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Effect of therapeutic plasma exchange on phenytoin plasma concentration in patients receiving intravenous fosphenytoin therapy

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We report for patients with encephalitis treated with plasma exchange (PE) and fosphenytoin. In patient 1, phenytoin levels decreased on the maintenance dose, and the phenytoin concentration was <10 µg/mL on day 12 of administration. In patient 2, the phenytoin levels was <10 µg/mL on day 4. Increasing the fosphenytoin dose pushed the phenytoin level into therapeutic range. There were no differences between the areas under the concentration-time curve of phenytoin with and without PE. We previously reported a decline in phenytoin levels after prolonged use of fosphenytoin. Therefore, dose adjustment of fosphenytoin in patients undergoing PE may be unnecessary.

1. Introduction

Plasma exchange (PE) is recommended as a first-line therapy for several immune-mediated neurologic disorders, including anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis (Smith et al. 2003; Dalmau et al. 2011). Although immune-mediated seizures can occur in anti-NMDA receptor encephalitis, there are no guidelines on the dose management of antiepileptic drugs in patients undergoing PE (Schwartz et al. 2016).

Fosphenytoin (fPHT) is a prodrug of phenytoin (PHT) that was designed to overcome the shortcomings associated with parenteral phenytoin and as a transient alternative to oral PHT (Nobelpharma Co et al. 2012). fPHT is almost completely converted to phenytoin within a few hours after administration by alkaline phosphatase in blood and tissue (Gerber et al. 1988). In addition, a few reports on PHT showed that serum PHT levels are not influenced by PE in the clinical setting (Lai et al. 1990; White et al. 1987; Nasca et al. 1985). However, we experienced two patients with anti-NMDA receptor encephalitis who were being treated with PE and receiving fPHT in whom the serum PHT concentration could not be controlled during treatment of PE. In this study, we evaluated the effect of PE on PHT levels in these patients.

2. Investigations and results

We report for two patients with encephalitis treated with plasma exchange (PE) and fosphenytoin. Patient 1 was a 17-year-old woman. She was admitted to our hospital because of being acutely deteriorated in their mental status. Neurological examination showed mild consciousness disturbance, exaggerated deep tendon reflexes in the lower extremities and mild generalized muscle weakness. Oral dyskinesia and tonic-clonic seizures were also noted. Ovarian MRI and ultrasonography showed no ovarian teratoma. Anti-NMDA receptor encephalitis was diagnosed based on the positive result of anti-NMDA receptor antibodies in the cerebrospinal fluid (CSF).

Two courses of intravenous methylprednisolone pulse therapy (IVMP; 1000 mg/d, 3d) were administered from admission (day 1) to day 3 and day 10 to day 12. fPHT therapy was also started based on the manufacturer's package insert at the time of admission, beginning with an initial loading dose of 22.5 mg/kg for rapid attainment of an effective trough concentration followed by a maintenance dose of 5–7.5 mg/kg (Fig. 1A). Twelve days after admission, PE (KM8600 using PlasmaflowOP-05W as a column, Asahikasei Medical, Japan) was started for treatment of anti-NMDA receptor encephalitis. A total of 2.8 L (body weight 41 kg) of plasma was exchanged over 2 h with 2.8 L of fresh frozen plasma in every session. A total of seven sessions (day 12, 14, 16, 19, 21, 23 and 26) were implemented. fPHT was administered until day 19. As seizures were uncontrolled, we retrospectively examined PHT concentration during the treatment of PE. The PHT level decreased in a time-dependent manner, and all values measured after the 12 days of administration of fPHT were less than the effective trough concentration (<10 µg/mL). After day 18, fPHT was changed to oral PHT at a dosage of 200 mg/day. The PHT level was maintained thereafter below the effective trough concentration. The epilepsy could not be controlled and seizures requiring administration of additional antiepileptic drugs were observed every 1–2 d during this period until day 26. After that, intravenous immunoglobulin (IVIg) therapy (0.4 g/kg day 29–33 and day 59–63) and three courses of IVMP therapies (day 48–50, 65–67 and day 76–78) were administered, and consciousness disturbance and oral dyskinesia disappeared. She was discharged on day 84.

Patient 2 was a 16-year-old woman. She was admitted to our hospital in an acutely deteriorated mental status, headache, and nausea. Neurological examination showed moderate consciousness disturbance, involuntary movements of the four extremities, exaggerated deep tendon reflexes, and frontal signs. Partial seizures and psychiatric symptoms were also noted. Bilateral ovarian teratomas were detected by computed tomography. Her CSF was positive for anti-NMDA receptor antibodies. We diagnosed her as having ovarian teratoma-associated anti-NMDA receptor encephalitis. We performed IVMP therapy for 3 d from the time of admission. fPHT therapy was also started based on the manufacturer's package insert at the time of admission (Fig. 1B). On day 2 of hospitalization, the ovarian teratomas were resected laparoscopically. PE was started for treatment of anti-NMDA receptor encephalitis on day 5. A total of 2.8 L (body weight 50 kg) of plasma was exchanged over approximately 2 h with 2.8 L of fresh frozen plasma in every cycle. A total of 7 sessions (day 5, 10, 11, 12, 15, 16 and 17) were implemented. PHT level on day 4 was 8.0 µg/mL. From day 10,

we changed the administration dose of fPHT on PE days from 325 mg/d at 6:00 to 1125 mg after PE, and PHT levels increased >10 μg/mL. The incidence of seizures requiring administration of an additional antiepileptic drug was frequently observed until day 25. After that, IVIg therapy (0.4 g/kg day 22–26 and day 84–88) and IVMP therapy (day 45–47, 77–79 and day 106–108) as additional treatments for the remaining symptoms of anti-NMDA receptor encephalitis were performed, and most symptoms disappeared. She was discharged on day 128 with mild cognitive dysfunction.
As shown in Table 1, there were no clinically sufficient differences between the area under the concentration-time curve (AUC) during PE and AUC without PE in all measurements. Additionally, serum albumin levels in patient 1 and 2 were at the range from 3.5 to 4.0 and from 3.2 to 3.8, respectively (Fig. 1A and 1B).

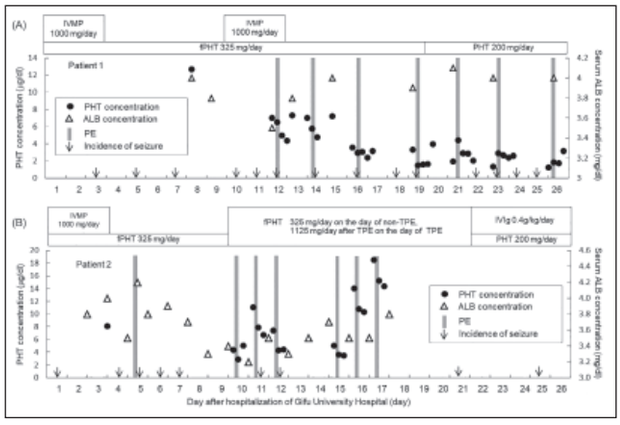

Figure 1: Time course of serum PHT concentration, and incidence of seizure in patient 1 (A) and patient 2 (B). PHT: Phenytoin; fPHT: fosphenytoin; ALB: Albumin; PE: Plasma exchange; IVMP: intra venous methylprednisolone pulse therapy; IVIg: intra venous immunoglobulin therapy

Table 1: Comparison between the AUC of phenytoin during PE and without PE

Patient 1

	(a) AUC during PE (mg·h/mL)	(b) AUC without PE (mg·h/mL)	(a)/(b)
Day 12	171.26	175.93	0.97
Day 14	194.07	195.82	0.99
Day 16	119.30	118.38	1.01
Day 19	223.19	221.32	1.01

Patient 2

	(a) AUC during PE (mg·h/mL)	(b) AUC without PE (mg·h/mL)	(a)/(b)
Day 10	246.11	231.43	1.06
Day 11	462.61	458.60	1.01
Day 12	591.69	584.01	1.01
Day 15	204.71	201.05	1.02
Day 16	493.50	484.43	1.02
Day 17	558.89	550.97	1.01

AUC: Area under the concentration-time curve, PE: Plasma exchange

3. Discussion

We describe two patients with anti-NMDA receptor encephalitis who were being treated with PE and were receiving fPHT whose serum PHT levels were difficult to maintain in the therapeutic range during treatment of PE. We showed in a pharmacokinetic analysis that PE does not influence the serum PHT concentration in patients receiving intravenous fPHT therapy.

fPHT is converted to PHT within 2 h after administration by alkaline phosphatase in blood and tissue (Gerber et al. 1988). In these patients, PE was implemented 8 h after fPHT administration; and we assumed that almost all fPHT had been converted to PHT. However, as seizures were uncontrolled for a few weeks from the time of admission in patient 1 while receiving the manufacturer's recommended dosage of fPHT, we examined PHT concentration during treatment with plasma exchange retrospectively. The serum PHT levels decreased in a time-dependent manner. Thus, in patient 2, we changed the administration dose of fPHT on PE days from 325 mg/d at 6:00 to 1125 mg after PE, the PHT level increased to >10 μg/mL. To our knowledge, there have been no reports on the pharmacokinetics of fPHT in patients undergoing PE. Thus, we evaluated the effect of PE on PHT levels in the patients in this study. On pharmacokinetic analysis, however, we saw no statistically significant difference between AUC during PE and AUC without PE. However, we could not examine the unbound PHT concentration in this study. Serum albumin level in patient 1 was in a normal range (3.5 - 4.0) and in patient 2, it was almost normal (3.2-3.8). Montgomery et al. (2019) reported that total PHT concentrations reflect unbound concentrations of PHT in patients with normal albumin concentrations, and measuring or estimating free PHT concentrations is unnecessary. Thus, we thought that the ratio of PHT unbound fraction largely unaffected by PE.
PHT is metabolized to 5-(4'-hydroxyphenyl)-5-phenylhydantoin and its glucuronide conjugate by CYP2C9 or CYP2C19 in the liver and excreted in urine (Veronese et al. 1991; Bajpai et al. 1996). PHT induces the expression of CYP3A4, CYP2B6, and p-glycoprotein (Faucette et al. 2004). Patients 1 and 2 did not have severe hepatic dysfunction and did not receive drugs that influence PHT metabolism.
We recently reported that prolonged use of fPHT is accompanied by a decrease in PHT level, and a concomitant increase in the risk of convulsion, in patients who received intravenous fPHT therapy, necessitating an increase in dose (Ohno et al. 2018). In addition, we also recommended as simulated by Bayesian analysis that patients requiring intravenous fPHT treatment for longer than 2 d require an increased dose of 780 mg/day. These findings are reflected in the case of patient 2, in which PHT levels were increased >10 μg/mL by changing the dose of fPHT at the time of PE from 325 mg/day at 6:00 to 1125 mg just after PE. Therefore, we concluded that the low PHT levels in patient 2 were induced by an insufficient maintenance dose of fPHT.
Some patients with encephalitis cannot tolerate oral PHT due to vomiting and/or autonomic gastrointestinal dysfunction. These patients also often require PHT treatment for long periods. We therefore consider that it is necessary to increase the maintanance dose of fPHT in these patients, and that this requirement is not influenced by PE.
In conclusion, dose adjustment of fPHT in patients undergoing PE may be unnecessary, except when the expected maintenance dose needs to be increased to maintain a therapeutic PHT concentration following fPHT use for more than 2 d. Further large scale studies including examination of the unbound PHT concentration are needed to elucidate them.

4. Experimental

4.1. Pharmacokinetic analysis

To evaluate the effect of PE on fPHT pharmacokinetics, blood sampling was conducted 46 times in total for each patient. Of these, 16, 10, 10 and 10 samples were taken in the morning (6:00) before injection of fPHT, immediately before PE, immediately after PE, and 2 h after PE, respectively. PHT in plasma was determined by particle-enhanced turbidimetric inhibition immunoassay using a phenytoin reagent set (Dimension® Flex reagent cartridge PTN, Siemens Healthcare Diagnostics, Tokyo, Japan) and automatic analyzer (Dimension® EXL 200 Integrated Chemistry System, Siemens Healthcare Diagnostics, Tokyo). AUC of phenytoin during implementation of PE was estimated from the blood concentration immediately before, immediately after and 2 h after implementation of PE. AUC was estimated based on the trapezoid method. The AUC of PHT during the periods that PE was not implemented was estimated from the blood concentration in the morning and immediately before implementation of PE.

4.2. Ethical considerations

This study was conducted in accordance with the guidelines for human studies adopted by the ethics committee of Gifu University Graduate School of Medicine, and notified by the Japanese government (institutional review board approval no. 2019-024).

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