individual AEDs, which may not adequately describe the concentration-response relationship in patients with epilepsy. Currently, the tendency in epilepsy treatment is changing from reference ranges to therapeutic ranges (or individual therapeutic concentrations)[36]. The latter can be defined as the concentration (or range of concentrations) that has been empirically found to produce the optimal response in the individual patient (i.e., complete seizure control without undesired effects or if that goal is not achievable, the best compromise between seizure suppression and concentration-related adverse effects[37]). Therefore, in our study, the therapeutic range was used instead of the reference range employed in the previous studies to assess the effect of missed or delayed doses and to make remedial dose recommendations.

In addition, the deviation time was used to assess the optimal remedial dose in the present study. The longer the deviation time, the more likely the patient will relapse

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with epilepsy or cause adverse drug reactions. It is a better index to describe the risks of patients being in the sub-therapeutic range than the trough and peak concentrations. So we used deviation time to assess the benefits of different remedial strategies in this study.

In this study, we first proposed three different treatment strategies for different clinical scenarios and conducted detailed investigations. Strategy A was more appropriate for patients who have low seizure frequency because the concentration gradually returned to the therapeutic range and these patients might have a higher risk of breakthrough seizures than other strategies. At the same time, strategy B allowed the VPA concentration to quickly return to the therapeutic range, which was more suitable for patients with epilepsy who have high seizure frequency. However, it may have caused more concentration-related adverse effects such as headache, dizziness, nausea, and emesis. Strategy C resulted in a greater fluctuation in VPA concentration than did the other two strategies and can be used only for patients who are unable to take the next planned dose as specified or with a delay time close to the next scheduled time. The clinician can choose the best remedial strategy based on the patient's condition.

Our study also showed that the effect of delayed or missed dose on the time-concentration profile of VPA is determined by the duration of delay and Ke of the patients. With increases in delay time from the scheduled dosing time, the total resumed dose decreased[15]. Based on the definition of therapeutic range, higher Ke leads to lower individual therapeutic range. Moreover, the decrease of concentration in higher Ke group was gentler than that of the lower Ke group, because its lower

chinaXiv:201907.00014v2

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limit of individual therapeutic range is closer to 0. All these indicated that, patients with higher clearance Ke need a higher remedial dose than those with lower Ke.

The most common co-therapy medications used with VPA are phenobarbital, phenytoin, and carbamazepine, which have a significant effect on the Ke of VPA. The effect of co-therapies on the pharmacokinetic profile of VPA was investigated. Additionally, sensitivity analysis was performed on the patients who had a wide range of individual body weights and different levels of Ka, which may make the results more applicable in clinical practice. These perimeters had no significant effect on the dose recommendation when a dose was delayed or missed.

Moreover, the recommended remedial approaches for delayed/missed doses could be extended to other AEDs,such as carbamazepine and lamotrigine.[15; 38]

This study has several limitations. The dose recommendation in the current study was based on the 90% of the virtually simulated patients. Physicians should carefully consider the risk of toxicity after patients take a remedial dose in cases of nonadherence, especially in paediatric and elderly patients. At the same time, this study only investigated sustained-release tablets and oral dosage forms, because of the lack of relevant PPK research.

5. CONCLUSION

Although the current study cannot represent all clinical settings, the findings could be helpful for the actual management of epilepsy, especially in light of the substantial degree of nonadherence observed in these patients. Our study showed that the dosing recommendations for delayed or missed doses are time related and regimen dependent. Monte Carlo simulation based on PPK is a useful tool to investigate the

chinaXiv:201907.00014v2

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effect of nonadherence and provide rational dose recommendations for clinicians to sufficiently maintain the appropriate therapeutic range.

chinaXiv:201907.00014v2

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chinaXiv:201907.00014v2

Corresponding author: Zheng Jiao (E-mail: zjiao@fudan.edu.cn)

chinaXiv:201907.00014v2

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TABLE AND FIGURE LEGENDS

TABLE 1. Dosing schedule design

TABLE 2. Dosing recommendations for patients with delayed or missed valproic acid doses.

TABLE 3. Sensitivity analysis

FIGURE 1. Percentage of the subjects outside their individual therapeutic ranges after the last dose.

(A) Children administered 120 mg q12h (8kg), 240 mg q12h (16kg) and 500 mg q12h (30kg) by the lowest and highest elimination rate (Ke). (B) Adults of 70-kg administered 500 mg q12h, 750 mg q12h and 1000 mg q12h by the lowest and the highest Ke.

FIGURE 2. Three remedial strategies identified for 70-kg adults administered 500 mg q12h simulated by the lowest elimination rate (Ke) model (Lin et al).

(A) Full adherence. (B) Remedial dosing using strategies A, B (C), and C (D) when the 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

chinaXiv:201907.00014v2

represent 0.5th and 99.5th percentiles of the simulated concentrations, respectively. Black dotted lines represent the individual therapeutic range (48 - 151 mg/L). Black solid line represents the deviation time.

FIGURE 3. Difference in the time that concentrations were outside the therapeutic range of VPA between patients with full adherence and patients with nonadherence.

Adults of 70-kg administered 500 mg q12h/750 mg q12h were simulated by the lowest elimination rate (Ke) group (0.043 h-1). And adults of 70-kg administered 500 mg q12h/750 mg q12h were simulated by the highest Ke model (0.074 h-1). The values in parentheses are the doses taken immediately and the dose taken at the next scheduled dose.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1: PRISMA flow diagram of study identifications.

Figure S2. Sensitivity analysis results

Table S1: The detailed information for population pharmacokinetics characteristics.

Appendix S1: A tool complied by Excel Macro for checking remedial dosing recommendations easily.

chinaXiv:201907.00014v2

Table 1. Dosing schedule design for simulation

Age	Body weight	Dose form	Dose (mg)	Dosing interval	Elimination rate (h^{-1})	
					Minimum	Maximum
Children						
8 month	8 kg	syrup	120	q12h (8:00, 20:00)	0.076	0.081
5 years	16 kg	syrup	240	q12h (8:00, 20:00)	0.062	0.080
6 years	20 kg	tablet	500	q24h (8:00)	0.027	0.066
10 years	30 kg	tablet	500	q12h (8:00, 20:00)	0.028	0.074
Adults						
30 years	70 kg	tablet	500	q12h (8:00, 20:00)	0.029	0.074
50 years	70 kg	tablet	1000	q12h (8:00, 20:00)	0.043	0.074
70 years	70 kg	tablet	750	q12h (8:00, 20:00)	0.035	0.074

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Table 2. Dosing recommendations for patients with delayed or missed valproic acid doses.

Regimens	Scenarios	Dosing recommendations		
		Dose (mg)	Percentage (%)[a]	Remedial strategy
Adults				
500 mg q12h	Delayed 0-6 h	1000	200	A/B
	Delayed 6-8 h	750 or 1000	150 or 200	A/B
	Delayed 8-12 h	750	150	A/B/C
	Missed one dose	750	150	C
	Missed two doses	1000	200	C
750 mg q12h	Delayed 0-3 h	1500	200	A/B
	Delayed 3-5 h	1250 or 1500	166 or 200	A/B
	Delayed 5-12 h	1250	166	A/B/C
	Missed one dose	1250	166	C
	Missed two doses	1250 or 1500	166 or 200	C
1000 mg q12h	Delayed 0-3 h	2000	200	A/B
	Delayed 3-5 h	1750 or 2000	175 or 200	A/B
	Delayed 5-12 h	1750	175	A/B/C
	Missed one dose	1500	150	C
	Missed two doses	1750	175	C

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Table 2. (continued)

Regimens	Scenarios	Dosing recommendations		
		Dose (mg)	Percentage (%)[a]	Remedial strategy
Children				
120 mg q12h	Delayed 0-3 h	240	200	A/B
	Delayed 4-10 h	240 or 200	200 or 166	A/B
	Delayed 10-12 h	200	166	A/B/C
	Missed one dose	160	133	C
	Missed two doses	200 or 160	166 or 133	C
240 mg q12h	Delayed 0-3 h	480	200	A/B
	Delayed 3-7 h	400	166	A/B
	Delayed 7-12 h	400 or 360	166 or 150	A/B/C
	Missed one dose	360	150	C
	Missed two doses	480	200	C
500 mg q12h	Delayed 0-3 h	1000	200	A/B
	Delayed 3-5 h	1000 or 750	200 or 150	A/B
	Delayed 5-12 h	750	150	A/B/C
	Missed one dose	750	150	C
	Missed two doses	1000	200	C
500mg q24h	Delayed 0-6 h	1000	200	A/B
	Delayed 6-10 h	1000 or 750	200 or 150	A/B
	Delayed 10-24 h	750	150	A/B/C
	Missed one dose	750	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 VPA dose to be given remedially compared to the original LTG dose.

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Table 3. Sensitivity analysis settings

Parameter	**Setting**
Weight	Children: 2.5 - 50 kg
	Adults: 50 - 100 kg
Combined medication	If there are covariates in the elimination rate (Ke)
absorption rate (Ka)	Children: 1.2 - 2.6 1/h
	Adults: 0.67 - 1.9 1/h
Dosing interval	Taking a dose 1 hour after the scheduled dose
	Taking a dose 1 hour before the scheduled dose

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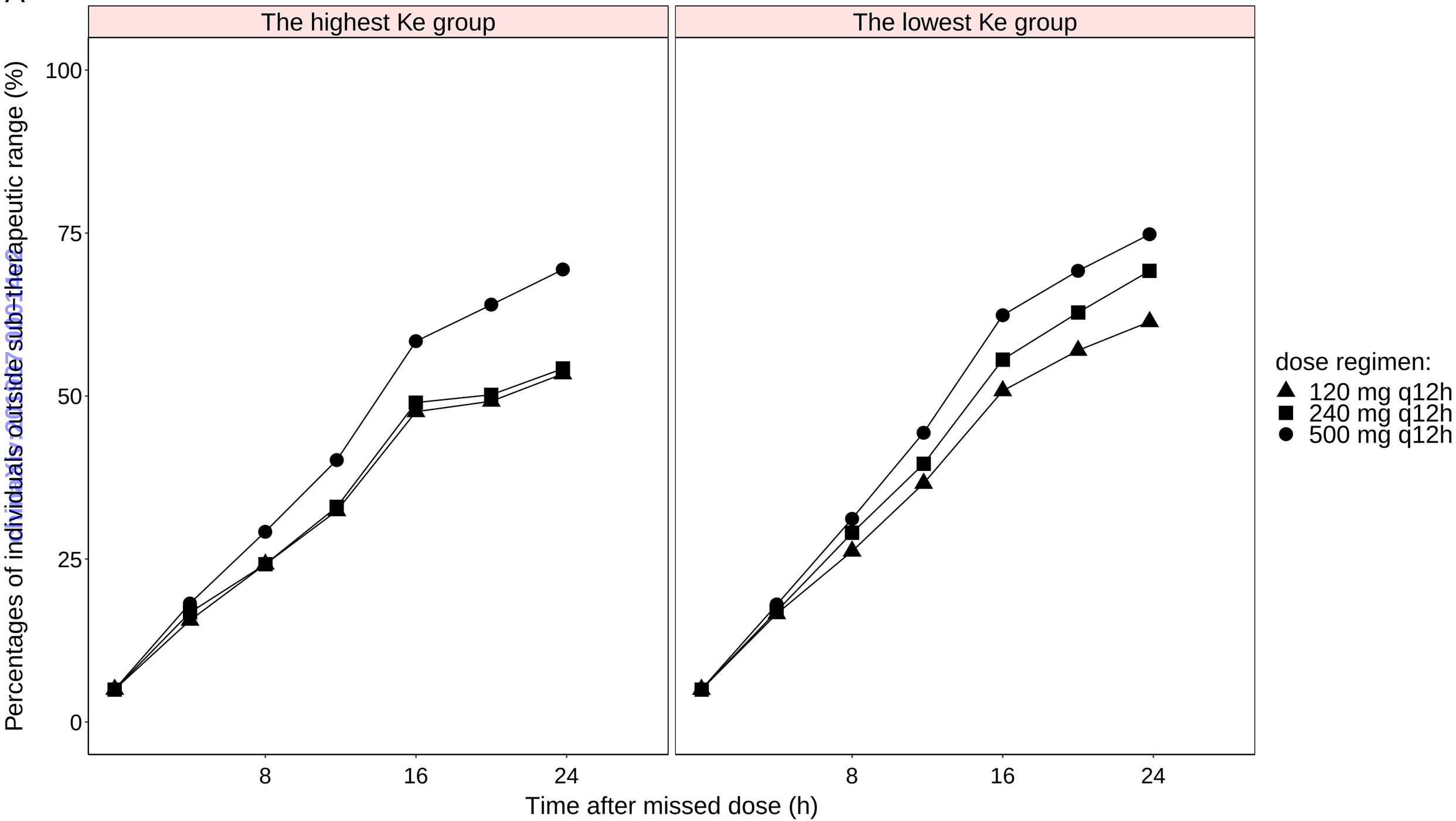
A


The highest Ke group
The lowest Ke group
Percentages of individuals outside sub-therapeutic range (%)
100
75
50
25
0
8
16
24
Time after missed dose (h)
dose regimen:
120 mg q12h
240 mg q12h
500 mg q12h

B

The highest Ke group

The lowest Ke group

Percentages of individuals outside the sub-therapeutic range (%)

100

75

50

25

0

8

16

24

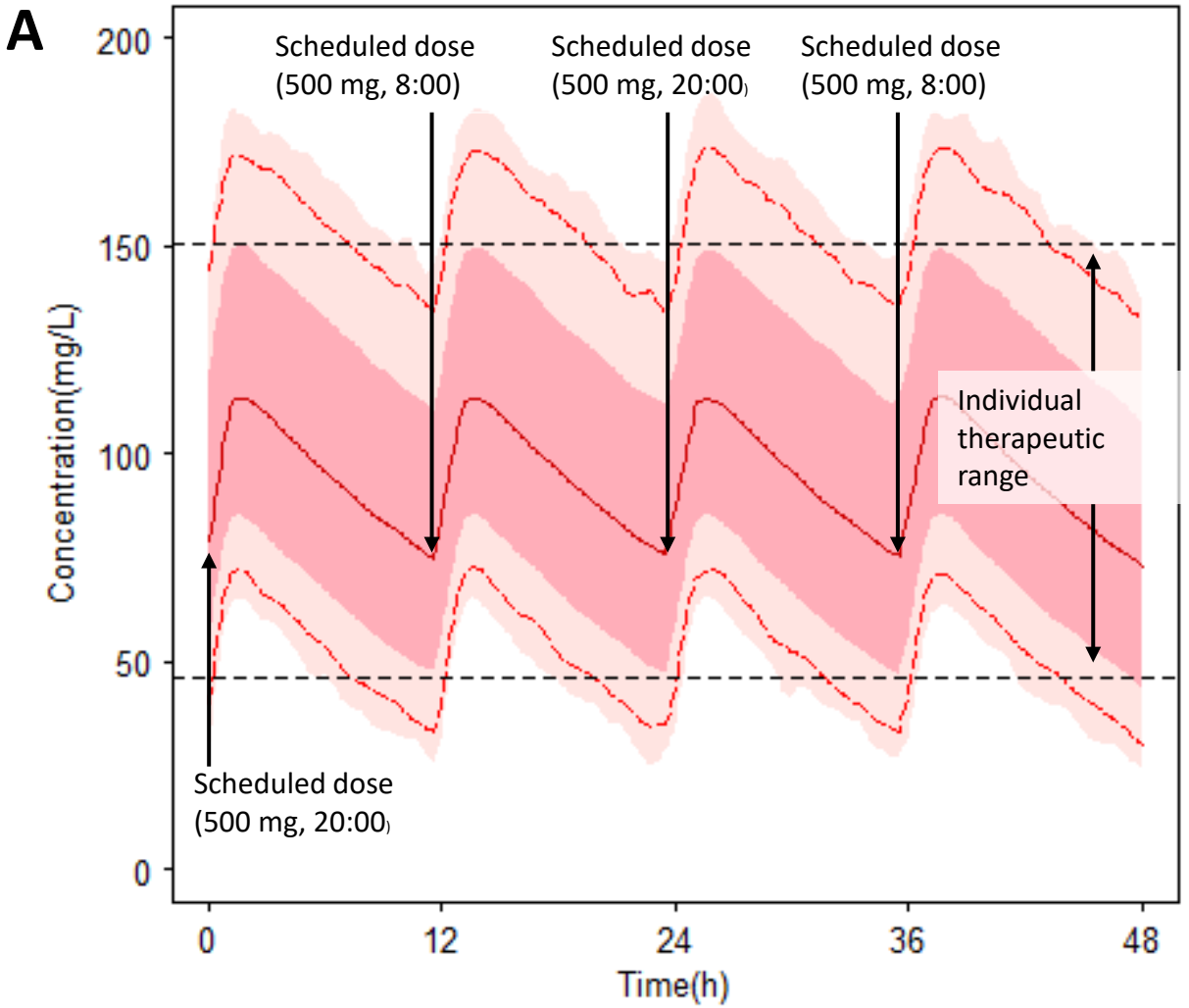
Time after missed dose (h)

Dose regimen:

500 mg q12h

750 mg q12h

1000 mg q12h



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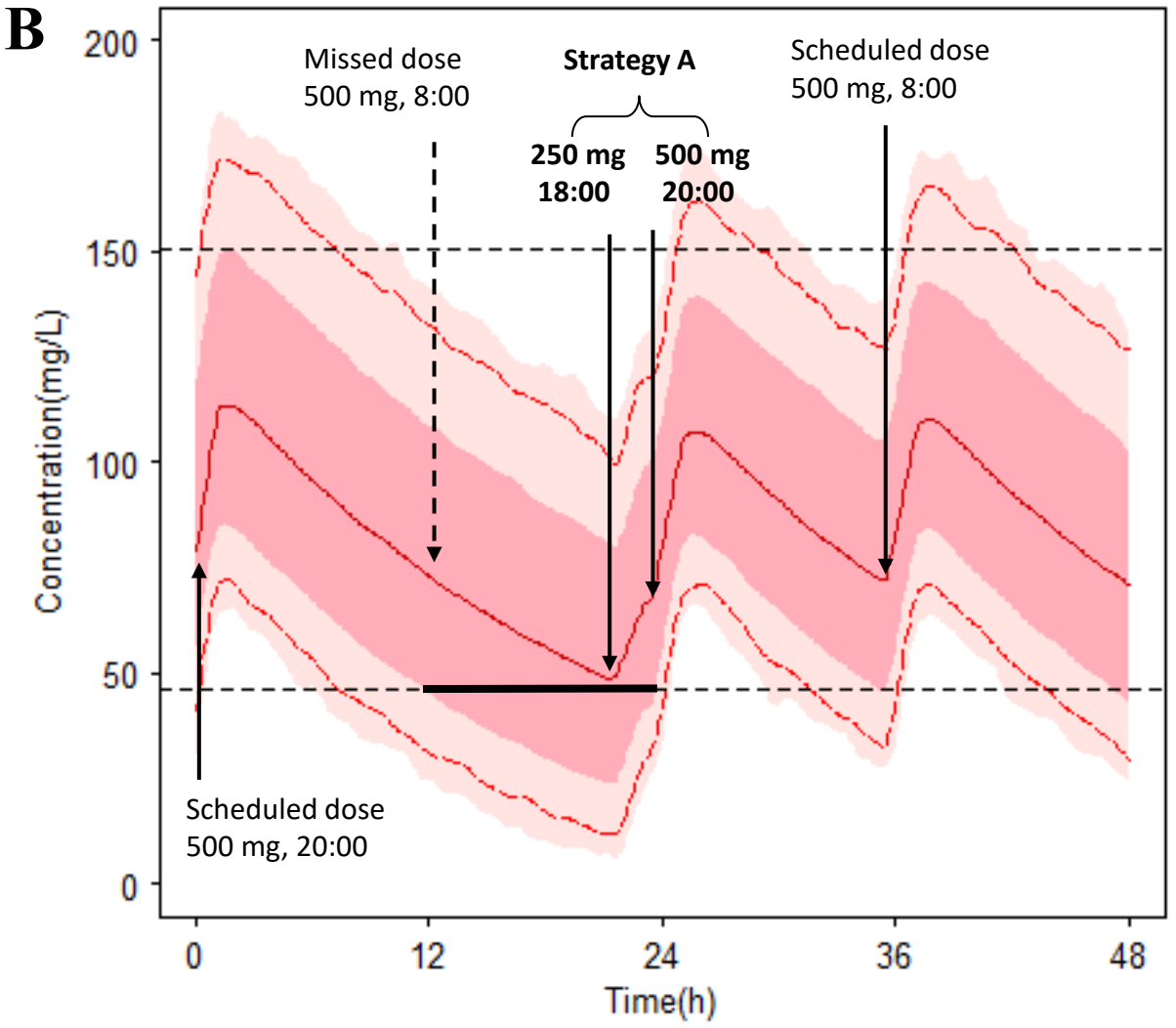

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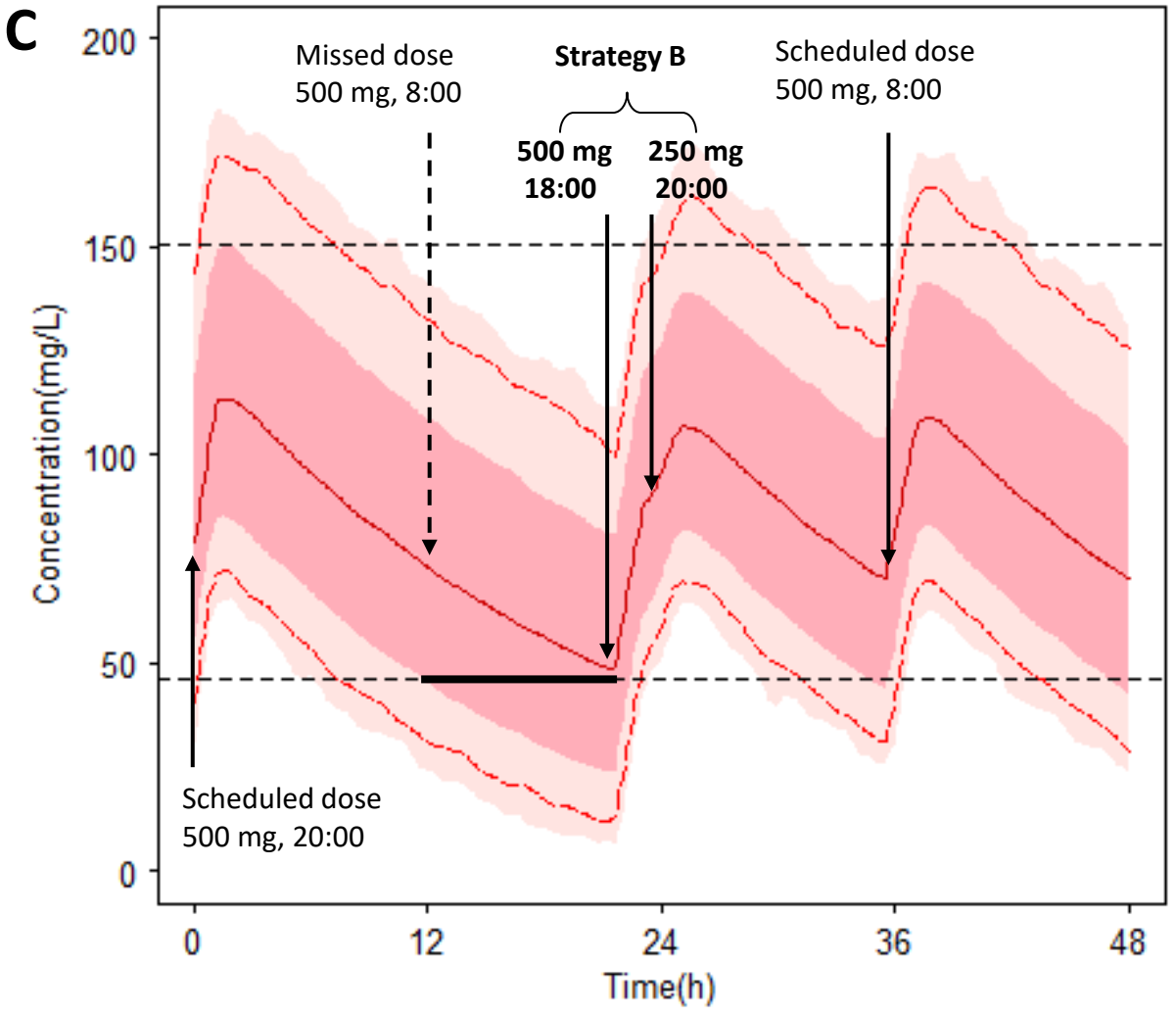

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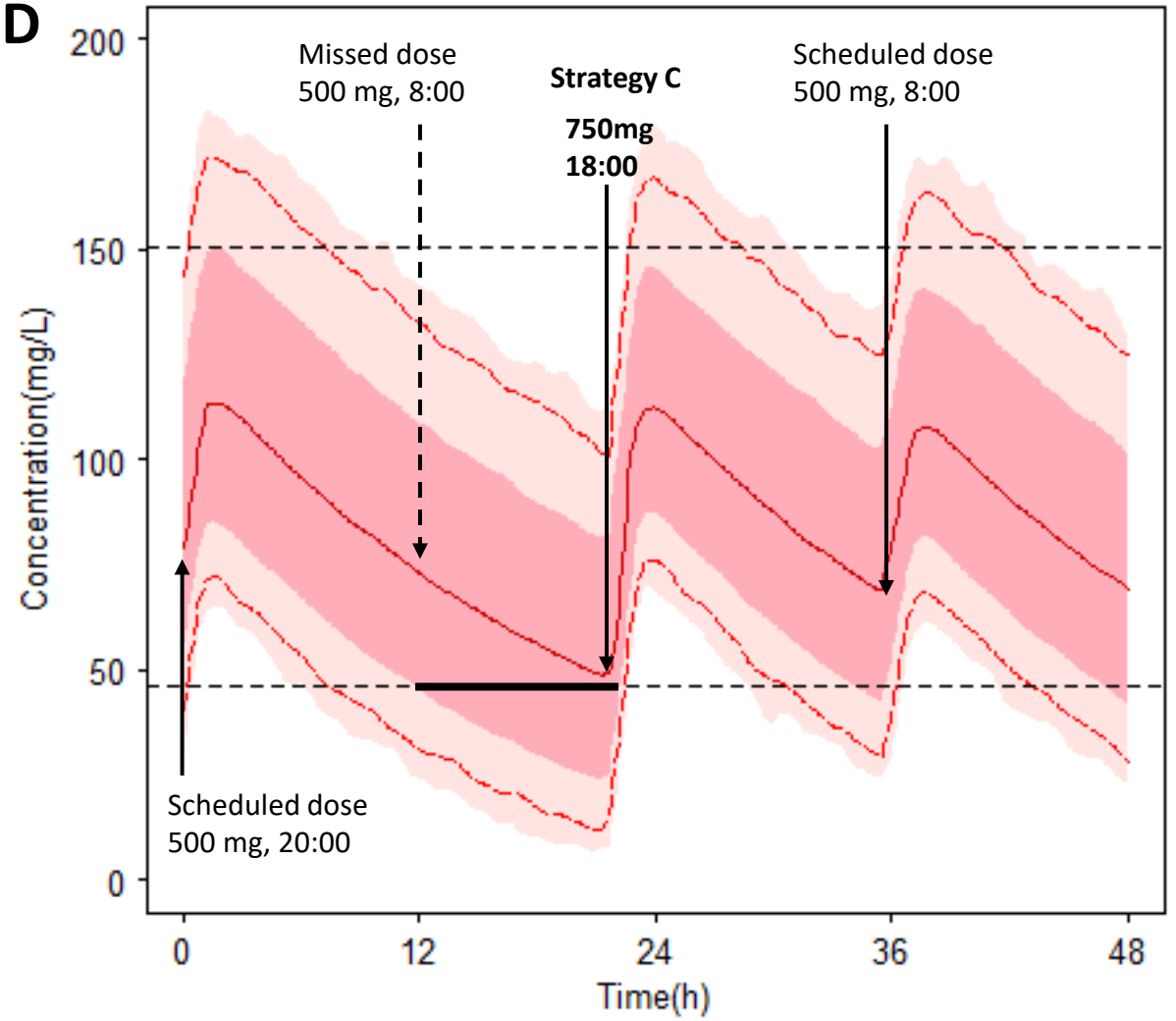

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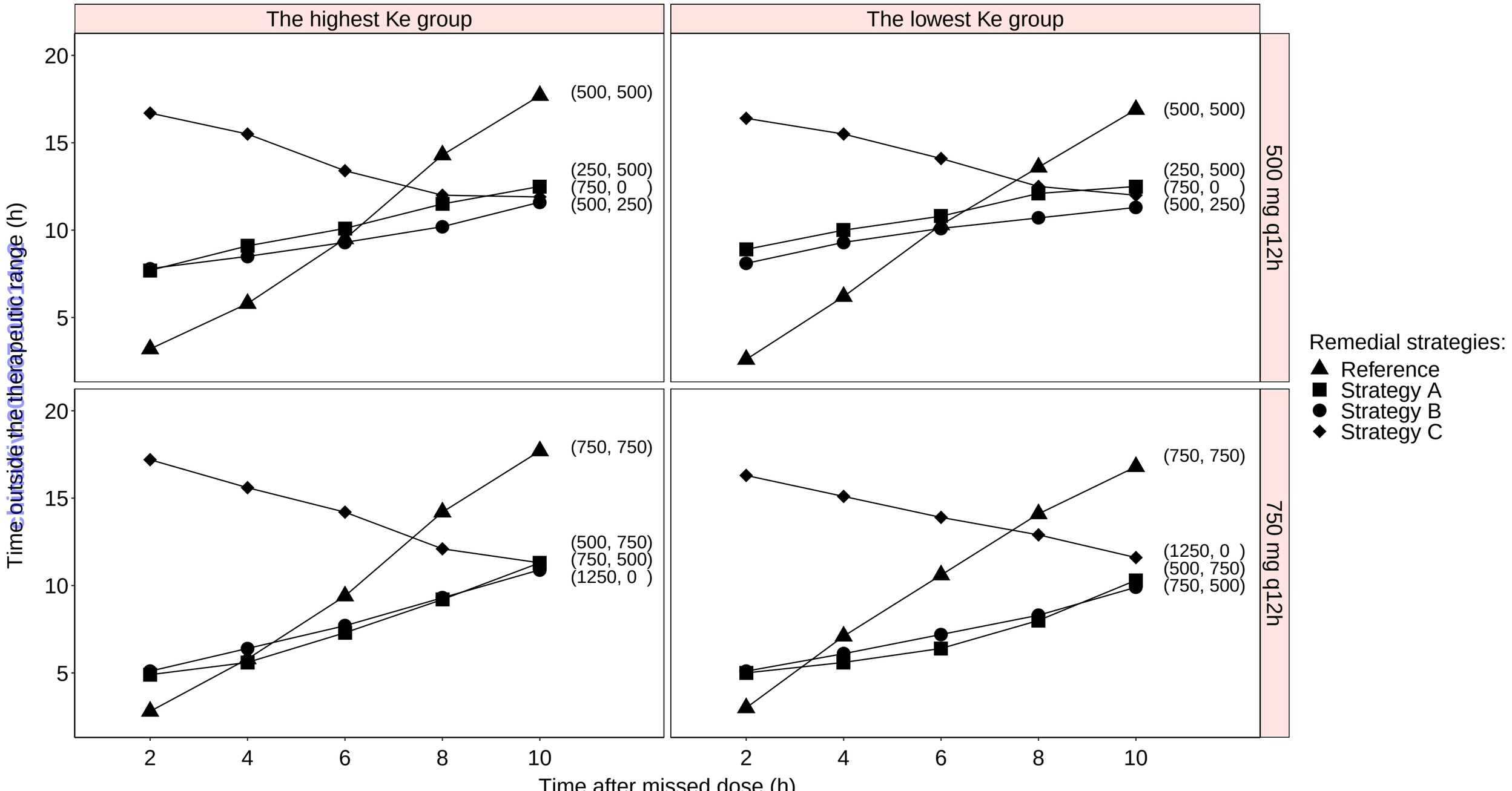
The highest Ke group
The lowest Ke group
500 mg q12h
750 mg q12h
Time outside the therapeutic range (h)
Time after missed dose (h)
20
15
10
5
2
4
6
8
10
(500, 500)
(250, 500)
(750, 0)
(500, 250)
(750, 750)
(500, 750)
(750, 500)
(1250, 0)
Remedial strategies:
Reference
Strategy A
Strategy B
Strategy C