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Original article

Fosphenytoin dosing regimen including optimal timing for the measurement of serum phenytoin concentration in pediatric patients

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Abstract

Introduction: We aimed to evaluate the pediatric fosphenytoin dosing regimen, including optimal timing for the measurement of total serum phenytoin concentration (C_{PHT}).

Methods: We retrospectively investigated pediatric patients with status epilepticus or seizure clusters treated with fosphenytoin between April 2013 and March 2018. Two C_{PHT} measurements were analyzed, one 2–4 h after the loading dose and another before the second dose. Individual pharmacokinetic parameters were estimated using the Bayesian method and were used to simulate C_{PHT}.

Results: The present study involved 12 pediatric patients; the loading dose of fosphenytoin was 22.1 (17.2–27.2) mg/kg. The C_{PHT} was 13.4 (8.6–18.9) μg/mL 2–4 h after the loading dose. The C_{PHT} estimated from individual pharmacokinetic parameters 12 and 24 h after the loading dose was 9.5 (6.7–14.2) and 5.8 (3.7–10.0) μg/mL, respectively. If fosphenytoin was administered at a loading dose of 22.5 mg/kg and a maintenance dose of 5 or 7.5 mg/kg (administered every 12 h, starting 12 h after the loading dose), then the C_{PHT} on day 8 was estimated to be 5.74 (2.6–15.4) μg/mL at 5 mg/kg and 13.9 (5.7–31.0) μg/mL at 7.5 mg/kg.

Conclusions: In pediatric patients, a maintenance dose of fosphenytoin should be started 12 h after the loading dose, and a maintenance dose of 5–7.5 mg/kg/dose every 12 h may be better than every 24 h. We recommend measuring C_{PHT} at 2 and 12 h after the loading dose to simplify and safely adjust the dosage in clinical practice.

Keywords: Fosphenytoin; Therapeutic drug monitoring; Pediatric; Total serum phenytoin concentration

1. Introduction

Fosphenytoin, which is rapidly converted to phenytoin by serum phosphatases, is a water-soluble prodrug of phenytoin. Phenytoin injections are insoluble in water, have a high pH, and cause local tissue irritation; therefore, fosphenytoin has been used in clinical practice to avoid these issues. Phenytoin also inhibits voltage-dependent sodium channels in neurons, showing anticonvulsant actions by inhibiting hyperexcitability. Fosphenytoin performed as well as levetiracetam and sodium valproate in a randomized controlled trial of patients with status epilepticus resistant to benzodiazepines [1], and fosphenytoin is

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the second-line drug for status epilepticus [2]. Fosphenytoin is advantageous compared with benzodiazepines because it has little effect on the patients' level of consciousness. Therefore, fosphenytoin may be continued when assessing the patients' level of consciousness, while preventing seizure recurrence. In Japan, for patients with status epilepticus, the dose of fosphenytoin for pediatric patients over 2 years of age is defined as follows: 22.5 mg/kg loading dose and 5–7.5 mg/kg/day maintenance dose. Therapeutic drug monitoring (TDM) is recommended to ensure the efficacy and safety of fosphenytoin, and the therapeutic range of total serum phenytoin concentration (C_{PHT}) is 10–20 μg/mL [3]. However, Takeoka et al. reported that a maintenance dose of 7.5–12 mg/kg/day fosphenytoin was less effective in maintaining the therapeutic range in infants [4], and Moffett et al. recommended a maintenance dose of 6 mg/kg/dose fosphenytoin every 8 h for critically ill pediatric patients [5]. Therefore, in Japan, the standard dosing regimen of fosphenytoin may not be able to maintain the therapeutic range, and a maintenance dose should instead be guided by TDM.

There are some clinical issues associated with adjusting the dose of fosphenytoin. Phenytoin is a nonlinear pharmacokinetic drug following the Michaelis-Menten equation [6], and it is more difficult to adjust the dose of fosphenytoin than that of drugs with linear pharmacokinetics. Nevertheless, the dose of fosphenytoin must be adjusted with as few blood samples as possible in clinical practice. Therefore, it is necessary to establish a dosing regimen that includes an appropriate time to measure C_{PHT}. In this study, we evaluated the fosphenytoin dosing regimen, including identifying the optimal timing for the measurement of C_{PHT}.

2. Methods

2.1. Patients

The present study was conducted at Tokyo Women's Medical University, Yachiyo Medical Center. We retrospectively investigated pediatric patients who were treated with fosphenytoin for status epilepticus or seizure clusters between April 2013 and March 2018 and had two measurements of C_{PHT}, one 2–4 h after the loading dose and another before the second dose. In addition, the patients had to be at least 2 years old as fosphenytoin is clinically indicated in Japan for patients aged 2 years or older. Considering the influence of serum albumin (Alb) on C_{PHT}, patients with Alb levels < 3.5 g/mL were excluded.

2.2. Data collection

Data on age, weight, sex, target disease, initial and maintenance doses of fosphenytoin, concomitant use of antiepileptic drugs during fosphenytoin treatment, C_{PHT}, and Alb were retrospectively collected from the electronic medical records of the patients.

2.3. C_{PHT} measurement method

C_{PHT} was analyzed using the chemiluminescence immunoassay with an ARCHITECT® analyzer i2000 SR (Abbott Japan Co., Ltd., Tokyo, Japan) in the hospital clinical laboratory.

2.4. Estimating of individual pharmacokinetic parameters and simulation

Individual pharmacokinetic parameters were estimated using the Bayesian method from C_{PHT} measurements with BMs-Pod ver 8.03 (https://bmspod.web.fc2.com/), which is freely available software based on Microsoft Excel (Microsoft, Redmond, WA). This software incorporates the population pharmacokinetic model reported by Odani et al. [7] and is a one-compartment model based on Michaelis-Menten kinetics. This pharmacokinetic model incorporates body weight as a covariate for maximum elimination rate. Thus, metabolic capacity varies with body weight in this model. We simulated C_{PHT} at 12 and 24 h after the loading dose from individual estimated parameters. In addition, we simulated and compared C_{PHT} when administered the standard fosphenytoin dosing regimen in Japan (22.5 mg/kg as the loading dose, and a maintenance dose of 7.5 mg/kg every 24 h from 24 h after the loading dose) and when administered two increased maintenance dose regimens. In one of the regimens, the increased maintenance dose is 22.5 mg/kg for the initial dose and a maintenance dose of 7.5 mg/kg every 12 h from 12 h after the first administration. The other regimen is the same loading dose and a maintenance dose of 5 mg/kg every 12 h.

2.5. Ethical approval

The present study was approved by the Ethics Committee of Tokyo Women's Medical University (approval number: 5102). Patients were allowed to opt out of this study at any time, and this information was available on the hospital website.

3. Results

3.1. Patient characteristics

Thirteen patients were initially selected, one patient was excluded because of Alb level < 3.5 g/mL, and 12 patients were included in this study. A summary of patient data is shown in Table 1.

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Table 1
Summary of patient data (n = 12).

Patient	Age (year)	Weight (kg)	Alb (mg/dL)	Loading dose of FOS (mg/kg)	Concomitant antiepileptic drugs	Seizure cause	Seizure conditions	Convulsions after FOS loading dose	Last convulsion date	Duration of FOS treatment (day)
1	10	19.8	4.6	22.7	TPM, LEV	Epilepsy	SC	occurred	day 3	3
2	5	20.2	4.4	27.2	PB, KBr	Epilepsy	SC	occurred	day 2	4
3	2	11.5	4.2	21.7	MDZ, LEV, VPA, CHL	Epilepsy	SC	occurred	day 1	5
4	12	43.7	4.9	17.2	LEV, VPA	Epilepsy	SC	none	day 1	2
5	4	21.2	4.3	21.2	DZP	Afebrile convulsion	SE	none	day 1	1
6	4	17.8	4.4	23.2	MDZ	AE	SE	occurred	day 2	6
7	4	16.2	4.2	23.1	LEV, VPA, LTG	Epilepsy	SC	occurred	day 3	4
8	5	15.6	3.9	21.6	MDZ, LEV, CBZ, CHL, THP	AE	SE	occurred	day 8	15
9	4	9.35	3.6	20.9	MDZ	Febrile convulsion	SE	none	day 1	4
10	4	15	3.6	22.5	MDZ, VPA	AE	SE	occurred	continue	5
11	2	10.7	3.8	21.0	MDZ	AE	SC	none	day 1	5
12	12	41.9	4.8	23.3	MDZ, VPA, TPM	Epilepsy	SE	occurred	day 1	3

Alb: serum albumin, FOS: fosphenytoin, AE: acute encephalopathy, SE: status epilepticus, SC: seizure clusters, TPM: topiramate, LEV: levetiracetam, PB: phenobarbital, KBr: potassium bromide, MDZ: midazolam, VPA: sodium valproate, CHL: chloral hydrate, DZP: diazepam, LTG: lamotrigine, CBZ: carbamazepine, THP: thiopental sodium.

The median (range) age and weight of patients at the initial administration of fosphenytoin was 4 (2–12) years and 17.0 (9.4–43.7) kg, respectively. Regarding the seizure conditions, 6 patients had status epilepticus and 6 patients had seizure clusters. The diseases that caused the seizures were acute encephalopathy in 4 patients, pre-existing epilepsy in 6 patients, febrile convulsion in 1 patient, and afebrile convulsion in 1 patient. The median (range) loading dose was 22.1 (17.2–27.2) mg/kg, and the C_{PHT} at 2–4 h after the loading dose of 13.4 (8.6–18.9) μg/mL; the C_{PHT} of one patient was subtherapeutic level (Fig. 1). Among the patients with status epilepticus, 2 patients did not have convulsions after the loading dose and 2 patients showed seizure resolution within 1–3 days without recurrence of status epilepticus or seizure clusters. In the other two patients, one had recurrent status epilepticus and the other had convulsions at least once a day during fosphenytoin maintenance. Among the patients with seizure clusters, 2 patients did not have convulsions after the loading dose and 4 patients showed seizure resolution within 1–3 days without recurrence of status epilepticus or seizure clusters (Table 1). The median (range) duration of fosphenytoin treatment was 4 (1–15) days. The number of patients who received concomitant antiepileptic drugs that could affect the pharmacokinetics of fosphenytoin was seven; of these, 5 patients received sodium valproate, 1 received carbamazepine, and 1 received phenobarbital. Adverse effects requiring treatment were not observed during fosphenytoin administration.

The pharmacokinetic parameters estimated from individual C_{PHT} values are shown in Table 2. The median (range) maximum elimination rate (Vmax) was calculated to be 272.6 (197.9–431.3) mg/day. The Vmax per body weight decreased with body weight.

3.2. Simulation of C_{PHT}

The median (range) estimated C_{PHT} at 12 and 24 h after the loading dose, calculated from individual pharmacokinetic parameters, was 9.5 (6.7–14.2) and 5.8 (3.7–10.0) μg/mL, respectively (Fig. 2). The ratio of C_{PHT} expected to be within 10–20 μg/mL was 41.7% at 12 h after the loading dose and 0% at 24 h after the loading dose.

We estimated the C_{PHT} for the standard dose regimen in Japan and for the two increased maintenance dose regimens (Fig. 3). The median (range) estimated C_{PHT} for the standard dose regimen in Japan was 3.7 (1.1–8.6) μg/mL on day 4 and 2.52 (0.9–7.8) μg/mL on day 8. The median (range) estimated C_{PHT} for the increased maintenance dose regimen of 5 mg/kg every 12 h was 7.1 (3.2–13.7) μg/mL on day 4 and 5.7 (2.6–15.4) μg/mL on day 8. The ratio of C_{PHT} expected to be within 10–20 μg/mL was 16.7% on days 4 and 8. Furthermore, for the increased maintenance dose regimen of 7.5 mg/kg every

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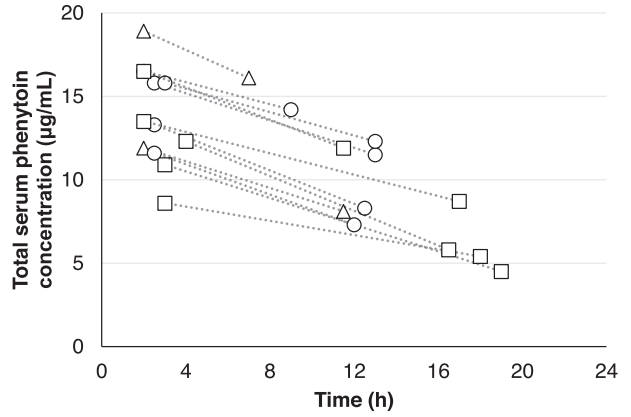

Fig. 1. Total serum phenytoin concentration after the initial loading dose (n = 12). The patients who did not receive concomitant medications affecting fosphenytoin pharmacokinetics are indicated with a white circle, patients who received sodium valproate are indicated with a white square, and patients who received cytochrome P450 enzyme inducers, phenobarbital and carbamazepine, are indicated with a white triangle.

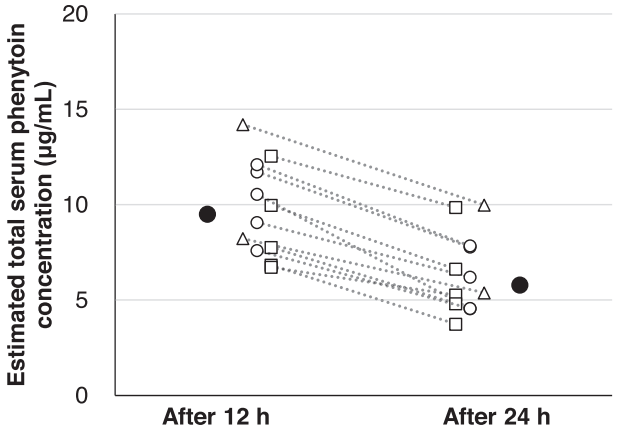

Fig. 2. Estimated total serum phenytoin concentration at 12 and 24 h after the initial loading dose, calculated from individual pharmacokinetic parameters. Black circles are median values; white circles are individual values for patients who did not receive concomitant medications affecting fosphenytoin pharmacokinetics; white squares are individual values of patients who received sodium valproate; white triangles are individual values of those who received cytochrome P450 enzyme inducers (carbamazepine or phenobarbital).

Table 2
Estimated pharmacokinetic parameters (n = 12).

Parameter	Value
Vmax (mg/day)	272.6 (197.9–431.3)
Vmax (mg/day/kg)	15.8 (9.9–21.2)
km (μg /mL)	9.1 (7.7–10.4)
Vd (L/kg)	1.1 (0.8–1.4)

Data are presented as median (range).
Vmax: maximum elimination rate, km: Michaelis-Menten constant, Vd: volume of distribution

12 h, the median (range) estimated C_{PHT} was 12.2 (6.1–20.6) μg/mL on day 4 and 13.9 (5.7–31.0) μg/mL on day 8. The ratio of C_{PHT} expected to be within 10–20 μg/mL was 58.3% on day 4 and 50.0% on day 8.

3.3. Measured C_{PHT} during a maintenance dose of fosphenytoin

Eleven of the 12 patients were treated with a maintenance dose of fosphenytoin; 1 patient received just one additional dose, 1 patient received the regular 7.4 mg/kg every 24 h, and 9 patients received 5.9–9.3 mg/kg every 12 h. C_{PHT} of 10 patients was measured during the maintenance dosing (Table 3). Two patients had Alb levels < 3.5 g/mL, and for the remaining eight patients, the median (range) trough level of C_{PHT} was 11.4 (3.0–19.4) μg/mL and the range of maintenance doses was 5.9–9.3 mg/kg/dose. Among the eight patients, the maintenance dosing interval was 24 h for one patient and 12 h for seven patients. Patient 8 was treated with fosphenytoin 7.2 mg/kg every 12 h, but status epilepticus recurred; C_{PHT} was then measured on day 8, and the observed value was 3.0 μg/mL.

4. Discussion

The results of the present study suggest that a loading dose of 22.5 mg/kg fosphenytoin is appropriate, and if fosphenytoin administration is to be continued, we recommend that a maintenance dose should be started 12 h after the loading dose. In Japan, the maintenance dose of fosphenytoin is 5–7.5 mg/kg every 24 h, but 7.5 mg/kg every 24 h is not likely to maintain the therapeutic range. According to our results, a maintenance dose of 5–7.5 mg/kg every 12 h could maintain the therapeutic range.

There is no clear evidence for the prevention of recurrence after the convergence of status epilepticus. However, in clinical practice, antiepileptic drugs are continued to prevent recurrence until the causative disease is determined. Fosphenytoin and levetiracetam are specifically selected for use during the evaluation of a patient's level of consciousness. The therapeutic range for fosphenytoin is generally 10–20 μg/mL [3], and a dosing regimen and TDM that can maintain this range are important. In patients who do not achieve seizure control within the therapeutic range or who have difficulty controlling C_{PHT} even with appropriate dosing regimens, other antiepileptic drugs should be considered. However, Borofsky et al. reported that C_{PHT} in pediatric patients with controlled epilepsy was above 5 μg/mL, and therefore, C_{PHT} of up to 5 μg/mL may be acceptable if seizures are controlled [8]. C_{PHT} less than 5 μg/mL is not recommended, and in fact, one

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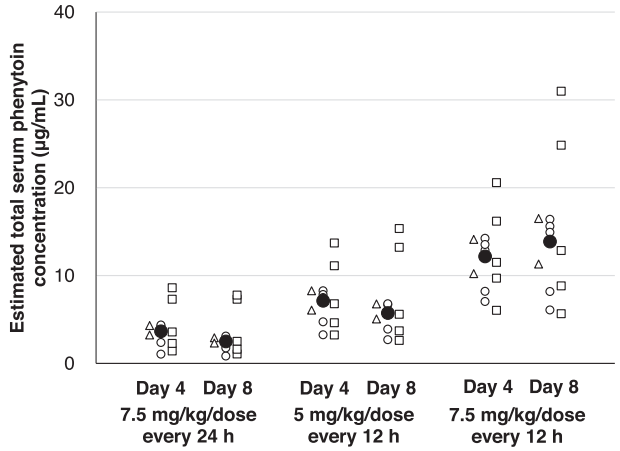

Fig. 3. Estimated total serum phenytoin concentration on day 4 and day 8 for the standard dosage regimen in Japan and for the two increased maintenance dose regimens. The standard regimen in Japan is 22.5 mg/kg as the initial dose, and a maintenance dose of 7.5 mg/kg every 24 h from 24 h after the first administration. In one of the increased maintenance dose regimens, the maintenance dose is 22.5 mg/kg for the initial dose and 7.5 mg/kg every 12 h from 12 h after the first administration. In the other, the same loading dose and a maintenance dose of 5 mg/kg every 12 h were used. Black circles are median values; white circles are individual values for patients who did not receive concomitant medications affecting fosphenytoin pharmacokinetics; white squares are individual values of the patients who received sodium valproate; white triangles are individual values of those who received cytochrome P450 enzyme inducers (carbamazepine or phenobarbital).

patient with recurrent status epilepticus had a C_{PHT} of 3.0 μg/mL. The patient was diagnosed with acute encephalopathy and continued to be treated with fosphenytoin for seizure prophylaxis but developed a late seizure. Further studies are needed to investigate the relationship between the efficacy of fosphenytoin in preventing recurrence and the therapeutic range of C_{PHT}.

Tanaka et al. performed population pharmacokinetic analysis of fosphenytoin and suggested that the loading dose of fosphenytoin in children should be 22.5 mg/kg [9]. In this study, the median C_{PHT} for 2–4 h was 13.4 μg/mL with a median loading dose of 22.1 mg/kg, and therefore, 22.5 mg/kg fosphenytoin is considered a safe and optimal loading dose. However, a phenytoin loading dose of 20 mg/kg is recommended for status epilepticus [10,11], which translates to 30 mg/kg fosphenytoin, as the ratio of fosphenytoin to phenytoin is 1.5. Thus, the loading dose of fosphenytoin could be increased from 22.5 mg/kg.

In children, the maximum elimination rate of phenytoin is higher than that in adults [12], and the time to reach below 10 μg/mL after the loading dose of fosphenytoin was also faster than that in adults [9]. In this study, the median C_{PHT} estimated from individual pharmacokinetic parameters was 9.5 μg/mL after 12 h and 5.8 μg/mL after 24 h from the loading dose. Therefore, the maintenance dose of fosphenytoin should be started 12 h after the loading dose. In a simulation of phenytoin using a physiologically based pharmacokinetic model, a loading dose of 18 mg/kg and a maintenance dose of 5 mg/kg every 12 h were the highest rates for maintaining a peak C_{PHT} of 10–20 μg/mL [13]. The results can be extrapolated to fosphenytoin with a loading dose of 27 mg/kg and a maintenance dose of 7.5 mg/kg. In our simulation with the estimate from individual pharmacokinetic parameters, a loading dose of 22.5 mg/kg and a maintenance dose of 7.5 mg/kg every 24 h starting at 24 h after the loading dose would not be able to maintain a trough C_{PHT} of 10–20 μg/mL, and 83.3% of the patients had C_{PHT} below 5 μg/mL. Whereas, with a loading dose of 22.5 mg/kg, followed by a maintenance dose of 7.5 mg/kg every 12 h starting at 12 h after the loading dose, the median trough C_{PHT} was expected to be 12.2 μg/mL on day 4 and 13.9 μg/mL on day 8. However, C_{PHT} increased over time in two patients, and it was estimated to be over 20 μg/mL on day 8. The population pharmacoki-

Table 3
Maintenance doses of fosphenytoin and total serum phenytoin concentrations.

Patient	Dose (mg/kg)	Dosing interval (h)	C_{PHT} (μg/mL)	Alb (mg/dL)	Date of measurement
1	7.6	12	19.3	4.6	day 4
2	7.4	24	11.9	4.5	day 5
3	7.0	12	10.2	4.3	day 5
6	5.9	12	9.3	3.5	day 5
7	9.3	12	19.4	3.9	day 4
8	7.2	12	3.0	4.1	day 8
11	7.0	12	10.8	3.8	day 4
12	6.4	12	15.5	4.8	day 4
4	17.2	24	–	–	–
5	–	–	–	–	–
9	6.4	12	(7.8) [a]	3.1	day 4
10	7.5	12	(7.5) [a]	3.4	day 5

C_{PHT}: total serum phenytoin concentration, Alb: serum albumin.
a: Reference value with Alb level < 3.5 g/mL

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netic model used in this study, proposed by Odani et al. [7], incorporates body weight as a covariate of Vmax, and Vmax per body weight decreases with increasing body weight. Other population pharmacokinetic models incorporate body weight or fat-free mass as a covariate for metabolic clearance [5,9]. Therefore, for the same dose (mg/kg), the C_{PHT} will be higher in patients with a higher body weight, because the elimination rate of phenytoin per body weight is lower in patients with a higher body weight. Both patients with an estimated supratherapeutic level were 12 years old, the oldest of the patients in this study, and over 40 kg. For heavier children, a regimen with a maintenance dose of 5 mg/kg every 12 h may be appropriate; when simulated with the population pharmacokinetic model of Odani et al. [7], 30 kg was the borderline weight for determining a maintenance dose of 7.5 or 5 mg/kg (data not shown). In contrast, Moffett et al. recommended that the optimum dosing regimen of fosphenytoin was a loading dose of 20 mg/kg and a maintenance dose of 6 mg/kg every 8 h [5], and this daily maintenance dose is higher than that determined in our study. Currently, the optimal maintenance dose is not clear, but the maintenance dose should be higher than 7.5 mg/kg every 24 h to maintain the therapeutic range, and a maintenance dose of 5–7.5 mg/kg every 12 h would help achieve this.

The C_{PHT} at 2 h after a loading dose of fosphenytoin is important in confirming that C_{PHT} is within the therapeutic range [14] and is needed for determining the maintenance doses if treatment with fosphenytoin should be continued. Immunoassays should not be performed up to 2 h after administration because serum fosphenytoin and phenytoin interact with each other in immunoassays [15]. In clinical practice, the C_{PHT} after 2–4 h of administration is considered the peak concentration with complete distribution. The concept of volume of distribution (Vd) is not different from that of other drugs; therefore, estimating the C_{PHT} that increases with a single fosphenytoin dose is possible. The median Vd of fosphenytoin was 1.1 L/kg in this study. In pediatric patients, the Vd of fosphenytoin was not affected by obesity and was found to be 0.92 L/kg in obese patients and 0.97 L/kg in non-obese patients [16], which was similar to our results. In contrast, it has been reported that the Vd of phenytoin was 1.6 L/kg at 1 year of age but decreased to 0.6 L/kg at 10 years of age [17]. Therefore, the Vd of fosphenytoin may be affected by age, and C_{PHT} measurement after 2 h of the loading dose was useful in determining the maintenance dose. Furthermore, Riviello et al. recommended that the C_{PHT} should be checked after 2 h of phenytoin loading, and if the C_{PHT} after 2 h is in the therapeutic range, the maintenance dose should be started after 12 h, and if the C_{PHT} is at a subtherapeutic level, the maintenance dose should be started earlier than 12 h [18]. In addition to their recommendation, we consider that the C_{PHT} should be measured before the maintenance dose. If C_{PHT} is obtained after 2 h and before the second dose, the C_{PHT} that increases with a single dose and the decrease in C_{PHT} with time can be estimated. In particular, the ideal timing of measurement before the second dose and the interval between maintenance doses should be 12 h. For instance, if fosphenytoin was administered at 22.5 mg/kg and C_{PHT} was 15 μg/mL at 2 h after the loading dose and 10 μg/mL at 12 h after the loading dose, the same C_{PHT} level should be continued at 7.5 mg/kg every 12 h beginning 12 h after the loading dose. However, individual pharmacokinetics may be altered, for example, due to drug interactions or changes in systemic conditions. C_{PHT} may also change, and this is commonly observed in clinical practice. Therefore, if continued treatment with fosphenytoin is needed after 3–4 days of fosphenytoin initiation, C_{PHT} should be measured before administration. For the seven patients who received fosphenytoin of 5.9–9.3 mg/kg every 12 h continuously, one patient had C_{PHT} of 3.0 μg/mL (subtherapeutic level) and two patients had C_{PHT} of 19.3 and 19.4 μg/mL, close to the supratherapeutic levels. One patient treated with a maintenance dose of 7.4 mg/kg every 24 h had a C_{PHT} of 11.9 μg/mL, in the therapeutic range. The cause of this variation has not been clarified, and further studies are needed.

This study had some limitations. First, the number of patients was small. Second, free serum phenytoin concentration was not measured. Third, C_{PHT} may have been affected by concomitant antiepileptic drugs. In this study, concomitant antiepileptic drugs that could decrease C_{PHT} were sodium valproate, phenobarbital, and carbamazepine [19]. In particular, the drug interaction between sodium valproate and phenytoin is that of plasma protein binding displacement, which decreases C_{PHT} but does not change free phenytoin concentration [20,21]. Tsanaclis et al. showed that the concomitant use of sodium valproate decreased the mean C_{PHT} from 13.4 μg/mL to 10.2 μg/mL [21]. Fourth, patients with hypoalbuminemia were not studied. In patients with hypoalbuminemia and/or concomitant use of drugs that cause plasma protein binding displacement, measurement of free phenytoin concentration is necessary, but it is not a routine practice. In such patients, it would be safe to control C_{PHT} around 10 μg/mL while monitoring the toxicity and Alb level. Lastly, genetic polymorphisms were not assessed in this study. Genetic polymorphisms in CYP2C9 and CYP2C19 have been reported to affect interindividual variation [22], and further research in this regard may result in more individualized dosing regimens.

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5. Conclusion

In pediatric patients, a loading dose of fosphenytoin at 22.5 mg/kg is appropriate, and maintenance dosing should be started 12 h after the loading dose to maintain the C_{PHT} in the therapeutic range. A maintenance dose of 5–7.5 mg/kg/dose every 12 h may be better than the current Japanese dosing regimen, and dosing should be adjusted according to TDM. We recommend that C_{PHT} be measured at 2 h and 12 h after the loading dose to confirm not only the therapeutic range but also to simplify and safely adjust the dosage.

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.

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Authorship statement

All authors met the ICMJE authorship criteria. GO and EK contributed to the conceptualization and design of the study. GO contributed to data collection. GO, EF, and KT performed data analysis. GO, KY, and JT interpreted the results. GO and EK contributed to drafting and editing the manuscript. EF, KT, KY, and JT provided suggestions on the study and revised the manuscript. All authors have read and approved the final manuscript.

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