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Original article

Efficacy and safety of fosphenytoin for benign convulsions with mild gastroenteritis

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Abstract

Objective: To clarify the efficacy and safety of fosphenytoin for seizures in children with benign convulsions and mild gastroenteritis.

Methods: Using the mailing list of the Annual Zao Conference on Pediatric Neurology, we recruited patients who met the following criteria: (1) clinical diagnosis of benign convulsions with mild gastroenteritis and (2) treatment with intravenous fosphenytoin. Benign convulsions with mild gastroenteritis were defined as a condition of (a) seizures associated with gastroenteritis without electrolyte imbalance, hypoglycemia, or dehydration in patients (b) between 6 months and 3 years of age with (c) no preexisting neurological disorders, (d) no impaired consciousness, and (e) a body temperature less than 38.0 °C before and after the seizures. The efficacy of fosphenytoin was categorized as effective when cessation of seizures was achieved.

Results: Data from 16 child patients were obtained (median age, 20 months). Seizures were completely controlled after the initial dose of fosphenytoin in 14 of 16 patients. The median loading dose of fosphenytoin was 22.5 mg/kg. In 10 patients, fosphenytoin was administered after other antiepileptic drugs such as diazepam and midazolam were used. Adverse effects of fosphenytoin, excessive sedation, or intravenous fluid incompatibility were not observed in any patients.

Conclusion: Fosphenytoin is effective and well tolerated among children with benign convulsions with mild gastroenteritis.

Keywords: Fosphenytoin; Benign convulsions with mild gastroenteritis; Efficacy; Safety

1. Introduction

Benign convulsions with mild gastroenteritis (CwG) were first reported by Morooka [1]. CwG is characterized by seizures, often occurring in clusters, associated with gastroenteritis in healthy children between 6 months and 3 years of age who have normal laboratory data, cerebrospinal fluid, interictal electroencephalogram results, and developmental outcomes [2,3]. CwG has been established as a benign condition with no neurological sequelae [3,4]. However, a diagnosis of CwG may not be easy during the first few hours after onset.

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A large majority of patients have a cluster of seizures, and clinicians may consider intensive antiepileptic treatment, even when CwG is suspected on the basis of clinical observation. In such situations, an effective and safe regimen of antiepileptic treatment is desirable. At present, the efficacies of carbamazepine (CBZ) and lidocaine (LD) have been confirmed [2,5,6].

Phenytoin (PHT) is an efficacious antiepileptic drug for status epilepticus or clustering seizures. One of the important advantages of PHT is its lesser effect on the level of consciousness [7]. There have been a few reports on the efficacy of PHT against CwG [8]. However, pediatricians and pediatric neurologists in Japan tend to avoid using PHT because of its adverse effects, including local irritation, phlebitis, intravenous fluid incompatibility, and purple glove syndrome. Fosphenytoin (fPHT) is a water-soluble prodrug of PHT with a neutral pH value that is expected to be as effective for CwG as phenytoin. Adverse effects of fPHT are presumed to occur less frequently than those of PHT.

We had planned a retrospective cohort study on the efficacy and safety of fPHT in children with acute encephalopathy using the mailing list of the Annual Zao Conference on Pediatric Neurology. Originally, we recruited patients who met the following criteria: (1) clinical diagnosis of acute encephalopathy, and (2) use of intravenous fPHT for treatment of seizures. However, we found that some children with CwG were included in the cohort. Because the efficacy and safety of fPHT for CwG have not been elucidated, we decided to summarize their data. Here we describe clinical data from children with CwG treated with fPHT.

2. Methods

We identified patients from the mailing list of the Annual Zao Conference on Pediatric Neurology who met the following criteria: (1) clinical diagnosis of CwG, and (2) treatment with intravenous fPHT. According to previous studies, CwG was defined as a condition of (a) seizures associated with gastroenteritis without electrolyte imbalance, hypoglycemia, or dehydration in patients (b) between 6 months and 3 years of age with (c) no preexisting neurological disorders, (d) no impaired consciousness, and (e) a body temperature less than 38.0 °C before and after the seizures [2,3]. The mailing list of the Annual Zao Conference includes more than 700 pediatric neurologists throughout Japan. From January 2012 to November 2013, we requested enrollment of the patients using the mailing list and provided a structured research form. The members of the mailing list were asked to fill out the research form if they had patients meeting the specified criteria. The completed research forms were returned to the first author by email. This study was approved by the institutional review board of Juntendo University Faculty of Medicine. The patients' data were collected anonymously.

The following items were included in the research form: age, gender, preexisting medical conditions, prodromal illness and its pathogen, onset of gastroenteritis, type of seizure (status epilepticus or clustering seizures), and fPHT outcome, efficacy, and adverse events. We also asked the participants to describe their seizure time course and use of antiepileptic drugs. According to our previous study [9], the efficacy of fPHT was categorized as follows based on clinical observations: effective: cessation of seizures; partially effective, 50% or more reduction in frequency and/or duration of seizures; ineffective, incompatible with the previous two conditions.

3. Results

Data from 16 child patients were obtained from three hospitals. The characteristics of these 16 patients are summarized in Table 1. All of them received a single fPHT administration course. The median loading dose of fPHT was 22.5 mg/kg (range, 20–25 mg/kg). The median rate of injection was 0.79 mg/kg/min (range, 0.67–3.0 mg/kg/min).

Among the patients (10 males and 6 females), the age at onset of CwG ranged from 12 to 49 months (median, 20 months). Five patients had a past history of febrile convulsions. No patient had a family history of epilepsy. Head CT and MRI were performed in one patient each and did not reveal any abnormalities. The median interval between the onset of gastroenteritis and that of seizure was 1 days (range, 0–4 days). The pathogens of gastroenteritis were rotavirus in three patients, norovirus in one, and unknown in 12. Before intravenous fPHT administration, no drugs were used in six patients, diazepam in five, midazolam in four, and diazepam plus thiopental in one. In four patients, fPHT was used after the occurrence of one seizure. The others experienced two or more seizures before administration of fPHT.

No seizures occurred in 14 of 16 patients after administration of fPHT. Thus, fPHT was deemed to be effective in these 14 patients. PHT levels in the serum were measured in five patients. The median concentration was 10.42 μg/mL (range, 1.0–10.7 μg/mL) 15–24 h after initial administration. Only the loading dose was given to 14 patients; the other two also received one maintenance dose of 7.5 mg/kg.

The clinical course of the two patients in whom fPHT was ineffective was as follows. Patient 5 was a 49-month-old boy with a past history of two febrile seizures and delayed psychomotor development. Diarrhea and vomiting due to rotavirus infection appeared on the day before seizure onset. He had a generalized seizure lasting for several minutes and was admitted to our hospital. He was treated with 22.5 mg/kg intravenous fPHT. Immediately afterward, he had a seizure with loss of