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Original article

Efficacy and safety of fosphenytoin for acute encephalopathy in children

Mika Nakazawa [a,b,*], Manami Akasaka [c], Takeshi Hasegawa [d], Tomonori Suzuki [e], Taiki Shima [a,f], Jun-ichi Takanashi [g], Atsuko Yamamoto [h], Yuuki Ishidou [i], Kenjiro Kikuchi [j], Shinichi Niijima [b], Toshiaki Shimizu [a], Akihisa Okumura [a,k]

[a] *Department of Pediatrics, Juntendo University Faculty of Medicine, Japan*
[b] *Department of Pediatrics, Juntendo University Nerima Hospital, Japan*
[c] *Department of Pediatrics, Iwate Medical University Faculty of Medicine, Japan*
[d] *Department of Pediatrics, Soka Municipal Hospital, Japan*
[e] *Department of Pediatrics, Kawaguchi Municipal Medical Center, Japan*
[f] *Department of Neuropediatrics, Nagano Children's Hospital, Japan*
[g] *Department of Pediatrics, Kameda Medical Center, Japan*
[h] *Department of Pediatrics, Tsuchiura Kyodo General Hospital, Japan*
[i] *Department of Pediatrics, St. Mary's Hospital, Japan*
[j] *Division of Neurology, Saitama Children's Medical Center, Japan*
[k] *Department of Pediatrics, Aichi Medical University, Japan*

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Abstract

Purpose: To evaluate the efficacy and safety of fosphenytoin (fPHT) for the treatment of seizures in children with acute encephalopathy.

Methods: Using responses from physicians on the Annual Zao Conference on Pediatric Neurology mailing list we chose patients who met the following criteria: clinical diagnosis of acute encephalopathy and use of intravenous fPHT for the treatment of seizures. We divided the patients into two groups: acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) and other encephalopathies. The efficacy of fPHT was considered effective when a cessation of seizures was achieved.

Results: Data of 38 children were obtained (median age, 27 months). Eighteen children were categorized into the AESD group and 20 into the other encephalopathies group. fPHT was administered in 48 clinical events. The median loading dose of fPHT was 22.5 mg/kg and was effective in 34 of 48 (71%) events. The rate of events in which fPHT was effective did not differ according to the presence or absence of prior antiepileptic treatment, subtype of acute encephalopathy, or the type of seizures. One patient experienced apnea and oral dyskinesia as adverse effects of fPHT, whereas arrhythmia, hypotension, obvious reduction of consciousness, local irritation, phlebitis and purple grove syndrome were not observed in any patient.

Conclusion: fPHT is effective and well tolerated among children with acute encephalopathy.

Keywords: Fosphenytoin; Acute encephalopathy; Acute encephalopathy with biphasic seizures and late reduced diffusion; Efficacy; Safety

* Corresponding author. Address: Department of Pediatrics, Juntendo University Faculty of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. Tel.: +81 3 3813 3111; fax: +81 3 5800 1580.
E-mail address: mknakaza@juntendo.ac.jp (M. Nakazawa).

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1. Introduction

Seizures are one of the most common neurological symptoms among children with acute encephalopathy and evolve often into status epilepticus. The early cessation of seizures is generally accepted as desirable to improve the outcome in children with encephalopathy. However, seizures in children with acute encephalopathy are often refractory to antiepileptic drugs.

Recently in Japan, treatment for acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), a characteristic subtype of acute encephalopathy in children, has become an important issue. AESD is characterized by prolonged seizure onset or status epilepticus followed by secondary seizures (late seizures) associated with deterioration of consciousness and widespread reduced diffusion in the subcortical white matter on magnetic resonance imaging (MRI) [1]. Late seizures occur usually in clusters and are refractory to antiepileptic drugs. Seizure control is also important in children with other subtypes of acute encephalopathy, such as acute necrotizing encephalopathy (ANE) [2] and acute disseminated encephalomyelitis (ADEM).

Phenytoin (PHT) is a useful antiepileptic drug for the treatment of seizures in children with acute encephalopathy. PHT has a lesser effect on the level of consciousness [3] and we previously reported its efficacy for seizures in children with AESD [4]. However, PHT has been known to occasionally cause local irritation, phlebitis and intravenous fluid incompatibility. Purple glove syndrome is also known as a rare but serious side effect of PHT. Thus, pediatricians and pediatric neurologists in Japan tend to avoid administering PHT. Fosphenytoin (fPHT) is a water-soluble prodrug of PHT with a neutral pH value. The adverse effects of fPHT are less frequent than those of PHT. fPHT was marketed in Japan in 2011 and given to children with several subtypes of acute encephalopathy. At present, the efficacy and safety of fPHT for the treatment of acute encephalopathy in children have not been elucidated. We collected clinical data of children with acute encephalopathy treated with fPHT to determine its efficacy and safety. We also focused on the efficacy of fPHT in Japanese children with AESD, a common and problematic subtype of acute encephalopathy [5].

2. Methods

Using responses from physicians on the Annual Zao Conference on Pediatric Neurology mailing list we chose patients who met the following criteria: clinical diagnosis of acute encephalopathy and use of intravenous fPHT for the treatment of seizures. In this study, acute encephalopathy was defined as a condition characterized by decreased consciousness with or without other neurological findings, such as delirious behavior and seizures, lasting for 24 h or longer in children with infectious symptoms including fever, cough and diarrhea. The Annual Zao Conference mailing list includes more than 700 pediatric neurologists throughout Japan. From January 2012 to November 2013, we asked for enrollment of patients through the mailing list. A structured research form was given to the members of the mailing list to fill out if they had patients meeting the 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 patient data were collected anonymously.

The following items were included in the research form: age, gender, subtypes of acute encephalopathy, preexisting medical condition, prodromal illness and its pathogen, onset of acute encephalopathy, EEG monitoring, type of seizure (status epilepticus or clustering seizures), treatment for acute encephalopathy (steroids, intravenous gamma globulin, hypothermia), outcome, efficacy and adverse events of fPHT. We also asked the participants to describe the scheme of seizure time course and the use of antiepileptic drugs. In this study, AESD was defined as acute encephalopathy presenting with onset of prolonged seizures or status epilepticus, biphasic clinical course characterized by late worsening of consciousness along with clustering seizures or status epilepticus and widespread reduced diffusion in the cortex and/or subcortical white matter involving unilateral or bilateral hemispheres [1]. Any encephalopathy that did not meet the definition of AESD was classified into other encephalopathies. The efficacy of fPHT was categorized as follows based on clinical observation: effective; cessation of seizures, partially effective; 50% or more reduction in frequency and/or duration of seizures, ineffective; incompatible with the former two conditions.

Statistical analysis of the efficacy rate between the two groups was performed by Fisher's exact probability test for qualitative variables using the SPSS Statistics version 17.0 software (SPSS Inc., Tokyo, Japan). Statistical significance was accepted at a level of $p < 0.05$.

3. Results

The data of 38 children were obtained from 16 hospitals. fPHT was administered for 48 clinical events.

3.1. Demographic data

Demographic data are shown in Table 1. The age at onset of acute encephalopathy ranged from 16 days to 163 months (median, 27 months). There were 22 males (58%) and 16 females (42%). Eighteen children were categorized into the AESD group and 20 into the other encephalopathies group. Among subjects with other encephalopathies, two children were diagnosed as