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Graphical abstract

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

Chen-yu Wang, Zheng Jiao a,b, Jun-jie Ding, Er-qian Yu a,d, Guo-xing Zhu e

a Department of Pharmacy, Huashan Hospital, Fudan University, Shanghai 200040, PR China
b Department of Pharmacy, Shanghai Chest Hospital, Shanghai Jiao Tong University, 200030, Shanghai, PR China
c World Wide Antimalarial Resistance Network, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, Oxford University, Oxford OX1 2JD, UK
d Department of Pharmacy, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, PR China
e Department of Neurology, Huashan Hospital, Fudan University, Shanghai 200040, PR China

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Highlights

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

Chen-yu Wang, Zheng Jiao, Jun-jie Ding, Er-qian Yu, Guo-xing Zhu

- Monte Carlo simulation based on population pharmacokinetics is used in the development of remedial dosing recommendation of valproic acid in patients with delayed or missed dose.
- Optimal remedial regimen is related to delay duration and daily dose. But weight, absorption rate constant, irregular dosing interval and concomitant medication have little impact on remedial dosing recommendation.
- Four remedial approaches are proposed and clinicians could select the optimal remedial dosing regimen according to the patient status.
Remedial dosing recommendations for delayed or missed doses of valproic acid in patients with epilepsy based on Monte Carlo simulations

Chen-yu Wang a, Zheng Jiao a,b, Jun-jie Ding c, Er-qian Yu a,d, Guo-xing Zhu e

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 previous 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 at the next scheduled time; D) Double doses are taken when missed one dose or two doses, and the regular regimen at the subsequent scheduled time is resumed. Results: The recommended remedial dosage 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 for delayed two doses. Conclusion: Simulations provide quantitative insight into the remedial regimen for nonadherent patients, and clinicians should select the optimal regimen for each patient based on the individual's status.

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Keywords: Epilepsy, Valproic acid, Nonadherence, Monte Carlo simulation, Remedial dose, Population pharmacokinetic.

1. Introduction

Epilepsy is one of the most common and disabling neurological disorders and requires long-term sometimes even lifelong antiepileptic drug (AED) treatment [1]. Adherence to the prescribed regimen is an important issue in the control of seizures [2]. Delayed or missed doses often occur in the treatment of patients with epilepsy [3]. It has been reported that approximately 30%–50% of patients with epilepsy are nonadherent to their prescribed AED therapies, and more than 70% of respondents in one study reported missed AED doses [4,5]. Such nonadherence can lead to subtherapeutic drug concentrations and increase the risk of seizures [4]. Excessive remedial doses may lead to clinical toxicity, with effects including somnolence, heart block and deep coma [6].

Valproic acid (VPA) is a broad-spectrum AED used in the treatment of both generalized and focal seizures [7–9]. This drug is also used in combination with other AEDs in patients with multiple seizure types [9]. As required by the US Food and Drug Administration (FDA), the daily package insert of VPA (Depakote® ER) carries the following recommendation: “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” [6]. 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 regimen has been performed.

Prospective studies in patients whose medications are intentionally delayed or interrupted for experimental purposes may not be acceptable for ethical reasons [10,11]. In addition, retrospective data are difficult to collect accurately. Monte Carlo simulation based on population...
pharmacokinetic (PPK) models provides the most appropriate means to investigate the effect of delayed or missed doses [12–15]. This method is widely accepted for the development of treatment protocols, avoiding unnecessary clinical studies.

Computer simulation based on population pharmacokinetics modeling provides the most appropriate means to investigate the influence of delayed or missed doses [12]. This study aimed to investigate the effects of delayed or missed doses on the pharmacokinetics of VPA and to provide practical recommendations for patients by Monte Carlo simulation.

## 2. Materials and methods

### 2.1. Typical patients and dose regimens

The characteristics of typical patients and the corresponding investigated dose regimen were based on the following criteria: (1) all patients were assumed to receive VPA monotherapy; (2) the dose regimen was selected according to the FDA-approved label and the treatment guidelines published by the International League Against Epilepsy [16], including the formulation, dose strength and dosing interval; (3) the weight of pediatric patients was based on the World Health Organization Child Growth Standards [17], and the weight of adult and elderly patients was fixed at 70 kg.

### 2.2. Population pharmacokinetic characteristics for Monte Carlo simulations

The PPK characteristics for the simulations and further investigations were extracted from previous studies. A systematic review of PPK studies published before November 30, 2019 was conducted using PubMed and Embase. The relevant identification, screening, and assessment steps followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [18].

Published studies were included if they (1) evaluated patients receiving valproate and (2) had complete PPK parameters. The studies were excluded if they (1) were reviews or focused only on methodology, (2) were published in non-English language articles, or (3) contained data or cohorts overlapping with those of another included study. In the case of such an overlap, only the most recent study or the one with the largest sample size was included. The 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 the NONMEM software (Version 7.4; Icon Incorporation, PA, USA) with the ONLYSIMULATION and SUBPROBLEMS options. Postprocessing of the output was performed in R (version 3.4.0, www.r-project.com).

Time–concentration profiles of VPA were simulated based on 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 [19]. Concentration–time profiles of VPA were generated using the PPK parameters extracted from the identified studies. Moreover, for each scenario, PPK parameters with the longest and shortest elimination half-life (T1/2) in the identified studies were employed for further investigation. T1/2 was calculated using Eq. (1), and the time–concentration profile was calculated using Eq. (2).

\[
T_{1/2} = \frac{0.693 \times V}{CL} \quad (1)
\]

\[
C_n = \frac{k_a \cdot F \cdot X_0}{V \cdot \left(\frac{k_a - CL}{CL} \cdot \frac{1 - e^{-\frac{n \cdot \tau}{V}}}{1 - e^{-\frac{\tau}{V}}} \cdot \frac{CL}{n \cdot \tau} - \frac{1 - e^{-\frac{k_a - CL}{V} \cdot \frac{n \cdot \tau}{V}}}{1 - e^{-\frac{\tau}{V}}} \cdot e^{\frac{n \cdot \tau}{V}}\right)} \quad (2)
\]

where \(k_a\) represents the absorption rate constant; \(T_{1/2}\) represents elimination half-life; \(F\) 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; \(\tau\) 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 were simulated for reference, followed by simulation of the perturbation of steady-state concentration that occurs with various delays in time or nonadherence to the regimen.

### 2.3.1. Nonadherence scenarios and remedial strategies

The delayed-dose scenarios for each medication regimen were 1–12 h of delay for each 12 h (q12h) dosing regimen or 1–24 h of delay 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 four remedial strategies listed below 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 combination of regular dose and a partial dose are taken immediately; the next scheduled time is skipped, and the regular dose is then taken at the subsequent scheduled time.
- Strategy D: double doses are taken; when missed, one two doses and the regular dose is taken at the subsequent scheduled time.

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

### Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Body weight (kg)</th>
<th>Formulation</th>
<th>Dose (mg)</th>
<th>Dosing interval (h)</th>
<th>(T_{1/2}) (h) a</th>
<th>Shortest</th>
<th>Longest</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Children</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 months</td>
<td>8</td>
<td>syrup</td>
<td>120</td>
<td>12</td>
<td>8.62</td>
<td>9.16</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>16</td>
<td>syrup</td>
<td>240</td>
<td>12</td>
<td>8.75</td>
<td>11.27</td>
<td></td>
</tr>
<tr>
<td>6 years</td>
<td>20</td>
<td>ER-tablet</td>
<td>500</td>
<td>24</td>
<td>9.36</td>
<td>16.24</td>
<td></td>
</tr>
<tr>
<td>10 years</td>
<td>30</td>
<td>ER-tablet</td>
<td>1000</td>
<td>12</td>
<td>10.52</td>
<td>13.14</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 years</td>
<td>70</td>
<td>ER-tablet</td>
<td>500</td>
<td>12</td>
<td>9.23</td>
<td>15.41</td>
<td></td>
</tr>
<tr>
<td>50 years</td>
<td>70</td>
<td>ER-tablet</td>
<td>1000</td>
<td>12</td>
<td>9.23</td>
<td>14.21</td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 years</td>
<td>70</td>
<td>ER-tablet</td>
<td>750</td>
<td>12</td>
<td>11.48</td>
<td>13.19</td>
<td></td>
</tr>
</tbody>
</table>

a. \(T_{1/2}\), elimination half-life. All simulated patients have VPA monotherapy at steady state. ER tablet, extended-release tablet.

Please cite this article as: C. Wang, Z. Jiao, J. Ding, et al., Remedial dosing recommendations for delayed or missed doses of valproic acid in patients with epilepsy, Epilepsy & Behavior, https://doi.org/10.1016/j.yebeh.2020.107265
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 the interval delineated by the 5th-percentile trough concentration and the 95th-percentile peak concentration for each regimen based on the guidelines for therapeutic drug monitoring of AEDs [10,19,20].

The deviation time was estimated for each scenario and remedial regimen, and it is defined as the time outside the individual therapeutic range, which is the sum of subtherapeutic and supratherapeutic concentrations. The regimen with the shortest deviation time was considered the most appropriate remedial regimen. 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 has a significant effect on the clearance of VPA in both pediatric, adult, and older patients [21–26]. In addition, when monotherapy is unsuccessful, combination therapy is usually tried in an attempt to improve efficacy, tolerability, or both. Combination therapy was used in 75% of adults and 75% of children [27]. The concomitant drugs in polytherapy may be inducers of VPA or inhibitors [21,24]. Moreover, the \( k_a \) values in the previous PPK models of VPA were fixed. Dosing intervals in our simulations were also fixed and may not accurately reflect real clinical scenarios.

Therefore, it is very helpful to perform a sensitivity analysis to investigate the effect of weight, \( k_a \), dosing interval and concomitant use of other AEDs on the concentration-time profile and dosage recommendation in the event of non-adherence [28]. Nonadherent patient missing one dose were assessed by sensitivity analysis. Moreover, for simplicity, we change one parameter at a time and investigate the impact on the deviation time and optimal remedial regimen.

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 design the remedial dose regimen. We investigated extended-release tablets for pediatric, adult, and older patients as well as syrup for pediatric patients. The detailed dosing regimens are listed in Table 1.
European, in the US and in Mexico. The details of each study are summarized in Supplementary Table S1.

The longest and shortest T1/2 in the eligible studies are listed in Table 1. T1/2 ranged from 8.62 to 23.72 h for infant and pediatric patients and 9.23 to 15.41 h for adult and elderly patients.

3.3. Effect of delayed or missed doses

The results of the Monte Carlo simulation showed that the percentage of subjects outside their individual therapeutic ranges for VPA was related to the delay time, daily dose and T1/2 (Fig. 1). The risk of patients being in the subtherapeutic range increased with delay time. For example, for 70-kg adult patients the shortest T1/2 (9.23 h) who received the VPA 500-mg q12h regimen [24], the percentage of subjects in the subtherapeutic range was 12% and 22% when the dose was delayed for up to 4 and 8 h, respectively (Fig. 1a).

The patients who received higher doses of VPA had a higher risk of being outside the individual therapeutic range than did the patients who received lower doses. For example, in 70-kg adult patients with the shortest T1/2 (9.23 h) [24], the percentages of subjects in the subtherapeutic range were 42.6%, 54%, and 65% for a dosing delay of up to 24 h from the scheduled time for the 500-mg, 750-mg, and 1000-mg q12h regimens, respectively (Fig. 1b).

Moreover, patients with longer T1/2 have a higher risk of being outside the individual therapeutic range than patients with shorter T1/2. For instance, the percentages of subjects in subtherapeutic range was 65% for 70-kg adult patients with T1/2 of 15.41 h who delayed 24 h for 500-mg q12h regimen [31]. The percentage was 42% for adult patients with T1/2 of 9.23 h [24].

3.4. Remedial dosing regimen

The dosing recommendations for remedial treatment after delayed and missed doses are shown in Table 2. The results show that remedial dosing recommendations were related to the delay time and daily dose. We have also developed a tool that can be used to check remedial 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 the patients' age and dosing interval (Fig. 2). For example, if a dose was delayed 8 h, an 70-kg adult patient receiving VPA on the 500-mg q12h regimen 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 the q12h regimen or delay time > 20 h for the q24h regimen).

With increasing delays from the scheduled dosing time, there was a decrease in the total remedial dose necessary to minimize the deviation time from the individual therapeutic range. For example, consider a 70-kg adult patient receiving VPA on the 500-mg q12h regimen and achieving a 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, i.e., a total of 1000 mg would be administered. If a dose was delayed for 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), i.e., a total of 750 mg would be administered (Fig. 3). In this situation, if a total of 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 individual therapeutic range was much longer than that of a

### Table 2

<table>
<thead>
<tr>
<th>Remedy Strategy and dose recommendation</th>
<th>Delay time (h)</th>
<th>Remedy Strategy and dose recommendation</th>
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<tbody>
<tr>
<td>A</td>
<td>0-4</td>
<td>A (120-120)</td>
</tr>
<tr>
<td>B</td>
<td>4-10</td>
<td>A (120-120); A (80-120); B (120-80)</td>
</tr>
<tr>
<td>C</td>
<td>10-12</td>
<td>A (80-120); B (120-80); C (200-120)</td>
</tr>
<tr>
<td>D</td>
<td>12</td>
<td>C (200)</td>
</tr>
<tr>
<td>E</td>
<td>24</td>
<td>D (240)</td>
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<tr>
<td>F</td>
<td>48</td>
<td>D (480)</td>
</tr>
<tr>
<td>G</td>
<td>72</td>
<td>D (720)</td>
</tr>
<tr>
<td>H</td>
<td>108</td>
<td>D (1080)</td>
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<tr>
<td>I</td>
<td>24</td>
<td>C (750-500)</td>
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<tr>
<td>J</td>
<td>24</td>
<td>C (750-500)</td>
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<td>K</td>
<td>24</td>
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<td>L</td>
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<td>M</td>
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<td>Z</td>
<td>24</td>
<td>C (750-500)</td>
</tr>
</tbody>
</table>
The results are presented in Supplementary Fig. S1. The results show that weight, \( k_a, T_{1/2} \), concomitant medications and dosing intervals could change deviation time, but have no significant impact on the proper remedial regimen when patient miss one dose.

4. Discussion

For the first time, we systematically established remedial regimens for missed or delayed doses of VPA by Monte Carlo simulation. Compared to previous studies using the conventional PK approach, our study fully considered the effects of between-subject variability, residual variability, and covariates on remedial dosing recommendations. Moreover, when performing the Monte Carlo simulation for each scenario, we chose two sets of PPK models — those with the longest and the shortest \( T_{1/2} \) among all previous population analyses across different countries. This approach helps to determine the range of remedial doses and could improve the applicability of our method to patients with various PK characteristics of VPA.

Moreover, we employed the individual therapeutic range instead of the reference ranges for VPA are 50–150 mg/L. However, the reference range has been a controversial concept because it was initially
to take the next planned dose as specified or who are near the next scheduled dosing time. Strategy D is not recommended for most of the nonadherent scenarios, especially when patients miss one dose, which is consistent with the approved label by FDA [6]. Strategy D may be only applied for the patients who miss two doses. The clinician can choose the best remedial strategy based on the patient’s condition.

There are still several limitations. The k1, of extended-release tablets reported in the classical PK studies is lower than that investigated in the previous population PK studies (0.18 - 0.19 versus 0.23 - 1.9) [35]. The current evidence may not fully cover these scenarios [36,37]. The impact of extended-release tablets needs further investigation. Moreover, the dose recommendation in the current study was based on typical patients. Physicians should carefully consider the risk of toxicity after patients take a remedial dose in cases of delayed a dose, especially in pediatric, pregnant and elderly patients.

5. Conclusions

This study reported a systematic investigation of remedial dosing recommendations for delayed or missed doses of VPA in patients with epilepsy using Monte Carlo simulation. We proposed four remedial strategies for patients delayed or missed doses. The optimal strategy for nonadherent patient is depended on delay time and daily dose. Based on Monte Carlo simulations, we suggest to take the delayed dose when it is remembered within 3 h and resume the regular regimen. If the patient remembers the dose over 3 h but before the next dose, we suggest to take a partial dose immediately and a regular dose at the next scheduled time or a regular dose immediately followed by a partial dose at the next scheduled time. When missed one dose, patients should avoid double dosing. Clinicians should always evaluate patients’ situation and select the optimal regimen based on the clinical status of patients.

Acknowledgments

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2020.107265.

References


