Clobazam in the treatment of epilepsy: prospective follow-up to 8 years

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Introduction

Clobazam is a 1,5 benzodiazepine launched in 1975 as an anxiolytic. Subsequently it was observed to have significant anticonvulsant properties which have been reviewed by Robertson[1]. Since that time there have been a number of publications pertaining to the use of clobazam as an adjunct therapy in persons with refractory seizures; one of the most recent being the Canadian experience with 1300 patients over 7 years[2]. The present paper reviews the experience of one clinician with the use of clobazam in 56 patients over a period of up to 8 years; an open, uncontrolled study.

Methods

Clobazam was introduced to the anti-epileptic drug (AED) regimen of the patients reported, if seizure control was deemed by the patient to be inadequate, despite standard AED therapy with drug concentrations in the therapeutic range. All patients were commenced on a dosage of 10 mg at night which was increased in some cases. The patients were then followed clinically with particular attention being paid to seizure control and drug side effects.

In analysing the data, the patients were divided into three categories: those with partial seizures including complex partial seizures (CPS), CPS which secondarily generalize, and simple partial seizures (SPS); primary generalized seizures and generalized seizures associated with physical and/or intellectual handicap. The efficacy of clobazam was graded as follows:

1 The eradication of seizures.
2 A reduction of seizures by more than 50% of the seizure frequency as assessed over the 4 months before clobazam was added.
3 No effect.
4 Seizures made worse.

As tolerance is known to be a potential problem with clobazam[1], this was closely looked for, as were any drug side effects.

Results

The group overall

Fifty-six patients (33 females) were studied. Their ages ranged from 6 to 59 years (mean 29.3±13.3), they had had epilepsy from 3 to 56 years (mean 17.3±11.6) with 34 having partial seizures (18 CPS secondary generalization, 14 CPS and two SPS) 15 primary generalized, and seven patients had generalized seizures with handicap. Twenty-nine of the patients were taking one standard AED, 22 two AEDs and five were taking three other AEDS. Carbamazepine was taken by 38 (67.9%) of the patients, sodium valproate by 30 (53.5%) and phenytoin 15 patients (26.7%). The maintenance dose of clobazam varied from 10 to 30 mg per day (mean 15.6±5.9) and it had been taken for 1 month to 8 years (mean 2.00±1.9).

In 14 patients, seizures were completely eradicated and in one patient with CPS and secondary generalization, the latter was eradicated whilst the CPS were significantly reduced. This represents an excellent result in 26.8% of patients. In addition, a greater than 50% reduction in seizure frequency was observed in 27 patients (48.2%). This means that 75.0% of the patients benefited from the administration of clobazam. In 10 patients, no beneficial effect was observed, in three patients (5.4%) seizure control deteriorated and in the final patient, the drug was used intermittently.

Of the 56 patients, 28 (50%) continue to take clobazam 3 months to 8 years (mean 3 years) after commencing it. Twenty-eight patients ceased taking the drug: 11 due to tolerance, 10 because of a lack of effect, five due to side effects, one patient died and the last patient decided to cease taking the drug for reasons best known to himself. Tolerance, namely an initial reduction in seizure frequency followed by an increase in seizure frequency, occurred, as mentioned above, in 19.6% of patients. Its occurrence varied from 3 months to 3 years (mean 1.36) after the commencement of clobazam.

Overall 14 patients (25%) suffered some drug side effects, with medication being ceased in five cases (9%) because of the side effects. These included troublesome drowsiness in six patients, weight gain in three patients (5, 7 and 12 kg), pedal oedema and an increase in seizure frequency, an increase in seizure frequency in two further patients, persistent dizziness and ejaculatory failure. It was in the latter five patients that clobazam was ceased because of the side effects, all of which disappeared over a matter of days to 3 months.

Finally, three patients took clobazam throughout a pregnancy. A 30-year-old woman with primary generalized epilepsy whose seizures had been eradicated for 8 years after commencing clobazam 10 mg twice daily, in addition to carbamazepine, had a normal infant. Whilst taking phenytoin previously, she had had a child with typical features of the so called 'hydantoin syndrome'. A 39-year-old woman with CPS whose seizure frequency had been reduced over the previous 7 years from two to three seizures/week to

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one a year with the addition of clobazam 30 mg/day to carbamazepine, had a child with no dysmorphic features but who exhibited a persistent fetal circulation and now shows features of the attention deficit disorder. Lastly, a 37-year-old woman, with CPS which secondarily generalized about twice a month whose seizures had been eradicated for 6 years with a clobazam dose of 5 mg twice daily in addition to carbamazepine, had an entirely normal infant.

Partial seizures

There were 34 patients (20 female) in this group; their ages ranged from 6-58 years (mean 29.6±12.8) and they had had epilepsy for 3-49 years (mean 17.1±11.2). Eighteen were receiving monotherapy, 14 were taking two other AEDs and two patients were taking three other AEDs.

These patients had been receiving clobazam for a month to 7 years (mean 1.95±1.93) in doses ranging from 10-30 mg/day (mean 15.0±6.0). In seven patients (20.5%), all seizures were eradicated for periods ranging from 1 to 6 years; in an additional patient with CPS and secondary generalization, the tonic clonic seizures were eradicated and the CPS greatly reduced over a 6 year period. In a further 17 patients there was a greater than 50% reduction in seizure frequency, seven patients there was no effect and in one patient there was an increase in seizure frequency. In the final patient in this group, clobazam was used intermittently after an initial seizure to try and prevent subsequent seizures; in this respect it was shown to be useful on most occasions.

Seven patients in this group developed side effects; three were significantly drowsy, three increased in body weight (5, 7 and 12 kg) and one patient developed pedal oedema associated with an increase in seizure frequency. Clobazam was ceased in this latter patient.

Of the 34 patients, 18 continue to take clobazam and 16 have ceased taking it; seven due to a lack of effect; six due to tolerance which occurred at 3, 6, 9, 12, 18 and 36 months, respectively; one patient died; one patient already discussed had an increase in seizure frequency and the final patient decided to cease all his therapy.

Generalized seizures

There were 15 patients (nine females) in this more disparate group, with ages ranging from 12 to 59 years (mean 34.2±13.2) and who had epilepsy for 6 to 56 years (mean 20.2±14.1). Eight were taking one AED, 6 two and one was taking three AEDs. These patients had been receiving clobazam for 6 months to 8 years (mean 2.2±2.1) in a dose ranging from 10 to 30 mg/day (mean 16.3±6.1).

Eleven of these patients had tonic clonic convulsions; seizures had been eradicated for 8 years in one patient, 4 years in another and 1 year each in two others. In 3 others, seizures were significantly reduced, in one patient there was no effect and in another, seizure frequency increased. Of the other four patients in the group: one had atypical absence epilepsy and clobazam had no effect; another had absences, myoclonic and tonic clonic seizures which responded to clobazam with a marked reduction in all seizure types for 4 years before he developed subclinical status controlled with phenytoin; another patient who had had tonic seizures had shown a quite marked improvement with clobazam until developing tolerance after a year; and the final patient with juvenile myoclonic epilepsy has shown a reduction in seizures for 6 months with clobazam being added to sodium valproate.

Of the 15 patients, seven continue to take clobazam, 3 months to 8 years (mean 2.8) after commencing it. Eight ceased the drug, three due to side effects (increased seizure frequency, persistent dizziness and ejaculatory failure), three due to tolerance at 1 year in one patient and 2 years in the other two cases and finally two patients stopped taking the drug because it had no effect.

Generalized seizures associated with physical/intellectual handicap

These seven patients have been placed in a separate group as it is often perceived that seizures associated with handicap are more difficult to control. The ages of these patients ranged from 11 to 29 years (mean 16.0±6.4), four of the patients were male and they had had epilepsy for 10 to 19 years (mean 12.3±3.1). Three were receiving monotherapy, two were taking two drugs and the remaining two patients were receiving three AEDs each. They received 10-20 mg/day of clobazam (mean 17.1±4.9) and had been taking it for 1 month to 5 years (mean 1.8±1.72).

In this group two exhibited only tonic clonic seizures. In one of these, the seizures have been eradicated for the past 5 years whilst in the other patient, they were significantly reduced until tolerance developed after 15 months of clobazam. The other 5 patients exhibited tonic clonic and atonic seizures (drop attacks); in two of these patients, seizures have been eradicated for 3 years and 3 months, respectively; in another there was a marked reduction in seizure frequency with tolerance developing after 15 months; and in one patient there was no effect; and in the final patient seizure control deteriorated and the drug was withdrawn with a decrease in seizure frequency. No side effects, except in the patient just referred to, were noted in this group of patients and of the seven patients, three continue to take clobazam.

As reported by Robertson[1], the overall frequency of seizure reduction was 65% (range 20-90%). This is similar to the 75% improvement in the present report and compatible with two other recent studies[2,4]. Of importance is that this effect is of considerable duration ranging from 3 months to 8 years (mean 3.4) in the 14 patients whose seizures have been eradicated by clobazam. This is similar to the data of Martin[5]. Further, of the 56 patients, 28 (50%) continue to take clobazam 3 months to 8 years after commencing it, suggesting that although, perhaps, not statistically significant, it is of value to a proportion of persons with refractory epilepsy. This is supported by the Canadian experience with clobazam[2] where 40 to 50% of patients continued to use the drug for more than 4 years.

As demonstrated in the present, uncontrolled study, clobazam may be effective in most of the common seizure types. Including eradication and the reduction of seizures by greater than 50% of pretreatment values, there was a 73.5% improvement in those with partial seizures, 60% in the generalized seizure group and 43% in the generalized seizure with handicap group. This is in agreement with the observations that clobazam is effective in complex partial seizures[6,7] and secondarily generalized epilepsy[8,9]. Again this is similar to the recently described Canadian experience[2]. Of interest is the observation of a poorer response rate in persons with intellectual handicap

as observed by Heller *et al.*[10]. It has been used once as monotherapy in a group of 24 children aged 6 months to 16 years, where it was effective in 17 patients of whom 16 had partial seizures. Complete seizure eradication occurred in 11 of the 24 children[11].

Overall, experience from this study would suggest that after a 2-3 month trial of clobazam, it will either have been effective or not. If not, it should be abandoned, but if effective should be continued, leading to the potential problem of tolerance. As reviewed by Robertson[1], the incidence of tolerance varied from 0 to 86% with a mean of 36%. The Canadian experience was 9.2% whilst the recent data of Guberman *et al.*[4] is unclear in this regard. In the present study, 11 patients (19.6%) developed tolerance. Of practical importance, tolerance occurred from 3 months to 3 years after commencing therapy, even in patients taking low doses of clobazam and in no case responded for any length of time to increasing the dose. Based on experience from the present study, once tolerance has occurred, the present data being similar to that of others[8,12], it is likely to continue and eventually clobazam will need to be withdrawn. It has been recommended that tolerance can be minimized by using it in low dosage[13]; the doses used in the present study were in the main quite low which may account for a tolerance rate of 19.6%, as opposed to the average of 36% described by Robertson[1]. Once tolerance has occurred, it is said that it may be overcome either by increasing the dose of clobazam or by by ceasing therapy for a few weeks[3,14]. In the present study neither of these approaches produced benefits of any duration, an observation in accord with that of Munn *et al.*[15].

Side effects were especially carefully sought in the follow up of these 56 patients and occurred in 14 cases. The initial drowsiness on commencing therapy was not considered a side effect of note. In only five cases were side effects sufficiently severe to warrant ceasing therapy and in all those cases, they receded. Guberman *et al.*[4] reported 40 of their 47 patients having side effects, but this appears to include the initial drowsiness which seems to be almost universal when commencing clobazam therapy. Excluding this phenomenon and comparing the data of Guberman *et al.*[4], the Canadian experience[2] and the present study, it would appear that drowsiness, ataxia and weight gain are the commonest side effects.

Conclusion

In conclusion, the present study supports the existing literature in suggesting that clobazam is a useful adjunct AED in most of the common seizure types and, in the view of the author, is often underrated as to its potential usefulness. Further, the present study, with a follow up period of up to 8 years reinforces the view that the beneficial effects of clobazam, despite the problem of tolerance, may well be prolonged. From a practical point of view, it is suggested that clobazam might best be used as follows:

1 In the lowest dose possible (5 to 20 mg/day) either as a single night time dose or twice daily.

2 After having mentioned the possibility of tolerance to the patient.

3 By suggesting, depending upon seizure frequency, a 1-3 month therapeutic trial. If there has been no response within this time, it is unlikely to occur and the drug should be withdrawn.

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