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Clobazam monotherapy in drug naïve adult patients with epilepsy

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Purpose: Evaluation of the efficacy and side effects profile of Clobazam in a 24-week open-labelled trial involving 26 cases of drug naïve adult patients with epilepsy.
Methods: The study was an open labelled unicentre trial in which only drug naïve cases with epilepsy were included. A total of 26 cases were recruited. One case was dropped because he did not complete the desired follow up. Seizure type and frequency were recorded and follow up was done at 4, 8, 12, 18 and 24 weeks after initiation of therapy. The change in seizure severity, the dose of Clobazam required and development of side effects were recorded.
Results: The seizure types included GTCS ($n = 16$), complex partial seizures ($n = 4$), focal motor seizures with secondary generalisation ($n = 3$) and juvenile myoclonic epilepsy ($n = 2$). Out of 25 patients, 16 (64%) became seizure free, while five (20%) had >50% reduction in their seizure frequency. Thus, these 21 patients (84%) were considered to be well controlled. The commonest side effect seen was sedation, which was noted in 4 of the 25 patients (16%). However, in none of these four patients sedation was significant enough to warrant stoppage of therapy. Weight gain, gait ataxia, loss of short-term memory and breakthrough seizures were noted in one patient each.
Conclusions: The efficacy of Clobazam coupled with the lack of significant side effects noted in our study makes it merit consideration as monotherapy in adult patients with epilepsy.

Key words: epilepsy; Clobazam; monotherapy.

INTRODUCTION

Epilepsy is considered to be the most common neurological condition in developing countries. In as many as 70–80% of epileptic patients, seizures can be controlled with the commonly prescribed antiepileptic drugs (Phenytoin, Phenobarbitone, Valproate and Carbamazepine). However, 20–30% of the patients continue to have seizures despite optimal therapy[1,2]. Further, many patients receiving the standard anti-epileptic drugs (AEDs) may develop unacceptable side effects. Thus, there is a need for another antiepileptic drug, especially one that can be prescribed as monotherapy. Clobazam is one of the promising antiepileptic drugs that has proved its efficacy as an add on drug in refractory partial and generalised seizures[3]. In view of the encouraging results with Clobazam as add on therapy in refractory epilepsy, The Canadian Clobazam Co-operative Group suggested that a monotherapy trial with Clobazam in less severe epilepsy is now desirable[3]. Though, recently the Canadian Study Group for Childhood Epilepsy suggested the usefulness of Clobazam as monotherapy in the paediatric age group[4], but to the best of our knowledge there is no published report on Clobazam Monotherapy in adult patients with epilepsy.

Clobazam is a 1,5-benzodiazepine, which differs from conventional 1,4-benzodiazepines (e.g. diazepam) in having 80% lesser anxiolytic activity, ten fold lesser sedative effects and no addictive potential[5]. Its antiepileptic effects are due to its action on the GABA (gamma amino butyric acid) receptor complex and also on voltage sensitive calcium ion conductance and sodium channels. Following single oral dose, peak serum concentration is reached in 2 hours[6].

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It is converted to its active metabolite (des-methyl Clobazam/nor-Clobazam) by hepatic oxidation[7]. Clobazam has minimal drug interactions except for a slight but significant reduction in the clearance of Valproic acid and Primidone. Adverse effect profile is generally mild and the discontinuation rate is much lower than that of the conventional AEDs. Side effects include sedation, dizziness, ataxia, blurred vision and diplopia. Though sedation is the most common side effect, the tendency to develop tolerance is considered to be the most problematic side effect[8]. Trials are required to define the role of Clobazam as monotherapy in epilepsy, covering all age groups. We report the results of the efficacy of Clobazam as monotherapy in adult patients with epilepsy in an open labelled study.

MATERIAL AND METHODS

A pilot open labelled study was formulated to study the efficacy and safety of Clobazam as first line monotherapy in the treatment of newly diagnosed drug naïve patients with epilepsy. The ethical clearance from the institution ethical committee was obtained before starting the trial.

The purpose of the clinical study and the nature of drug treatment were explained to all the patients and a written informed consent was obtained. An option was given to the patients to opt out of the study at any time. A total of 26 cases (above the age of 12 years) were recruited. One patient was dropped, as he did not follow up after 12 weeks of therapy. The mean age was 20.84 years (range = 13–36 years) and the patients included 14 males and 11 females (male/female ratio = 1.27:1). The change in seizure severity, the dose of Clobazam required and development of side effects were recorded at 4, 8, 12, 18 and 24 weeks after initiation of therapy as per the defined protocol. The patients were instructed to report immediately if they had recurrence of seizures or developed adverse events.

The inclusion criteria were as follows:

1. Newly diagnosed untreated patients with epilepsy having a seizure frequency of at least two seizures per 4 weeks in the last 12 weeks.
2. Patients of both sexes aged 12 years and above.

The exclusion criteria were as follows:

1. Pregnant women or those planning a pregnancy in the next 6 months.
2. Patient with severe liver, renal, cardiac, gastrointestinal or progressive neurological disease.
3. Past history of psychosis or behavioural problems.
4. History of drug/alcohol abuse or addiction.
5. Inability to keep a good seizure calendar and attend the epilepsy clinic at regular intervals for follow up evaluation.

Routine investigations (haematology, liver function and renal function tests) were done to rule out any coexisting disease. Cranial CT scan was done in all patients. Clobazam (Frisium, Aventis Pharma Ltd.) was started at an initial dose of 10 mg and increased to 20 mg after a week. In subjects whose seizures were not controlled with 20 mg, further increments of 10 mg per week were added till seizure control was attained. At the end of follow up of minimum of 24 weeks, patient's seizure control was classified as:

• Excellent	If patient was seizure free
• Improved	If patient had seizures at a frequency <50% of baseline
• Minimally improved	If patient had seizures at a frequency >50% of baseline
• Not controlled	If patient had no change in frequency of seizures
• Worsened	If seizure frequency increased compared to baseline

RESULTS

Our study analysed 26 patients, of which one was not available for follow up. The duration of follow up was 15.64 months (range = 7–24 months). Average dose of Clobazam used was 26.86 mg (range 20–80 mg).

The seizure types included GTCS ($n = 16$), complex partial seizures ($n = 4$), focal motor seizures with secondary generalisation ($n = 3$) and juvenile myoclonic epilepsy ($n = 2$).

Of the 25 patients, 16 (64%) became seizure free, while five (20%) had >50% reduction in their seizure frequency. Thus, these 21 patients (84%) were considered to be well controlled. Considering the seizure subtypes, 14 out of 16 patients with GTCS were well controlled, two out of four (50%) with CPS were well controlled, all three patients with focal seizures and both the patients with juvenile myoclonic epilepsy were well controlled.

Sixteen out of 20 (80%) patients with a normal CT scan were well controlled, while all five patients (100%) with abnormality on CT scan also responded well to Clobazam monotherapy. All the patients with CT abnormality had single ring enhancing lesions. Focal seizures were the presenting feature in three of these patients, while two patients had GTCS.

Of these 21 patients whose seizures were considered well controlled, 16 (76%) were controlled by the 4th week, four were controlled by the 8th week and one was controlled by the 12th week.

The commonest side effect seen was sedation, which was noted in 4 of the 25 patients (16%). Weight gain, gait ataxia and loss of short-term memory were noted in one patient each. Breakthrough seizures were seen in one patient with GTCS. This patient was taking a dose of Clobazam 40 mg per day. The dose was increased to 80 mg in the next 4 weeks but the seizures were not well controlled. Carbamazepine was added and seizures were well controlled on a dose of 25 mg/kg body weight per day and Clobazam was slowly tapered. None of the other side effects warranted discontinuation of therapy.

DISCUSSION

In our study, no correlation was noted between efficacy and side effects of Clobazam with either age or sex of the patient. Of the 25 patients who completed the study, 16 (64%) were seizure free, while five (20%) had greater than 50% reduction in seizure frequency. This figure compares well with the Canadian Study Group for Childhood Epilepsy[4] and also with other studies using Lamotrigine[9] or Topiramate[10] as monotherapy in which the seizure free percentage of patients varied from 45 to 65%. To the best of our knowledge there is no other trial using Clobazam as monotherapy in adults with epilepsy, hence no comparison is possible.

The drop out rate in our study was a 1 out of 26 patients in the mandatory first 6-months study period. Another one out of the remaining 25 patients who developed an increase in seizure frequency (breakthrough seizures) in the fourth month had to be changed to another drug but was available for follow up till 24 weeks of the study period. Thus 96.0% patients completed the study, which compares very well with other trials using Lamotrigine and Topiramate.

Among 21 patients who had good seizure control, 16 (76.0%) patients were controlled by the 4th week of therapy; four by the 8th week and one was controlled by the 12th week. It was noted that if seizures were not controlled by the third month of treatment then they were unlikely to respond to Clobazam monotherapy.

Sedation was the commonest side effect noted, but it was not disabling. Weight gain, gait ataxia, loss of short-term memory and break through seizures were other adverse effects noted. The side effect profile noted in our series is in concordance with other studies, which used Clobazam as add on therapy. Significantly, however, we did not find tolerance to be a major side effect in our series. The Canadian Study Group for childhood epilepsy found tolerance to be a problem in 7.5% of their patients. Small sample size was the main drawback of our study. Unlike other studies the efficacy of Clobazam as a monotherapy in comparison to standard antiepileptics was not undertaken in the present study.

The efficacy of Clobazam coupled with its lack of significant side effects, as seen in our patient series, makes it a potentially useful drug in the physician's armamentarium in the battle against epilepsy. Also this drug is not very expensive compared to the other newer antiepileptic drugs available. In India, per day cost of therapy with Clobazam is one third of topiramate, half of lamotrigine and approximately the same as that of Valproate and Carbamazepine therapy. This pilot study may thus be considered as a starting point for formulating further trials using Clobazam as monotherapy so as to define its role further in the management of epilepsy. A multicentre trial comparing Clobazam with other antiepileptic drugs like Carbamazepine or Phenytoin needs to be planned.

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