

Clobazam for the treatment of intractable childhood epilepsy

Mohammed M. Jan, MBChB, FRCP(C), Ali O. Shaabat, MD, FRCP(C).

ABSTRACT

Objective: Clobazam is a newer 1,5-benzodiazepine used for the treatment of epilepsy. It is better tolerated and less sedating than other benzodiazepines. It has yet to gain wide use for epilepsy in the Middle East. Our objective is to report our experience with clobazam for the treatment of childhood epilepsy.

Methods: A cohort of children with intractable epilepsy, defined as recurrent seizures after at least 3 anti-epileptic medication trials, were included prospectively. Clobazam was added to a maximum dose of 2 mg/kg/day. Follow-up by two pediatric neurologists was performed. Therapeutic response was recorded as complete (no seizures), good (>50% seizure reduction), fair (<50% seizure reduction), or none.

Results: Thirty one children (21 males - 10 females), aged 2 months-15 years (mean 4.6 years) were followed for 3-12 months. Most children (68%) had daily seizures

and were on multiple anti-epileptic drugs (mean 2.3, +/- SD 1). Fourteen (45%) children had Lennox-Gastaut Syndrome. After the introduction of clobazam, 11 (35.5%) became completely seizure free and 14 (45%) had >50% seizure reduction. Side effects were reported in 7 (22.5%) in the form of excessive sedation, vomiting, irritability, behavioral change, and ataxia. In 4 children these side effects resolved either spontaneously or with dose reduction.

Conclusion: Clobazam is a well tolerated, safe, and very effective antiepileptic drug. It has a broad spectrum of antiepileptic activity, minimal side effects, and is relatively inexpensive. Wider use of this drug is recommended in children with intractable epilepsy.

Keywords: Clobazam, child, intractable, epilepsy, seizures.

Neurosciences 2000; Vol. 5 (3): 159-161

Clobazam is a newer benzodiazepine used for the treatment of epilepsy.¹ It is a 1,5-benzodiazepine that is better tolerated and results in less sedation when compared to the other benzodiazepines.²⁻⁴ The half life of clobazam is 18 hours and up to 42 hours for its active metabolite.⁴ Several studies examined the efficacy of clobazam in partial and generalized seizures.⁵⁻⁸ The Canadian Clobazam Cooperative Study Group reported a 50% improvement in 40% of patients with intractable seizures.⁸ In other studies up to 21% of children became seizure free and half had at least 50% seizure reduction.⁹ The drug had a low incidence of drug interactions, however, enzyme inducers can lower its serum level. Clobazam can reduce phenytoin hepatic

clearance and increase carbamazepine levels.¹⁰⁻¹² Few side effects have been reported in up to 25% of patients, mainly sedation, behavioral change, memory defects, and tolerance.^{4,8}

Although clobazam is cheaper than the other new anti-epileptic drugs and is readily available in the Middle East, it is not widely used for epilepsy and its use has been primarily in the field of psychiatry as an anxiolytic agent. We report our experience with clobazam for the treatment of childhood epilepsy.

Methods. A cohort of children with intractable epilepsy was included prospectively. Patients were identified through referrals and consultations to the

From the Department of Pediatrics (Neurology), King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia.

Published simultaneously with special permission from Saudi Medical Journal.

Address correspondence and reprint request to: Dr Mohammed M. S. Jan, The Department of Pediatrics (Neurology), King Abdulaziz University Hospital, PO Box 6615, Jeddah 21452, Kingdom of Saudi Arabia. Tel. + 966 2 640 1000 Ext 20208. Fax. + 966 2 640 3975.

Table 1 - Causes of intractable epilepsy in the study cohort (n=31).

Diagnosis	Number (Percentage)
Cerebral Palsy	7 (23%)
Idiopathic Epilepsy	6 (19%)
Syndromic/CNS Malformation	5 (16%)
Cryptogenic Epilepsy	4 (13%)
Neurodegenerative Disorder	3 (10%)
Post-meningitis or Post-encephalitis	3 (10%)
CNS Tumor	1 (3%)
Post-traumatic Epilepsy	1 (3%)
Mesial Temporal Sclerosis	1 (3%)

Pediatric Neurology Service at King Abdulaziz University Hospital (KAUH) from August 1, 1998 to July 31, 1999. King Abdulaziz University Hospital is a multispecialty adult and pediatric hospital providing primary care to the Jeddah area, as well as secondary and tertiary care for most of the regional population of western Saudi Arabia. King Abdulaziz University Hospital is the main teaching center of western Saudi Arabia and is linked to King Abdulaziz University Medical School. Patient and disease related data were collected during the initial visit. Intractable epilepsy was defined as recurrent seizures that failed to respond to at least three anti-epileptic medication trials singly or in combination despite of using maximum doses or doses resulting in therapeutic drug levels. After obtaining verbal consent, clobazam was added to the other anti-epileptic drug therapy at a starting dose of 0.25 mg/kg/day (minimum starting dose of 2.5 mg/day). Clobazam was gradually increased by doubling the dose every 5-7 days until the minimum effective dose was reached (achieving a seizure free outcome) or up to a maximum dose of 2 mg/kg/day. Follow up by two pediatric neurologists was performed to document therapeutic response and occurrence of side effects. Therapeutic response was recorded as complete (no seizures), good (>50% seizure reduction), fair (<50% seizure reduction), or none (no response).

The data was tabulated using Epi Info, version 6^{13,14}, and the results were examined by Chi-square statistics to identify the magnitude of significant associations when present. A p-value less than 0.05 was considered statistically significant.

Results. Thirty-one children with intractable epilepsy were identified and followed for 3-12 months. There were 21 (68%) males and 10 (32%)

females, aged 2 months-15 years (mean 4.6, SD 3.1 years). Twenty-four (77%) children had mental retardation. Fourteen (45%) children had Lennox-Gastaut Syndrome with multiple seizure types, 9 (29%) had partial seizures with or without secondary generalizations, 4 (13%) had myoclonic epilepsy, and 4 (13%) had isolated generalized tonic clonic seizures. The underlying causes of their epilepsy are summarized in Table 1. The most common diagnosis was cerebral palsy (23%). Idiopathic epilepsy (normal development and central nervous examination (CNS)) and cryptogenic epilepsy (abnormal development and CNS exam with no recognized disease) were present in 19% and 13% of the children (Table 1). The age of seizure onset ranged between 1 month – 6 years (mean 1.8, SD 1.7 years). The duration of epilepsy prior to the initiation of clobazam ranged between 2 months – 10 years (mean 2.9, SD 2.5 years). Most children (68%) had daily seizures and were on multiple anti-epileptic drugs (range 1-5, mean 2.3, +/- SD 1). Eleven (35.5%) children were on 3 or more antiepileptic drugs. Clobazam was added to the other antiepileptic drugs with a final dose ranging between 5-40 mg/day divided twice per day. After the introduction of clobazam, 11 (35.5%) children became completely seizure free, 14 (45%) had >50% seizure reduction, 4 (13%) had <50% seizure reduction, and 2 (6.5%) had no response. None of the children had worsening of their seizures. Table 2 shows a summary of the seizure count before and after clobazam. Children with Lennox Gastaut Syndrome had a relatively less favorable response as more children continued to have daily seizures when compared to those with other seizure types (3/14 vs 1/17, p=NS). The number of anti-epileptic drugs also decreased after the introduction of clobazam to 1-3 (mean 1.7, SD 0.5). Only one child was on 3 anti-epileptic drugs. Electroencephalograms (EEG) were recorded before starting the clobazam and repeated while the child was on it in 10 children. Nine (90%) of these children showed marked EEG improvement in terms of epileptiform discharges and 8 out of these 9 were seizure free. No side effects were noted in 24 (77.5%) children. The remaining 7 (22.5%) children

Table 2 - Seizure count before and after the initiation of clobazam.

Seizure Count	Before Clobazam Number (%)	On Clobazam Number (%)
Daily	21 (68%)	4 (13%)
Weekly	7 (22%)	6 (19.5%)
Monthly	3 (10%)	10 (32%)
None	0.00	11 (35.5%)

had some side effects including; excessive sedation in 4, vomiting in one, irritability and behavioral change in 2, and ataxia in one child. The sedation and ataxia were transient and resolved in 4 children either spontaneously or with dose reduction. Clobazam had to be withdrawn in 3 children due to repeated vomiting or behavioral changes.

Discussion. The study results confirm several observations. Clobazam is a very effective and well tolerated anti-convulsant drug. Most of our patients had significant seizure reduction and 1/3 became completely seizure free. This is very impressive, as all of them had very difficult seizure disorders. Also, the number of anti-epileptic drugs decreased following the introduction of clobazam. Whenever carried out, most EEGs also showed marked improvement in terms of epileptiform discharges. Our findings are similar to those reported by the Canadian Clobazam Cooperative Study Group⁸, however, our seizure free rate (35.5%) was slightly higher than the 21% rate that was reported in other studies.⁹ This may be the result of our relatively shorter follow-up, as some of these children may have more seizures when followed for longer periods of time. A more recent study compared the effectiveness of clobazam to carbamazepine and phenytoin in children with epilepsy and found seizure control equivalent for all three medications.¹⁵ In our study, clobazam side effects were minimal and the drug was well tolerated. Only 7 (22.5%) children had side effects including; excessive sedation, vomiting, irritability, behavioral change, and ataxia. Other studies reported side effects in up to 25% of patients.^{4,8} Our lower rate is likely the result of the slow rate of drug introduction and the tendency to use the minimum effective dose. The other possible explanation is the rate of mental retardation in the study sample. Most of our patients (77%) were mentally handicapped which may interfere with the reporting of side effects. Most of the side effects were transient or responded to dose reduction. The cognitive and behavioral side effects of clobazam appear to be similar to those of standard therapy¹⁶, however, clobazam induces slightly more behavioral effects when compared to carbamazepine or phenytoin.¹⁵ In our series, clobazam had to be withdrawn in 3 children due to behavioral changes. The drug may need to be avoided in children with epilepsy and severe behavioral or attention disorders to prevent exacerbating these effects.

In conclusion, clobazam is a well tolerated, safe, and very effective anti-epileptic drug. It has a broad spectrum of anti-epileptic activity, minimal side effects, and is relatively inexpensive. Wider use of

this drug is recommended in children with intractable epilepsy.

Acknowledgments. We wish to thank the pediatric consultants at King Abdulaziz University Hospital who participated with their referred patients. We particularly would like to thank Dr. Saad Al-Saadi, Dr. Wasim Anshasi, Dr. Hussein Bamashmous, and Dr. Amal Al-Dabbag.

References

1. Fisher R. Newer antiepileptic drugs. In: *The Treatment of Epilepsy Principles and Practice*. 2nd Edition; Baltimore, Maryland: Williams & Wilkins; 1997. p. 920-930.
2. Allen JW, Oxley J, Robertson MM, Trimble MR, Richens A, Jawad SS. Clobazam as adjunctive treatment in refractory epilepsy. *Br Med J Clin Res Ed* 1983; 286: 1246-1247.
3. Wildin JD, Pleuvry BJ, Mawer GE, Onon T, Millington L. Respiratory and sedative effects of clobazam and clonazepam in volunteers. *Br J Clin Pharmacol* 1990; 29: 169-177.
4. Remy C. Clobazam in the treatment of epilepsy: A review of the literature. *Epilepsia* 1994; 35(Suppl 5): S88-S91.
5. Buchanan N. Clobazam in the treatment of epilepsy: A prospective follow up to 8 years. *J R Soc Med* 1993; 86: 378-380.
6. Keene DL, Whiting S, Humphreys P. Clobazam as an add-on drug in the treatment of refractory epilepsy of childhood. *Can J Neurol Sci* 1990; 17: 317-319.
7. Shorvon SD. Benzodiazepines: Clobazam. In: Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic drugs*. 4th ed. New York, NY: Raven Press Ltd; 1995: 763-777.
8. Canadian Clobazam Cooperative Study Group. Clobazam in the treatment of refractory epilepsy: the Canadian experience. A retrospective study. *Epilepsia* 1991; 32: 407-416.
9. Schmidt D. Clobazam for the treatment of intractable epilepsy: a critical assessment. *Epilepsia* 1994; 35(Suppl 5): S92-S95.
10. Sennoune S, Mesdijan E, Bonneton J, Genton P, Dravet C, Roger J. Interactions between clobazam and standard antiepileptic drugs in patients with epilepsy. *Ther Drug Monit* 1992; 14: 269-274.
11. Zifkin B, Sherwin A, Andermann F. Phenytoin toxicity due to interaction with clobazam. *Neurology* 1991; 1: 313-314.
12. Munoz JJ, De Salamanca RE, Diaz-Obregon C, Timoneda FL. The effect of clobazam on steady state plasma concentrations of carbamazepine and its metabolites. *Br J Clin Pharmacol* 1990; 29: 763-765.
13. Dean AG, Dean JA, Burton A, Dicker R. Epi Info: A general-purpose microcomputer program for public health information systems. *Am J Prev Med* 1991; 7: 178-182.
14. Dean AG, Dean JA, Coulombier D. Epi Info, Version 6: A word processing, database, and statistics program for public health on IBM-compatible microcomputers. Centers for Disease Control and Prevention, Atlanta, Georgia, USA, 1995.
15. Canadian Study Group for Childhood Epilepsy. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. *Epilepsia* 1998; 39: 952-959.
16. Bawden HN, Camfield CS, Camfield PR, Cunningham C, Darwish H, Dooley JM, et al. The cognitive and behavioral effects of clobazam and standard monotherapy are comparable. Canadian Study Group for Childhood Epilepsy. *Epilepsy Res* 1999; 33: 133-143.