TREATMENT OF FEBRILE SEIZURES WITH INTERMITTENT CLOBAZAM

MARIA LUIZA G. MANREZA, JOSÉ LUIZ D. GHERPELLI, LÚCIA R. MACHADO-HAERTEL, CRISTIANE C. COSTAS PEDREIRA, CARLOS O. HEISE, ARON DIAMENT

ABSTRACT - Fifty children, 24 female and 26 male, with ages varying from 6 to 72 months (mean=23.7 m.) that experienced at least one febrile seizure (FS) entered a prospective study of intermittent therapy with clobazam. Cases with severe neurological abnormalities, progressive neurological disease, afebrile seizures, symptomatic seizures of other nature, or seizures during a central nervous system infection were excluded. Seizures were of the simple type in 25 patients, complex in 20 and unclassified in 5. The mean follow-up period was 7.9 months (range=1 to 23 m.), and the age at the first seizure varied from 5 to 42 months (mean=16.8 m.). Clobazam was administered orally during the febrile episode according to the child's weight: up to 5 kg, 5 mg/day; from 5 to 10 kg, 10 mg/day; from 11 to 15 kg, 15 mg/day, and over 15 kg, 20 mg/day. There were 219 febrile episodes, with temperature above 37.8 °C, in 40 children during the study period. Twelve children never received clobazam and 28 received the drug at least once. Drug efficacy was measured by comparing FS recurrence in the febrile episodes that were treated with clobazam with those in which only antipyretic measures were taken. Ten children (20%) experienced a FS during the study period. Of the 171 febrile episodes treated with clobazam there were only 3 recurrences (1.7%), while of the 48 episodes treated only with antipyretic measures there were 11 recurrences (22.9%), a difference highly significant ($p<0.0001$). Adverse effects occurred in 10/28 patients (35.7%), consisting mainly in vomiting, somnolence and hyperactivity. Only one patient had recurrent vomiting which lead to drug interruption. These effects did not necessarily occurred in every instance the drug was administered, being present in one febrile episode and not in the others. We conclude that clonazepam is safe and efficacious in preventing FS recurrence. It may be an alternative to diazepam in the intermittent treatment of FS recurrence.

KEY WORDS: febrile seizures, clobazam, antiepileptic drugs.

Tratamento de convuslsões febris com clobazam intermitente

RESUMO - Avaliamos prospectivamente o uso intermitente do clobazam na profilaxia de convulsão febril em 50 crianças, 24 do sexo feminino e 26 do masculino, com idades entre 6 e 72 meses (média = 23,7 meses) que haviam apresentado pelo menos um episódio de convulsão febril. Foram excluídas crianças com anormalidades neurológicas severas, doença neurológica progressiva, crises durante infecção do SNC e crises epilépticas sintomáticas outras. As convulsões febris foram classificadas como simples em 25 crianças, complicadas em 20 e em 5 crianças não foi possível a classificação. O tempo médio de seguimento foi 7,9 meses (1-23 meses) e a idade, na primeira crise, variou de 5 a 42 meses (média = 16,8 meses). O clobazam foi administrado por via oral, durante os episódios febris, na dose de 5 mg/dia, em crianças até 5 kg; 10 mg/dia, de 5-10 kg; 15 mg/dia, de 11-15 kg, e 20 mg/dia, acima de 20 kg. Quarenta crianças apresentaram febre (T > 37,8 °C), num total de 219 episódios febris. Doze crianças não chegaram a receber clobazam e 28 receberam pelo menos uma vez. A eficácia do tratamento foi avaliada comparando a recorrência de convulsão febril entre os episódios febris tratados com clobazam e aqueles tratados apenas com medicação anti-pirética. Dez crianças (20%) apresentaram recorrência de convulsão febril, durante o período de estudo. Dos 171 episódios febris tratados com clobazam, houve apenas 3 (1,7%) recorrências, enquanto dos 48 episódios tratados apenas com anti-térmicos houve 11 (22,9%) recorrências, uma diferença altamente significativa ($p < 0,0001$) Efeitos colaterais foram observados em 10/28 (35,7%), principalmente vômito, sonolência e hiperatividade. A interrupção da medicação devido a efeitos colaterais foi necessária em um paciente, com vômitos recorrentes. Concluímos que o clobazam é droga eficaz e segura na prevenção de recorrência de convulsão febril na infância, podendo ser uma alternativa ao tratamento com diazepam intermitente.

PALAVRAS-CHAVE: convulsão febril, clobazam, drogas anti-epilépticas.

Serviço de Neurologia Infantil, Divisão de Clínica Neurológica, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (FMUSP). São Paulo SP, Brasil. Aceite: 1-agosto-1997.

Dr. Maria Luiza Giraldes de Manreza M.D. - Serviço de Neurologia Infantil, Divisão de Clínica Neurológica do Hospital das Clínicas da FMUSP - P.O. Box 8091 - 05403-970 São Paulo SP - Brasil. FAX: 55-11-852 0063.

Febrile seizures (FS) have an estimated incidence of 2 to 5% in infancy what makes them one of the most common neurological disturbances in children[1,5,8,20,24,27,28]. The natural history of children with FS shows that the long-term outcome is excellent, with rare cases of neurological sequelae following the seizure episodes even in those children that develop status epilepticus[9,20,22,25,26]. Children that have experienced FS have a slightly higher incidence of epilepsy than the general population[1]. Several risk factors were associated with a higher rate of later epilepsy in children with FS such as complex partial seizures, family history of epilepsy, abnormal neurological or developmental examination and, according to some reports, recurrent FS[3,29,35]. The recurrence rate of FS in a child varies from 25 to 50%, depending on the age at onset, with 50% of those who recur having their second episode within a 6 month period after the first seizure, 75% within one year, and 90% within 2 years[14,25].

Treatment of FS is a controversial issue, in face of its benign course and of the adverse effects of antiepileptic drugs (AED) administration, especially in infancy. On the other hand, FS recurrence pose stressful situations for the child's parents, either because they may be prolonged, or frequent, or evolve into status epilepticus. Finally, their relationship with the later development of epilepsy is not completely established[16-18]. Several therapeutic approaches were tried. Continuous treatment with phenobarbital, and later with sodium valproate, were largely used for several years, but nowadays are being abandoned due to the incidence of adverse effects and to lack of efficacy in preventing FS recurrence, according to some reports in the literature[6,12,13]. Several studies reported the efficacy of intermittent diazepam administration during febrile episodes in prevention of FS recurrence, either orally or rectally, but adverse effects were also observed such as somnolence, ataxia, and irritability[15,19,20,21,31].

Clobazam, a 1,5-benzodiazepine, is completely absorbed 1 to 4 hours after oral administration, has a mean half-life of 18 hours (range 10-30), and less sedative and behavioral effects than diazepam[33]. There is only one report of its efficacy in preventing FS recurrence[34]. The purpose of this study was to test the efficacy and safety of orally administrated clobazam in prevention of FS recurrence. The efficacy was measured in relation to the febrile episodes so that the children served as their own control group.

PATIENTS AND METHODS

We selected children between 3 months and 7 years of age that had experienced one or more FS. Children with severe neurological abnormalities, progressive neurological diseases, afebrile seizures, symptomatic seizures of other nature, or seizures during a central nervous system infection were excluded.

During the initial visit, a detailed medical history was obtained that included characterization of the seizure type and duration, degree and duration of the fever that triggered the seizure, nature of the infectious process, family occurrence of FS, epilepsy, or single seizures. A neurological and physical examination was performed and the children that were receiving an AED, had the drug discontinued. Parents received a "diary" and were instructed to annotate further febrile episodes, with their degree and cause, medication used, adverse effects, and seizure recurrence. They received information concerning antipyretic drug usage according to the child's age and weight. They were instructed to administrate clobazam orally, during the febrile episodes, according to the scheme showed in Table 1. The drug should be administered at the beginning of every febrile episode, independently of the child's recurrence risk for febrile seizures, in all the children that participated in the study.

Statistical analysis was based on the χ^2 test, and the significance level was $p=0.05$.

RESULTS

Fifty children entered the study, 24 female and 26 male, with ages ranging from 6 to 72 months (mean=23.7 m.). The neurological examination disclosed abnormalities in 10 children. Macrocephaly in 4, language delay in 4, hypotonia in one and a skull exostosis in one patient. Family history of epilepsy was present in 18 cases, of FS in 11, and of single unprovoked seizure in

Table 1. Clobazam dosages according to weight.

Weight	Dosage
up to 5 Kg	5 mg / day
6 to 10 Kg	5 mg B.I.D.
11 to 15	7.5 mg B.I.D.
> 15 Kg	10 mg B.I.D.

Table 2. Time to follow-up in the study group.

Time to follow-up (months)	N	%
3 - 5	**22**	44
6 - 11	**14**	28
12 - 18	**10**	20
> 18	**4**	8
Total	**50**	100

4 cases. EEG examination was obtained in 45 patients, being abnormal in 2 (both with focal spikes). Simple febrile seizures occurred in 25 children, complex in 20, and we were unable to classify them in 5. Of the 20 patients with complex febrile seizures, 11 had multiple seizures during a single febrile episode, 7 had seizures with either partial, or unilateral onset, and 2 had a seizure lasting more than 15 minutes.

The age at the first seizure varied from 5 to 42 months (mean=16.8 m.). The mean follow-up period was 7.9 months (range=1 to 23 m.), as shown in Table 2. During the study, 40 children had febrile episodes higher than 37.8°C. Ten children (20% of the total group, or 25% if only we consider the 40 cases that had another febrile episode) experienced 14 FS during the study period. Twelve children never used clobazam and 28, used it at least once. Thus, drug efficacy was evaluated in relation to the febrile episodes, with the children of the febrile group serving as their own control group.

There were 219 febrile episodes in the 40 children that experienced at least one febrile episode. Table 3 shows the recurrence rate of FS according to treatment strategy. Of the 171 febrile episodes treated with clobazam there were only 3 instances of FS recurrence (1.7%), while of the 48 febrile episodes that were treated only with antipyretic measures, we observed 11 cases of recurrence (22.9%), a highly significant difference ($p < 0.0001$). Clobazam was not administered to 48 children that received only antipyretic measures, either because they had seizure as the first manifestation of the febrile episode (2 patients), or because of lack of protocol adherence by the care-givers.

Of the 3 recurrences in the treated group, one child had 2 seizures. Although this child vomited the medication in both episodes, she was included in the treated group.

Table 3. Frequency of recurrence according to treatment and febrile seizures, according to treatment.

	Recurrence		Number of febrile episodes
Treatment	Yes	No	
Yes	3	168	171
No	**11**	37	48
Total	14	205	219

$\chi^2 = 24.62$ $p < 0.0001$

Table 4. Adverse effects observed in the children that used clobazam.

Effect	Number of patients	%
Vomiting	**4**	**14.2**
Somnolence	**4**	**14.2**
Hyperactivity	**2**	**7.1**
Insomnia	**1**	**3.5**
Irritability	**1**	**3.5**

Of the 10 children with abnormalities in the neurological examination, only one child with language delay had a recurrence.

Adverse effects were observed in 10/28 patients that received clobazam (Table 4). The most common were somnolence, vomiting and hyperactivity. Only in one case, that experienced recurrent vomiting, the effect was sufficiently severe to justify withdrawal of the drug.

DISCUSSION

Prophylactic treatment for febrile seizure recurrence has been criticized by several authors on the ground that they have a benign outcome, and that AED have short and long-term adverse effects especially for the lower age group[4,7,23,36]. There are recent reports showing no beneficial effect of phenobarbital in preventing recurrence, a widely used drug in the prophylactic treatment, and at the same time leading to cognitive effects[6,12]. Valproic acid, another drug used in prophylactic treatment, carries the risk of severe adverse effects, especially in children below one year of age[6]. Thus, continuous drug treatment for FS recurrence is theoretically being abandoned[4,7].

The decision of not treating FS implies in the risk of seizure recurrence during febrile episodes. Even if these seizures are rarely responsible for neurological sequelae, they are a cause of stress for the family. Every febrile episode carries the perspective of a new seizure, and for parents the sight of a seizure, sometimes prolonged, is definitely not a pleasant one[35]. On the other hand, there are reports that have observed a relationship between temporal lobe epilepsy with mesial temporal sclerosis and prolonged febrile seizures in infancy[2,10,16,18,30,32]. These studies brought back the issue of FS treatment, preferably with drugs that are efficacious and have few short and long-term adverse effects. Benzodiazepines, given only during the febrile episodes, were found to be effective in FS recurrence in several studies with few short-term and no long-term adverse effects[15,19,20,21,31].

In the present study, the recurrence rate of FS was 20% when the total original group (50 cases) is taken into account, and 25% if we consider only the children that have experienced febrile episodes (40 cases). These 40 children experienced 219 febrile episodes and 10 cases recurred, with a total of 14 seizures. Although having experienced fever, 12 children never received clobazam, while 28 received the drug at least once. Thus therapy efficacy could be better evaluated in relation to the febrile episodes and the children served as their own control group. This strategy was adopted because clobazam was either used or not in a group of children (28 cases), while in others (12 cases) it was not used at all. Daugbjerg et al.[11] also noticed the difficulty in treatment adhesion when intermittent therapy is used. Kishi et al.[19], in a study of intermittent therapy with diazepam, used the recurrence rate in relation to the febrile episodes.

The results showed that in 171 treated febrile episodes, there were only 3 (1.75%) recurrences, two in the same child that vomited the medication soon after ingestion, while among the 48 non-treated episodes, there were 11 (22.9%) recurrences, a highly significant difference ($p<0.0001$). Tondi et al.[34] reported a recurrence rate of 2.6% in a group of 39 children treated with intermittent clobazam. These recurrence rates are lower than those observed in studies that used intermittent diazepam and found rates varying from 5 to 29%[21].

Adverse effects were observed in 10/28 patients (35.7%) and generally were mild and well tolerated, leading to treatment interruption in only one child, that experienced repeated vomiting. This frequency is lower than that reported for diazepam, that ranges from 36.8 to 77%[11,15,21,31]. It is interesting to notice that the adverse effects observed in a child were not consistent (it could be observed in only one episode and not in others).

We conclude that clonazepam is safe and efficacious in preventing FS recurrence. It may be an alternative to diazepam in the intermittent treatment of FS recurrence.

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