

INTERMITTENT CLONAZEPAM IN THE PREVENTION OF RECURRENT FEBRILE SEIZURES

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Abstract

Objective

To evaluate the efficacy and common side effects of intermittent clonazepam in febrile seizures.

Materials & Methods

This study was an experimental trial designed to determine the efficacy of intermittent clonazepam in febrile seizures. Thirty patients with an age range of 6 months to 5 years (60% male, 40% female) were studied. Children with a history of psychomotor delay, abnormal neurological examination, a history of antiepileptic drug consumption, and afebrile seizures were excluded from the study. Patients received a single dose of prophylactic Clonazepam (0.05 mg/kg/day) on the first day of febrile illness and twice daily during the course of fever. An antipyretic medication (Acetaminophen) was advised if fever exceeded 38°C. Patients were followed up for one year after the study inclusion date.

Results

Three patients were excluded from study since they did not follow the treatment and three patients experienced afebrile seizures. Twenty four patients had 162 febrile episodes during the course of the study and all patients were seizure-free after 1 year.

Conclusion

Clonazepam was 100% effective but lethargy and ataxia were common side effects in patients. Fortunately, their parents continued treatment because they had prior awareness of the possible side effects of clonazepam. Clonazepam is efficacious as an intermittent therapy for febrile seizures if parents are informed of its side effects.

Keywords: recurrent febrile seizures, clonazepam, intermittent prophylaxis

Introduction

A febrile seizure (FS) is defined as seizure activity associated with a fever in a previously healthy child between 6 months and 5 years of age, who has no evidence of intracranial infection or defined cause, and no prior history of afebrile seizures. Another definition from the International League Against Epilepsy (ILAE) is a seizure occurring in childhood after 1 month of age associated with a febrile illness not caused by an infection of the central nervous system (CNS), without a previous neonatal seizure or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures (1). Febrile seizures are the most common convulsion event in childhood; they occur in 2-5% of the children below 5 years of

age. The probability of recurrent simple febrile seizures is 50% for children younger than 12 months at the time of the first seizure and 30% for children older than 12 months. Of those children who do have a second febrile seizure, 50% have a chance of having at least 1 additional recurrence (2). Risk factors for recurrent febrile seizures include (1) those with the first seizure occurring below the age of 12 months, (2) family history of febrile seizures in a first-degree relative, and (3) children experiencing seizures with a low grade fever, a brief duration between the fever onset and the initial seizure, and multiple initial febrile seizures during the same episode (1, 2, 3).

Although the etiology of febrile seizures is unknown, it is thought to be genetic with an autosomal dominant pattern of inheritance with reduced penetrance. Although the exact molecular mechanisms of febrile seizures are yet to be understood, underlying mutations have been found in genes encoding sodium channels and gamma-aminobutyric acid A receptors. Both of these channels are also associated with severe myoclonic epilepsy of infancy, which often begins with prolonged febrile seizures (either complex febrile seizures or febrile status) and with subsequent seizures precipitated by fever (3, 4).

Febrile seizures are very strongly related to mesial temporal sclerosis. There are reports of a relationship between temporal lobe epilepsy and mesial temporal sclerosis and prolonged febrile seizure in infancy. Some studies have shown a relationship between complex infantile febrile seizures and mesial temporal sclerosis. Patients with complex febrile seizures (duration >15 min, evidence of focal or lateralized convulsive activity, or >3 seizures within 24 h) have an increased incidence of mesial temporal sclerosis. Based on the number of complex features, the incidence of mesial temporal sclerosis in patients who have had complex febrile seizures is 4-50 %. (5, 6, 7, 8).

The goal of long-term treatment is to prevent recurrent febrile seizures. This is achieved either by continuous long-term anticonvulsant therapy or intermittent prophylaxis. Continuous anticonvulsant treatment may be effective for reducing recurrence in children with a history of simple febrile seizures, but is associated with adverse effects. For example, Phenobarbital is associated with cognitive impairments and behavioral adverse

effects (e.g., hyperactivity, irritability, aggressiveness). Doses of primidone at 15-20 mg/kg reduce the recurrence of febrile seizures. Side effects of Primidone include behavioral disturbances, irritability and sleep disturbances. Sodium valproate is effective in the prevention of recurrent febrile seizures. Adverse effects of sodium valproate are fatal hepatotoxicity, pancreatitis and gastrointestinal disturbances. Therefore, continuous therapy is effective in the prevention of simple febrile seizures in children but is not recommended because the risk for anticonvulsant toxicity outweighs its possible benefits (1-3). Benzodiazepines administered intermittently, only during the febrile episodes, have been found effective in preventing the recurrence of febrile seizures. Diazepam has been commonly used either orally or rectally, but high doses of Diazepam are required (1 mg/kg/day divided into 3 doses) for prophylaxis. Since children are confused and ataxic after taking the first dose of Diazepam, their parents usually discontinue it. Many studies have reported the efficacy and safety of intermittent Clobazam in febrile seizures (9, 10).

Clonazepam is a benzodiazepine with a long half-life. Duration of action after a single dose is determined by redistribution rather than metabolism. Clonazepam is rapidly and completely absorbed after oral administration. Maximum plasma concentrations of clonazepam are reached within 1 to 4 hours after oral administration (11, 12). We studied the effect of oral Clonazepam for the prophylaxis of febrile seizures, because the half-life of Clonazepam is prolonged and even a single dose/day is enough for the prevention of seizures during a febrile illness.

Materials & Methods

In an experimental study between October 2005 and March 2006, thirty patients were enrolled from the outpatient child neurology clinic and inpatient emergency department in a teaching hospital (Alzahra Hospital), after obtaining clearance from the ethical committee of the institution. Inclusion criteria were children between 6 months and 5 years with one or more episodes of FS. Children less than 1 year of age at the time of the first attack and also children who were older than 1 year with two or more episodes of FS (with 50% chance of relapse)

were selected. Patients with intracranial infection, mental retardation, developmental delay, past history of afebrile seizures, systemic diseases (renal or hepatic dysfunction), and those taking antiepileptic drugs were excluded from the study. All patients had normal neurological exams and a negative family history of afebrile seizures. Clonazepam (0.05 mg/kg/day) was administered orally in a single dose on the first day of the disease. The same amount of Clonazepam was divided in 2 doses for oral administration on the following days of disease until the fever subsided (maximum 48-72 hours). Antipyretic treatment was given if fever exceeded 38°C. All patients were followed up every 3 months for a period of 1 year and the parents provided us with the episodes of febrile illnesses, seizures per febrile episode or afebrile seizure, and side effects of Clonazepam. Parents were informed of the side effects of Clonazepam, especially ataxia, sedation, and excessive salivation in young children.

Results

Thirty patients were enrolled in the study (characteristics of the patients are presented in Table 1 and 24 subjects continued the follow-up for 1 year. Three patients experienced afebrile seizures and continuous antiepileptic treatment was administered. Additionally, in three patients, seizure occurred before fever and their parents were not aware of their children's disease. Family history of FS was present in 50% of the cases. About 65% of the patients had simple febrile seizures and 25% had focal or multiple seizures (complex FS). There were 162 febrile episodes occurring in 24 patients during the follow-up period of 1 year but none of them experienced seizures. Drowsiness and ataxia were common side effects but none of the parents discontinued treatment.

Discussion

Febrile seizures are the most common etiology of seizure in children less than 5 years of age, especially in those less than 3 year of age. Treatment of febrile seizure is a controversial issue, since it is a benign disease and the adverse effects of antiepileptic drug administration, especially in infancy, might be even worse than recurrence of the seizure. On the other hand, recurrence of febrile seizures poses a stressful situation for the child's parents, either because they may be

prolonged or frequent or evolved into status epilepticus. Children with simple febrile seizures do not have an increased mortality risk. However, seizures that are complex and occur before 1 year of age, or are triggered by a temperature of 39°C are associated with a two-fold increased mortality rate during the first 2 years after seizure occurrence (1). Children with febrile seizures have a slightly higher incidence of epilepsy compared to the general population (2% vs. 1%). Risk factors for epilepsy later in life include complex febrile seizure, family history of epilepsy or neurological abnormality, and developmental delay. Patients with 2 factors have up to a 10% chance of developing afebrile seizures (1-3). The risk of developing epilepsy is increased in children with a history of complex febrile seizures. A strong association exists between febrile status epilepticus or febrile seizures characterized by focal symptoms and later development of temporal lobe epilepsy (4, 5). Parental anxiety regarding seizure recurrence and also lack of available medical services are the biggest problem for physicians who attend children with febrile seizures. The goal of long-term treatment is to prevent recurrent seizures, which is achieved either by long-term anticonvulsant therapy or intermittent prophylaxis. Continuous anticonvulsant prophylaxis for FS can effectively prevent recurrence in patients, but the side effects of continuous prophylaxis with Phenobarbital or Sodium Valproate may be worse than recurrence of the seizure. Diazepam has been commonly used either orally or rectally. Intermittent oral Diazepam is recommended for the prophylaxis of FS. The required high dose of Diazepam (1 mg/kg/day), and its short half-life, which requires it to be divided up and administered three times daily, as well as its adverse effects including somnolence, ataxia and irritability, often causes parents to discontinue Diazepam after the first dose and consequently seizure recurs.

Clobazam has been used successfully an intermittent anti-convulsive therapy for prevention of febrile seizures (9, 10).

Clonazepam has a plasma half-life of 20-43 h, and thus has a longer duration of action than Diazepam, Lorazepam or Midazolam. The oral absorption of Clonazepam is 80% or more. Peak levels are generally reached within 1-4 h after administration (11).

The studies concerning the effect of Clonazepam on prophylaxis in FS are limited and only few studies have mentioned Clonazepam as an intermittent prophylaxis for FS. In addition, there is no solid work available. We studied the effect of Clonazepam in the prophylaxis of FS with a single dose on the first day of febrile disease, followed by the same amount divided into two doses on the next days. The results showed that it was very effective in the prophylaxis of FS. We recommend oral Clonazepam administration upon observing the first symptom of the disease before fever is detected by parents or as soon as possible when the child is febrile. Other studies are recommended to further evaluate Clonazepam in the prophylaxis of FS.

Table 1. characteristics of the patients

Parameters	Detail
Mean age	24±12
Male: Female	16:14
Family history of the febrile seizure	15(out of 30)
Family history of epilepsy	8(out of 30)

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