The relationship between drug treatment and the clinical characteristics of febrile seizures

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Original article

Background: **Drugs such as theophylline, antihistamines, and antiallergics with anti-histaminic actions have been shown to induce febrile seizures. The relationship between febrile seizures and medications has not been actively investigated. The present study aimed to investigate the relationship between the clinical characteristics of febrile seizures and the use of medications.**

Methods: **Two hundred and sixty-five children treated at our emergency room due to febrile seizures were studied to investigate the relationship between the clinical characteristics of febrile seizures, such as the type and duration of convulsions, and the drug treatment.**

Results: **The duration of convulsions was longer among children who took theophylline and antihistamines than among children who did not take these medications. Of the antihistamines, mequitazine did not prolong the duration of convulsion.**

Conclusions: **Theophylline should not be used in febrile children, particularly infants. Cautions should be taken in using histamine H1 antagonists in young infants because such drugs could potentially disturb the anticonvulsive central histaminergic system. However, mequitazine appears to be a suitable antihistamine for use in children with febrile seizures, since it does not prolong convulsions.**

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Introduction

Febrile seizures develop in infants or young children in association with fever, and the neurological and developmental prognosis of such patients is good, unlike that of patients with central nervous infections or acute encephalopathy. The prevalence of febrile seizures is relatively high (7%-8%) in Japan,[1] theophylline is widely used as a basic bronchodilator in asthmatic children and other patients with severe cough. But recent papers have reported that theophylline can induce convulsions.[2-4] With respect to the relationship between convulsive disorders and histaminic drugs, Churchill and Gammon[5] first reported that antihistamines, such as diphenhydramine and tripelennamine, activated epileptic discharges on electroencephalography (EEG) and produced clinical manifestations of psychomotor seizures in adult epileptic patients. Drugs such as theophylline, antihistamines, and antiallergics with antihistaminic actions have been shown to induce febrile seizures.[2-8] In the patients who are suspected of having drug-induced febrile seizures, however, reproducibility is not high, and other factors, such as fever and infection, can induce febrile seizures. Furthermore, the relationship between febrile seizures and medications has not been actively investigated.

In the present study, children who visited our emergency room because of febrile seizures were investigated using a checklist designed to collect information to assess the relationship between the clinical characteristics of febrile seizures (type and duration) and the use of medications.

Methods

Children aged 6 months to 6 years were treated at the emergency room of the Nihon University Nerima Hikarigaoka Hospital, Tokyo, Japan, from November 2001 to July 2002, and from December 2002 to March 2003. They were diagnosed as having febrile seizures according to the guidelines for the management of febrile

seizures.[1] Seizure events in infants or young children accompanied by a temperature of 38ºC or higher were defined as febrile seizures. Patients with seizures with definable causes such as acute central nervous infections, acute encephalopathy, intracranial lesions, and acute abnormal metabolism as well as seizures associated with fever in patients with a history of afebrile seizure were excluded from the febrile seizure group.

In the emergency room, the attending physicians used the checklist to ascertain the following items: age; sex; the disease causing the fever; the presence of diarrhea; the number, type, and duration of convulsions; the history of seizure disorders in first-degree relatives; maximum temperature measured in the axilla immediately after seizure occurrence; underlying disease; and medications administered before seizure occurrence. Particular attention was paid to theophylline and antihistamines because they have been shown to induce convulsions. With respect to antihistamines, the duration of convulsions was investigated for mequitazine separately from the other antihistamines (chlorpheniramine, cyproheptadine, oxatomide, and ketotifen). Informed consent was obtained from the patients' parents. The Mann-Whitney non-parametric test was used for the statistical analysis. Differences were considered statistically significant at a $P<0.05$.

Results

Clinical characteristics of febrile seizure episodes

Of the 273 patients with febrile seizures who were treated in our hospital during the study period, 265 (97.1%) presented no evidence of a specific etiology. Eight patients were excluded from the study with a history of afebrile seizure and mental retardation. Thus, 265 patients with febrile seizures (145 males and 120 females) were enrolled in the present study. The clinical characteristics of the patients with febrile seizures are shown in Table 1.

Relationship between drug treatment and seizures

The relationship between the use of drugs and seizure duration is shown in Table 2. The 125 children who did not take theophylline or antihistamines showed an average duration of seizure for 4.8±6.5 minutes. The duration was less than 5 minutes in 87 patients (69.6%), and the seizure persisted for 15 minutes or longer in 11 patients (8.8%). The 52 children who only took antihistamine had an average seizure duration of 4.5±5.8 minutes; seizure duration was less than 5 minutes in 36 patients (69.2%), and the seizure persisting for 15 minutes or longer was noted in 4 patients (7.7%). The 8 patients who only took theophylline had an average seizure duration of 9.1±11.3 minutes; seizure duration was less than 5 minutes in 3 patients (37.5%), and the seizure persisted for 15 minutes or longer in 1 patient (12.5%). The 11 children who took both theophylline and an antihistamine drug had an average seizure duration of 7.0±6.1 minutes; seizure duration was less than 5 minutes in 7 patients (63.6%), and the seizure persisted for 15 minutes or longer in 2 patients (18.2%). The data for mequitazine and the other antihistamines are shown in Fig. The 5 children who took theophylline and mequitazine had an average seizure duration of 3.8±3.6 minutes. The 6 children who took theophylline and an antihistamine drug other than mequitazine had an average seizure duration of 9.7±6.8 minutes. The seizure duration tended to be longer among children who took theophylline and antihistamines than among those who did not take these medications. Of the various antihistamines, mequitazine did not prolong the seizure duration. There was a significant difference

Table 1. Clinical characteristics of the 265 patients

Variables	*n* (%)
Male	145 (54.7)
Age (mean±SD)	29.7±16.9 mon
Positive history of seizures in first-degree relatives	105 (39.6)
Times of previous febrile seizures	
None	183 (69.1)
One time	42 (15.8)
Two times	22 (8.3)
Three times	9 (3.4)
Four times	6 (2.3)
More than four times	3 (1.1)
Body temperature at seizure occurrence (mean±SD)	39.4±0.8ºC
Seizure manifestations	
Generalized tonic-clonic convulsions	253 (95.5)
Seizure durations	
Average (mean±SD)	4.7±6.4 min
Within 5 min	184 (69.4)
From more than 5 to less than 15 min	60 (22.6)
From 15 to less than 30 min	13 (4.9)
30 min or more	8 (3.0)
Diarrhea	40 (15.1)
No medications before seizure occurrence	125 (47.2)

Table 2. Relationship between drug treatment and seizure duration

Drug treatment	*n*	Duration (min)
No drugs	125	4.8±6.5*
Antihistamine only	52	4.5±5.8
Theophylline only	8	9.1±11.3
Theophylline and antihistamine	11	7.0±6.1
Theophylline and mequitazine	5	3.8±3.6
Theophylline and antihistamine other than mequitazine	6	9.7±6.8*

*: $P<0.05$, comparison between childrn who took no drug and those who took theophylline and an antihistamine other than mequitazine.

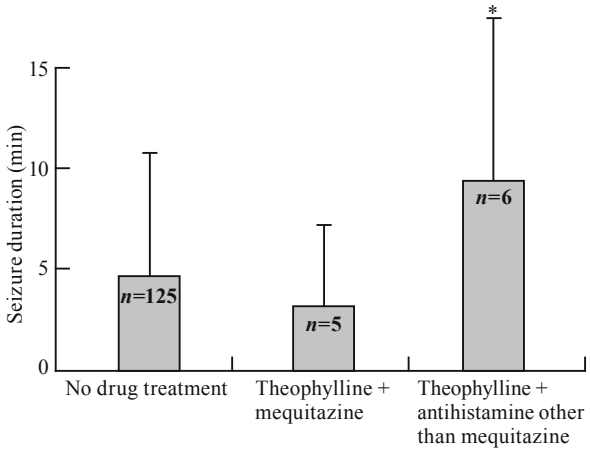

Fig. Relationship between drug treatment and seizure duration.
*: $P<0.05$, compared with the group with no drug treatment.

in the seizure duration between children who did not took theophylline or antihistamine and those who took theophylline and an antihistamine other than mequitazine ($P<0.05$).

Discussion

In the present study, seizure duration tended to be longer in the patients with febrile seizures who took theophylline and antihistamines than in those who did not take theophylline or antihistamines. Compared to the other antihistamines, mequitazine had less effect on the central nervous system[9] and did not prolong the seizure duration when taken with theophylline. Thus, mequitazine does not prolong the seizure duration, but antihistamines other than mequitazine increased the seizure duration.

Theophylline is widely used as a bronchodilator for the treatment of bronchial asthma and neonatal apnea.[10] However, several reports have shown that theophylline at therapeutic doses occasionally induces convulsions and status epilepticus in children, particularly in infants and younger children.[10,11] Since fever can induce asthmatic attack, theophylline is often given to children with febrile seizures.

According to Hirano and colleagues,[12] a significant number of children on theophylline therapy who developed febrile seizure had seizures lasting longer than 10 minutes. Previously, theophylline was thought to suppress the synthesis of gamma-aminobutyric acid (GABA), a neurotransmitter that suppresses seizures. Continuous theophylline administration has been shown to significantly decrease blood vitamin B6 levels, as theophylline functions as a coenzyme for vitamin B6 synthesis.[13]

Anti-allergics with antihistaminic actions (histamine H1 antagonists) are often co-administered with theophylline. Histamine H1 antagonists suppress the reactions caused by histamine release, which is involved in the onset of type I allergies. It has been shown that histamine acts as a neurotransmitter in the central nervous system and is involved in the suppression of seizures via histamine receptors.[14] Yokoyama et al[15] reported that histamine H1 antagonists exacerbated seizures in juvenile mice.

Anti-histaminic drugs are classified into two categories: sedative or first-generation drugs (e.g., ketotifen, chlorpheniramine) and non-sedative or second-generation drugs (e.g., epinastine). Terfenadine, astemizole and mequitazine are among the first compounds to be introduced as non-sedating, second-generation antihistamines in the 1980s. Mequitazine is one of the earliest second-generation antihistamines on the market.[9]

Kiviranta et al[16] evaluated the possible role of histamine in the pathomechanism of febrile seizures by measuring histamine concentrations in the cerebrospinal fluid of children with febrile seizures. Febrile children without seizures had a significantly higher histamine concentration than children with febrile seizures, while non-febrile children with seizures and non-febrile children without seizures had similar histamine concentrations. The increased susceptibility to seizures during fever may be related to a lack of increase in the cerebrospinal fluid histamine level in children with febrile seizures. Central histaminergic neuron systems may be involved in inhibiting seizures associated with febrile illnesses in childhood.

Yokoyama et al[14] investigated the use of drugs, including histamine H1 antagonists, in children with febrile seizures. Histamine H1 antagonists were taken by 10 (45.5%) of 22 patients with febrile seizures and 10 (22.7%) of 44 control subjects; the use of histamine H1 antagonists was significantly higher in the patients with febrile seizures than in the control subjects. The histamine H1 antagonists taken by the children in that study were carbinoxamine and promethazine, which are present in over-the-counter drugs for common cold.

Antihistamines induce seizures in healthy and epileptic children; oxatomide and ketotifen have been shown to cause West syndrome,[17,18] and chlorpheniramine and mequitazine can induce localization-related epilepsy.[19] Classical anti-histaminics such as diphenhydramine, methapyrilene, tripelennamine and pyranisamine are associated with seizures, especially in children under 2 years of age.[5-6] For young infants, the histaminergic system, developmentally an older neuron system than the GABA system, plays an important role in inhibiting seizures. Thus, histamine H1 antagonists might induce

seizures. Second-generation drugs, such as terfenadine, epinastine, and evastin are histamine H1 antagonists that are less likely to pass through the blood-brain barrier. Thus, these drugs are safer than first-generation drugs in young children including those with febrile seizures and epilepsy. However, these drugs are usually available only in tablet form; only epinastine is available in liquid and dry-syrup formulation.

In conclusion, due to their central nervous system effects, H1 antagonists and theophylline should not be co-administered to patients with febrile seizures and epilepsy. Theophylline should be avoided in febrile children, particularly infants. Furthermore, cautions should be taken on the use of histamine H1 antagonists in young infants because these drugs could potentially disturb the anticonvulsive central histaminergic system. In the present study, however, mequitazine appears to be a suitable antihistamine for use in children with febrile seizures, since it does not prolong the seizure duration.

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References

1 Seki T, Otsuka T, Miura H, Hara M. Guidelines for the management of febrile seizures (in Japanese). Jpn J Pediatr (Tokyo) 1996;49:207-215.
2 Korematsu S, Miyahara H, Nagakura T, Suenobu S, Izumi T. Theophylline-associated seizures and their clinical characterizations. Pediatr Int 2008;50:95-98.
3 Weinberger M, Hendeles L. Theophylline in asthma. N Engl J Med 1996;334:1380-1388.
4 Bahls FH, Ma KK, Bird TD. Theophylline-associated seizures with "therapeutic" or low toxic serum concentrations: risk factors for serious outcome in adults. Neurology 1991;41:1309-1312.
5 Churchill JA, Gammon GD. The effect of antihistaminic drugs on convulsive seizures. J Am Med Assoc 1949;141:18-21.
6 Wyngaarden JB, Seevers MH. The toxic effects of antihistaminic drugs. J Am Med Assoc 1951;145:277-283.
7 Schwartz JF, Patterson JH. Toxic encephalopathy related to antihistamine-barbiturate antiemetic medication. Am J Dis Child 1978;132:37-39.
8 Yokoyama H. The role of central histaminergic neuron system as an anticonvulsive mechanism in developing brain. Brain Dev 2001;23:542-547.
9 Theunissen EL, Vermeeren A, van Oers AC, van Maris I, Ramaekers JG. A dose-ranging study of the effects of mequitazine on actual driving, memory and psychomotor performance as compared to dexchlorpheniramine, cetirizine and placebo. Clin Exp Allergy 2004;34:250-258.
10 Gaudreault P, Guay J. Theophylline poisoning. Pharmacological considerations and clinical management. Med Toxicol 1986;1:169-191.
11 Yoshikawa H. First-line therapy for theophylline-associated seizures. Acta Neurol Scand Suppl 2007;186:57-61.
12 Hirano Y. Theophylline-associated seizures (in Japanese). Pediatr Japan (Tokyo) 1994;35:1385-1391.
13 Weir MR, Keniston RC, Enriquez JI, McNamee GA. Depression of vitamin B6 levels due to theophylline. Ann Allergy 1990;65:59-62.
14 Yokoyama H, Iinuma K. Histaminergic neurons and epilepsy. Methods Find Exp Clin Pharmacol 1996;18(Suppl A):181-186.
15 Yokoyama H, Onodera K, Iinuma K, Watanabe T. Proconvulsive effects of histamine H1-antagonists on electrically-induced seizure in developing mice. Psychopharmacology (Berl) 1993;112:199-203.
16 Kiviranta T, Tuomisto L, Airaksien EM. Histamine in cerebrospinal fluid of children with febrile convulsions. Epilepsia 1995;36:276-280.
17 Yamashita Y, Isagai T, Seki Y, Ohya T, Nagamitsu S, Matsuishi T. West syndrome associated with administration of a histamine H1 antagonist, oxatomide. Kurume Med J 2004;51:273-275.
18 Yasuhara A, Ochi A, Harada Y, Kobayashi Y. Infantile spasms associated with a histamine H1 antagonist. Neuropediatrics 1998;29:320-321.
19 Hamada Y, Hirao T, Kurokawa K, Akutagawa H, Kakiuchi T. Seizures induced by two kinds of antihistaminergic drugs and carbamazepine—a case report of localization-related epilepsy (in Japanese). Jpn J Pediatr 1999;52:105-109.

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