Intermittent Clobazam Therapy in Febrile Seizures

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Abstract. Objective: To evaluate the efficacy of intermittent clobazam therapy in preventing the recurrence of febrile seizures and to assess its safety. Methods: The study was a prospective, randomized, double-blind placebo-controlled trial conducted in the Department of Child Health, Christian Medical College Hospital, Vellore between July 2001 and September 2002. Neurologically normal children between 6 months and 3 years of age with a history of febrile seizures and no evidence of acute CNS infection or EEG abnormality were included into the study. 19 children in a clobazam group and 20 in the placebo group were randomly allocated. Temperature reduction measures with paracetamol and tepid sponging were advised to all children. In addition the dispensed medication was to be administered at the onset of fever and continued for 48 hours irrespective of the duration of fever. The children were then monitored for seizures and adverse effects of clobazam. The children were followed up for a mean period of 9.9 months. The analysis was done on the number of febrile episodes in both the groups. Results: There were a total of 110 episodes of fever during the study period. Mean number of febrile episodes in the clobazam group was 3.1 and in placebo group 2.56. Six (12.5%) of the 48 episodes in placebo group and one (1.7%) of 60 episodes in clobazam group had seizure recurrence. This was statistically significant (p = 0.01). Drowsiness and weakness were present equally in both clobazam and placebo groups whereas ataxia was present only in the clobazam group, the difference being statistically significant (p=0.04). Conclusion: Intermittent clobazam therapy is an effective measure in the prevention of recurrence of febrile seizures. The ataxia due to clobazam was much lower than that reported with diazepam.

Key words: Intermittent clobazam therapy, Febrile seizures

Febrile seizures are the most common types of seizure with a prevalence on 3 to 4 percent. They are age dependent and are rare before 9 months and after 5 years of age. Febrile seizures frequently recur, with a recurrence rate of 33 percent overall and 50% when the first febrile seizure occurs before one year of age. Half the recurrences occur within six months of the first febrile seizure, three quarters within a year and 90% within two years. Prevention of the febrile seizures is highly desirable. For the past 3 decades various regimes such as daily phenobarbitone, daily sodium valproate, intermittent rectal or oral diazepam have been tried with various degrees of success. Clobazam is the first and only 1,5 benzodiazepine to be used in the management of epilepsy. It is an effective anti-epileptic drug in adults and children. The side effects of clobazam are typical of benzodiazepines: drowsiness, psychomotor retardation, muscular weakness and pseudoataxia. These side effects are however, less marked than those occurring with 1,4 benzodiazepines. As clobazam is a superior benzodiazepine with fewer side effects, this study aimed at evaluating the use of intermittent clobazam therapy in the prevention of recurrence of febrile seizures.

Materials and Methods

The study was prospective, randomized, double-blind placebo controlled trial conducted in the Department of Child Health, Christian Medical College Hospital, Vellore between July 2001 and September 2002. It has been found in previous studies that the recurrence of febrile seizures with the use of antipyretic administration only, is 24% and 6% with intermittent diazepam therapy within one year. Assuming that intermittent clobazam therapy is at least as effective as intermittent diazepam therapy, statistical analysis was done to find the number of episodes that need to be studied to be statistically significant. With an alpha error of 5% and power of 80% the sample size was calculated to be 62 febrile episodes in each arm. With an average of 3 episodes of fever per person per year, the number of children to be studied would be 21 in each arm.

As the study was double-blind, the clobazam and the placebo were randomized and blinded. The pharmacists had the randomization codes and prepared the drug accordingly. Only the pharmacist, till the completion of the study, knew the code. The investigator was given only random numbers to be assigned to the patients. Clobazam is available only in tablet form. As a suitable placebo tablet to blind the study could not be procured, a suspension of the clobazam was prepared, with a suitable placebo suspension without the active component of
The clobazam suspension contained clobazam in the concentration of 5 mg per 2.5 ml. Both the drug and placebo were dispensed in similar looking brown bottles and had the same taste and the flavouring agent. The stability of the clobazam suspension was one month.

The therapeutic dosage of clobazam ranges from 0.3 to 1 mg/kg/day. The dosage schedule for the purpose of this study was allocated according to the subject's weight as follows:

- Upto 5 kg: 5 mg per day
- 6 kg to 10 kg: 5 mg twice daily (bd)
- 11 kg to 15 kg: 7.5 mg twice daily bd
- > 15 kg: 10 mg twice daily bd

The dispensed medicine was to be administered immediately at the onset of fever and continued for 48 hours and stopped after 48 hours irrespective of whether the fever persisted or not.

Children with one or more episodes of febrile seizures aged 6 months to 3 years were recruited. The seizures should be generalized should have occurred within 24 hours of onset of fever. Children with history of a febrile seizure and proved acute CNS infection, abnormal electroencephalogram, developmental retardation, proven CNS malformation, progressive neurological disease, proven chromosomal abnormalities and those on any other anticonvulsant were excluded.

The prospective candidates underwent a detailed medical history. A general physical and neurological examination was performed. EEG was performed in all the patients and CSF analysis done in those children who had clinical evidence to suspect an acute CNS infection. A written consent was then obtained from the parent or guardian of those who fulfilled all the inclusion criteria and none of the exclusion criteria.

On inclusion into the study, each patient was then allocated a study number. The parents then received a diary and were instructed to annotate further febrile episodes, with their degree, associated symptoms, medication used, adverse effects and seizure recurrence. They were also instructed to administer the medication at the beginning of each febrile episode for a period of 48 hours from the start of fever. The parents were also instructed to administer paracetamol and institute temperature control measures at the onset of fever and continue it through the duration of the illness.

The children under the study were followed up every month from the time of induction into the study till September 2002. During each visit they were reviewed along with their parents or guardians and the 'diary' scrutinized and updated. As the stability of the clobazam suspension was one month, their drug was also renewed every month.

The analysis was done on the number of febrile episodes in both the groups to assess the effectiveness of clobazam against placebo in prevention of febrile seizures using the t-test of significance. The side effects were evaluated and significance assessed statistically by the t-test. The data was analysed on the principle of intention to treat.

### RESULTS

Of the 40 children recruited, one child in the clobazam group was lost to follow up. So, the final analysis was on 39 children. Three each in both clobazam and placebo groups were aged less than 24 months. Seven and six children were above 24 months of age in clobazam and placebo groups respectively. There were 13 males and 7 females in the clobazam group and 13 males and 6 females in the placebo group. The mean period of follow up was 9.9 months, range (0-14 months). The 39 children had 108 episodes of fever during the follow up period. Sixty of those episodes were treated with clobazam and 48 with placebo. Mean number of febrile episodes during the follow up was 3.4 episodes of fever per years. Mean number of febrile episodes in the clobazam group was 3.1 and in placebo group 2.56. Six (12.5%) of the 48 episodes treated with placebo had seizure recurrence. One (1.7%) of 60 episodes in clobazam group had seizure recurrence. This was statistically significant (P=0.01).

The three major side effects reported were drowsiness, ataxia and weakness. However, drowsiness and weakness were present almost equally in both the clobazam and the placebo group (drowsiness-46.8% and 52.1% and weakness-4.8% and 4.2% respectively). The difference was not statistically significant. Ataxia was present in 5 (8.3%) in clobazam group and none in the placebo, the difference being statistically significant (p=0.04).

### DISCUSSION

Intermittent diazepam therapy for the prevention of recurrence of febrile seizures has been well studied and proven to be effective. This study was aimed at evaluating clobazam, a 1,5 benzodiazepine with less side effects than diazepam, in the prevention of recurrence of febrile seizure.

The children recruited in this study were in the age group between 6 months and 3 years with a majority of them (57%) being in the second year of life. There was a predominance of boys (67.5%) in both the groups. However, the proportion of the boys and girls were similar in the clobazam (65%) and the placebo group (70%). In the final analysis there were 39 children with 108 episodes of fever during the follow up period.

Sixty of those episodes were treated with clobazam and 48 episodes with placebo. The mean number of febrile episodes during the follow up period was 3.4 episodes of fever per year.

Of the 108 episodes of fever, 7 episodes were associated with seizures in 7 different children. The other children did not have any seizures in spite of febrile