Effect of clobazam as add-on antiepileptic drug in patients with epilepsy

Rupa Joshi, Manjari Tripathi*, Pooja Gupta & Yogendra Kumar Gupta

Adverse Drug Reaction Monitoring Centre, Department of Pharmacology & 'Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

Received July 8, 2013

Background & objectives: The use of clobazam in epilepsy has increased since its introduction in 1975. However, it has not been audited for its overall usefulness in Indian set up. The present study was aimed to evaluate usage pattern, retention rate, effectiveness and tolerability of clobazam during routine practice in an outpatient epilepsy clinic of a tertiary care hospital in New Delhi, India.

Methods: This study was performed on the patients prescribed antiepileptic medication who had clobazam as last added drug in their treatment regimen during October 2010 - March 2012. These patients were followed up for two OPD visits. The primary points evaluated were retention rate, percentage of seizure-free patients and reasons for discontinuing clobazam.

Results: Of the 417 consecutive patients, 132 (31.7%) were on clobazam treatment for more than four years (median 6 yr, range 4-15 yr). No seizure for previous 12 months was considered as seizure free and was observed in 151 (36.2%) patients. There was no improvement in seizure control in 32 (7.7%) patients. A decrease in seizure severity without any change in seizure frequency was observed in 76 (18.2%) patients. Clobazam was discontinued by 15 (3.6%) patients due to complaints like drowsiness (13), fatigue/tiredness (8), headache (6), poor memory (6), irritable behaviour (5), abdominal pain (3) and dizziness (3).

Interpretation & conclusions: Our results provide valuable information about the clinical use of clobazam as add-on antiepileptic drug therapy in the management of patients with epilepsy.

Key words Antiepileptic drugs – clobazam – epilepsy - prescription audit - retention rate - seizures

Clobazam (CLB) is in use for almost four decades since its introduction in 19751. Its use has expanded from anxiety to epilepsy including Lennox-Gastaut syndrome (LGS)2,3. This broad spectrum antiepileptic prevents recurrence of febrile seizures also4. According to a Canadian study, more than 10 per cent treatment refractory patients achieved seizure freedom with clobazam over a period of seven years2. Despite being a benzodiazepine, clobazam has lower sedative effects5. Adverse effects associated with clobazam, generally transient and dose-related, include somnolence, dizziness, mood changes, irritability, depression and aggression6.

Efficacy and safety of a drug are established through rigorous randomized controlled trials. However, audits
in clinical practice compliment the information derived from these trials. Audits also take into consideration the ethnic variations which especially play an important role in the pharmacotherapy of epilepsy. Though studies in Indian population have demonstrated the efficacy of CLB as monotherapy in adult patients and in refractory childhood epilepsy, data regarding the usage pattern, efficacy and safety of clobazam in different treatment regimens are limited. Hence, in the present study, patients with epilepsy (PWE) prescribed CLB were assessed for usage pattern, retention rate, drug load, outcome in terms of seizure freedom, improvement in seizure severity and discontinuation due to adverse effects in a tertiary healthcare set up in north India.

**Material & Methods**

The present study was an observational study in which patients were recruited from a consecutive sample of consenting PWE attending the epilepsy clinic in outpatient department (OPD) of Neurology, All India Institute of Medical Sciences (AIIMS), New Delhi, India, between October 4, 2010 and March 7, 2012. Patients of all age and either gender taking CLB were included in the evaluation. CLB was the last antiepileptic drug (AED) added to the regimen for these patients. Patients, for whom another AED was added to the regimen after CLB addition, were excluded from the evaluation. Exclusion criteria also included patients with symptomatic chronic illness or other co-morbid condition like hypertension, metabolic syndrome, renal disorder, etc. which predated epilepsy. Patients who had, during the clinical audit period, a surgical resection for CLB discontinuation were enrolled. Age at the onset of seizures varied from infancy (≤1 yr) to 56 yr (mean 13.1, median 11 yr). The duration of CLB use was 6.5–270 months (mean 13.3, median 18 months). The number of patients with age ≤18 yr and between 19-40 yr were 184 (44.1%) and 201 (48.2%), respectively. Only 7.7 per cent (32/417) patients were above the age of 40 yr. The detailed characteristics are mentioned in the Table.

**Results**

A total of 417 patients with epilepsy (male/female: 274/143; aged 3-66 yr, mean 22.1 yr, median 20 yr), on CLB treatment were enrolled. Age at the onset of seizures varied from infancy (≤1 yr) to 56 yr (mean 13.1, median 11 yr). The duration of CLB use was 6.5–270 months (mean 13.3, median 18 months). The number of patients with age ≤18 yr and between 19-40 yr were 184 (44.1%) and 201 (48.2%), respectively. Only 7.7 per cent (32/417) patients were above the age of 40 yr. The detailed characteristics are mentioned in the Table.

**Type of seizures:** According to the newer classification of seizures, patients were divided into generalized seizures (46.3%, 193/417) and focal seizures (53.7%, 224/417). Among generalized seizures, 23 per cent patients presented with the symptoms of LGS such as clonic, tonic and atonic seizures. Among focal seizures,
consciousness was impaired in two-third of the patients. Most patients (61%) had focal seizures with secondary generalization.

**Concomitant antiepileptic drugs:** CLB was in use in different treatment schedules *i.e.* as 1st, 2nd, 3rd and 4th add on AED. The mean number of AEDs used per person was 2.8 ± 0.8 (range 1-5). The frequency of use of older AEDs *i.e.* valproate, carbamazepine and phenytoin in combination with clobazam was 45.8, 33.8 and 26.9 per cent, respectively. Among newer AEDs, use of levetiracetam (30.9%) was higher followed by lamotrigine (12%), oxcarbazepine (10.3%), zonisamide (4.8%), topiramate (6%) and lacosamide (1.9%). Maximum protection from seizures was observed in the patients who were on two or three add-on AEDs including CLB. The most frequently used concomitant antiepileptic drug treatment regimens in 151 patients who remained on CLB for at least 12 months is shown in the Table.

**Retention rate:** The retention rate analysis was performed with all 417 patients (range 6.5-270 months). The retention rates at 12, 24, 48 and 96 months were 66.9, 44.8, 19.7 and 6.5 per cent, respectively. Clobazam was discontinued in 15 patients (Fig. 1). Of these, CLB was first, second and third add-on therapy in 4, 8 and 3 patients, respectively.

**Seizure freedom:** In total, 151 patients (36.2%) were seizure free during the study evaluation period, *i.e.* 12 months of CLB treatment. Among seizure free patients, 62 (41.2%) patients were on CLB as first add-on drug. There was no change in seizure control in 32 (7.7%) patients. The percentage of seizure-free patients in each treatment regimen is elucidated in the Table.

### Table. Characteristics of patients in different outcome groups

<table>
<thead>
<tr>
<th></th>
<th>Seizure free</th>
<th>&gt;50% seizure reduction</th>
<th>&lt;50% seizure reduction</th>
<th>No change in seizure frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>151 (36.2%)</td>
<td>158 (37.9%)</td>
<td>76 (18.2%)</td>
<td>32 (7.7%)</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>98 (23.5%)</td>
<td>21 (5.0%)</td>
<td>48 (11.5%)</td>
<td>107 (25.7%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>22</td>
<td>19.5</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Range</td>
<td>5-66</td>
<td>4-59</td>
<td>3-50</td>
<td>4.5-36</td>
</tr>
<tr>
<td>Age at onset of seizures (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>13</td>
<td>11.5</td>
<td>9</td>
<td>4.5</td>
</tr>
<tr>
<td>Range</td>
<td>0-56</td>
<td>0-43</td>
<td>0-45</td>
<td>0-22</td>
</tr>
<tr>
<td>Clobazam dose (mg/kg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Range</td>
<td>0.04-1.25</td>
<td>0.06-1.03</td>
<td>0.06-1.03</td>
<td>0.11-1.75</td>
</tr>
<tr>
<td>Duration of clobazam use (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>24</td>
<td>18</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Range</td>
<td>7-270</td>
<td>6.5-186</td>
<td>7-186</td>
<td>7-126</td>
</tr>
<tr>
<td>Treatment regimens with clobazam n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First add-on (n=165)</td>
<td>68 (41.2%)</td>
<td>70 (42.4%)</td>
<td>27 (16.4%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Second add-on (n=186)</td>
<td>66 (35.5%)</td>
<td>69 (37.1%)</td>
<td>38 (20.4%)</td>
<td>13 (7.0)</td>
</tr>
<tr>
<td>Third/fourth add-on (n=66)</td>
<td>17 (25.8%)</td>
<td>19 (28.8%)</td>
<td>11 (16.7%)</td>
<td>19 (28.8%)</td>
</tr>
<tr>
<td>Frequently used regimens with CLB n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin (n=48)</td>
<td>16 (33.3%)</td>
<td>25 (52.1%)</td>
<td>7 (14.6%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Carbamazepine (n=47)</td>
<td>20 (42.6%)</td>
<td>18 (38.3%)</td>
<td>9 (19.1%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sodium valproate (n=43)</td>
<td>19 (44.2%)</td>
<td>16 (37.2%)</td>
<td>8 (18.6%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Levetiracetam (n=10)</td>
<td>6 (60)</td>
<td>3 (30)</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Phenytoin+Sodium valproate (n=36)</td>
<td>11 (40.7%)</td>
<td>12 (44.4%)</td>
<td>3 (11.1%)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Carbamazepine+Sodium valproate (n=27)</td>
<td>8 (29.6%)</td>
<td>11 (40.7%)</td>
<td>5 (18.5%)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Carbamazepine+Levetiracetam (n=25)</td>
<td>11 (44)</td>
<td>8 (32)</td>
<td>6 (24)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sodium valproate+Levetiracetam (n=22)</td>
<td>6 (27.3)</td>
<td>10 (45.5%)</td>
<td>3 (13.6)</td>
<td>3 (13.6)</td>
</tr>
</tbody>
</table>
Dosages of clobazam: Clobazam was administered at 0.04-1.8 mg/kg/day, once daily or divided into two daily doses. The median dose of CLB was 0.3 mg/kg/day. The average CLB dose remained stable in 151 patients who were seizure free for 12 months. Throughout the study, patients in all four response categories took a wide range of CLB doses which varied from 0.1 mg/kg/day in seizure free patients to 1.8 mg/kg/day in patients who discontinued the drug (Fig. 2). The dose of CLB was found to be higher in patients with <50 per cent reduction in seizures and those with poor seizure control.

Clobazam tolerability and reasons for discontinuation: A total of 1360 adverse effects were reported by 417 patients with an average of 3.3 adverse effects per patient. The most frequent adverse effects experienced were somnolence (163, 39.1%), fatigue or tiredness (142, 34.1%), irritability (139, 33.4%), poor memory (151, 36.2%), headache (126, 30.2%) and loss of appetite (72, 17.3%). In majority of the patients, the adverse effects were either self-limiting or resolved after the adjustment of CLB dosage. In total, 15 (3.6%) patients discontinued CLB treatment which was most frequent within the first six months of treatment. Two patients discontinued CLB for lack of efficacy, and 13 patients for adverse events. Most patients, who discontinued CLB due to adverse effects, complained of sedation and drowsiness which affected their daily routine. The adverse effects experienced by the patients included somnolence (13), fatigue (8), headache and poor memory (6 each), irritability (5), tremors (4), abdominal pain, blurred vision, constipation, dizziness, loss of appetite, weight gain, slurred speech (3 each), acidity (2), and depression (1).

Discussion

The present study showed clobazam as an effective and well tolerated add-on antiepileptic drug. The use of a single antiepileptic drug at the minimally effective dose, up to the maximum tolerated dose, is the standard therapy for epilepsy. However, many patients need more than one AED to improve seizure control. CLB is commonly used as add-on therapy, but it has demonstrated efficacy as monotherapy as well.

Clobazam is used as a first-line antiepileptic drug in paediatric epilepsy in many countries and in spite of availability of other options, it continues to be used as an adjunctive therapy for patients with resistant epilepsy. Two retrospective studies on the efficacy
of clobazam as add-on therapy for paediatric patients reported significant reductions in seizure frequency. In the present study, CLB was found to be prescribed more frequently in children as compared to patients above 40 years.

The most frequent combinations of CLB were with carbamazepine, valproate, phenytoin, levetiracetam, lamotrigine and oxcarbazepine. In the present study, clobazam being broad spectrum was selected as add-on AED for patients with epilepsy who were not responding to other AEDs (focal seizures, focal evolving to bilateral convulsive and generalized seizures). Clobazam was used for varying reasons, firstly, during up titration and waiting period in patients who required build up of AEDs like lamotrigine (11.9%) and topiramate (5.9%); secondly, in drug resistant epilepsy with at least two add-on AEDs; thirdly, in case of drug rash with first line AEDs. The seizure control may or may not be directly attributable to CLB addition per se as patients were also receiving other first and second line AEDs.

Doses of 0.2–3.8 mg/kg/day have been used in trials evaluating the use of clobazam. Observed dose range in the present study varied from 0.04-1.8 mg/kg/day on body weight basis. This dose range was in accordance with the previous studies. Doses up to 0.2-0.3 mg/kg/day were most frequently prescribed and resulted in maximum percentage of patients gaining seizure control. Rarely, higher doses up to 1.8 mg/kg/day were prescribed in patients with poor seizure control. This is in contrast to the results of Ng et al, where significant seizure reduction occurred at medium (0.5 mg/kg/day) and high (1 mg/kg/day) doses as compared to low (0.25 mg/kg/day) dose. It is likely that in Indian population, CLB is more effective at low dose (0.2-0.3 mg/kg/day). The doses prescribed were the maximum tolerated doses beyond which patients reported drowsiness or sedation interfering with daily activities (5/417, 1.2%). Evidence also supports lower likelihood of psychomotor impairment and sedation at lower doses of CLB.

Retention rate (RR) is useful in prescription audits to explain the extent of tolerability and efficacy. In the present study, RR was calculated to see how clobazam faired in the present set up. So, if the new
add-on AED (clobazam) is not effective, it would be replaced with another AED and gradually tapered off. The range of retention period for CLB varied widely (6.5-270 months) in the present study suggesting a better tolerability. About 85 per cent patients completed four years on CLB treatment. Previous studies have also demonstrated persistent efficacy of more than one comparable year in as many as 85 per cent patients17.

Clobazam is considered as a safe and effective AED. It has fewer side effects than phenytoin or carbamazepine13. In addition to decrease in seizure frequency, CLB improves global assessment consistent with improved cognitive and behavioural performance15,19,24-26. The percentage of patients who discontinue treatment due to adverse effects was 3.6 per cent in the present study as compared to the reported 12.5 and 16.6 per cent, respectively for low and high doses19. In the present study, CLB was preferred in patients with rash induced by other AEDs like phenytoin (n=2), carbamazepine (n=3) and valproate (n=2). This is in contrast to the findings of previous study in which combination of CLB triggered the lamotrigine and valproate induced Steven Johnson Syndrome27. Somnolence followed by fatigue and tiredness were the common complaints in patients who discontinued CLB treatment. Studies have suggested that slow dose titration may help to avoid adverse effects and that when present, adverse effects may be reduced or eliminated with dose reduction20,28.

Kaplan-Meier analysis showed a little decrease in patients remaining on CLB reflecting a good retention rate. Efficacy was seen even in low doses of 10-20 mg daily. Seizure freedom is most likely to be seen in patients on first and second add on therapy with CLB. Although this finding was in concordance with the earlier observation that chances of seizure freedom declined with successive drug regimens29, the present study provided the evidence for the same. The percentage of seizure reduction was reported only after the addition of CLB while keeping the other treatment regimens constant.

Since the present study did not assess the role of concomitant AEDs in seizure freedom, head-on comparison with use of other AEDs as first add-on drug are needed to conclude with certainty if CLB reduces prescription load as first add-on therapy. In some patients, CLB could be substituted for other broad-spectrum AEDs, resulting in seizure freedom or a substantial reduction in seizure frequency.

The present results showed that clobazam was effective in both types of seizures i.e. generalized as well as focal. Seizure freedom was likely achieved in patients on first and second add-on therapy with clobazam.

Acknowledgment

Authors acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for providing financial assistance (9/6(431)/2011, EMR-I) to the first author (RJ), and thank Shrimati M. Kalaivani from the department of Biostatistics for her support in statistical analysis of data.

References


*Rerprint requests*: Dr Manjari Tripathi, Professor, Department of Neurology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India
e-mail: manjari.tripathi1@gmail.com