

# Clobazam as Add-on Therapy for Temporal Lobe Epilepsy and Hippocampal Sclerosis

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**ABSTRACT: Background:** Clobazam is a benzodiazepine with known antiepileptic action; however, it is not considered first line therapy in the treatment of epilepsy. The objective of this study was to evaluate the efficacy of clobazam as add-on therapy in adults with temporal lobe epilepsy associated with MRI evidence of hippocampal sclerosis (HS). **Method:** This is a retrospective study, conducted at our epilepsy clinic which evaluated clobazam as add-on therapy in patients with temporal lobe epilepsy and MRI signs of HS. Clobazam was prescribed based on the minimum effective dose up to the maximum tolerated dose. **Results:** Seventy-eight patients met the inclusion criteria (51 women), ages ranging from 16 to 76 years old (mean=42.2). Dosage of clobazam ranged from 5 to 60 mg/day (mean=22.6 mg/day). Clobazam was used from one month to eight years (mean=29 months). Sixteen (20.5%) patients were seizure-free, 20 (25.5%) had more than 75% improvement in seizure control, eight (10%) had more than 50% and 20 (26%) were non responders to clobazam. In 14 (18%) we could not determine seizure frequency during follow-up. The improvement in seizure control lasted for more than one year in 30 (68%) patients. **Conclusion:** Our data suggest that clobazam should be considered as add-on therapy in the treatment of patients with temporal lobe epilepsy associated with MRI signs of HS.

**RÉSUMÉ: Le clobazam comme traitement adjuvant de l'épilepsie temporale et de la sclérose de l'hippocampe. Introduction:** Le clobazam est une benzodiazépine qui a un effet antiépileptique. Cependant, cette substance n'est pas considérée comme un médicament de première ligne dans le traitement de l'épilepsie. L'objectif de cette étude était d'évaluer l'efficacité du clobazam comme traitement adjuvant chez les adultes souffrant d'épilepsie temporale et ayant une sclérose de l'hippocampe (SH) à l'IRM. **Méthode:** Il s'agit d'une étude rétrospective menée à la clinique d'épilepsie de notre hôpital universitaire. Nous avons évalué les patients recevant du clobazam comme traitement adjuvant parmi un groupe de 100 patients consécutifs souffrant d'épilepsie temporale et ayant des signes de SH à l'IRM. La dose de clobazam prescrite variait de la dose minimale efficace à la dose maximale tolérée. **Résultats:** 78 patients (51 femmes et 27 hommes), dont l'âge variait de 16 à 76 ans (âge moyen 42,2 ans) rencontraient les critères d'admission dans l'étude. Le dosage du clobazam était de 5 à 60 mg/j (dose moyenne de 22,6 mg/j). La durée du traitement était de 1 mois à 8 ans (durée moyenne 29 mois). Seize patients (20,5%) n'avaient plus de crises, 20 (25,5%) avaient une amélioration de plus de 75% dans le contrôle des crises, 8 (10%) avaient une amélioration de plus de 50% et 20 (26%) étaient des non-répondeurs. Chez 14 (18%), la fréquence des crises pendant le suivi n'a pu être déterminée. L'amélioration dans le contrôle des crises a duré plus d'un an chez 30 patients (68%). **Conclusion:** Selon ces données, le clobazam est sûr et efficace dans le traitement de patients ayant une épilepsie temporale et des signes de SH à l'IRM.

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The use of a single antiepileptic drug (AED) based on the minimum effective dose up to the maximum tolerated dose is the standard therapy for epilepsy. After first monotherapy failure most epileptologists prescribe a second AED monotherapy before considering the combination of antiepileptic drugs.<sup>1</sup> However, the use of more than one AED is sometimes required

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and can render seizure control in some patients with refractory epilepsy.<sup>2</sup>

Although epilepsy surgery is the standard treatment for patients with refractory temporal lobe epilepsy (TLE)<sup>3,4</sup> and magnetic resonance imaging (MRI) signs of hippocampal sclerosis (HS), some of these patients may improve dramatically after the introduction of clobazam.<sup>5-7</sup> Clobazam has been known for more than three decades and its efficacy has been evaluated by several studies.<sup>7-14</sup> However, to our knowledge, no study addressed the efficacy of clobazam in patients with refractory TLE and HS.

The objective of this study was to evaluate the efficacy of clobazam as add-on therapy in adults with refractory TLE associated with MRI signs of HS.

## METHODS

This is a retrospective study, conducted at the epilepsy clinic of our university hospital. We evaluated the patients that met all the inclusion criteria from a group of 100 consecutive patients with TLE and MRI signs of HS, from March to October 2003. We collected data from patient's routine visits and clinical files.

Inclusion criteria were:

- Diagnosis of TLE established by clinical and electroencephalographic (EEG) findings according to the International League Against Epilepsy syndromic classifications.<sup>15</sup>
- Hippocampal atrophy and other signs of HS, including hyperintense T2 signal, identified by visual analysis of high resolution MRI performed by professionals with experience in neuroimaging investigation of patients with epilepsy.

## EEG

Interictal EEG recordings were performed routinely, using the International 10–20 System for electrode placement. Long term EEG monitoring was performed when appropriate.

## MRI

Magnetic resonance imaging was performed in a 2.0T scanner, using our epilepsy protocol.

## Introduction of clobazam

Clobazam was introduced as add-on therapy (starting with 10 mg/day) in patients with previous failure – that is, lack of complete seizure control – of at least two monotherapies. The titration rate was according to clinical response, but the interval to increase doses was no shorter than weekly. The dose escalation was of 10 mg for each step. Initial dose was 10 mg/day at bedtime, up to 60 mg/day, twice a day. Clobazam was prescribed using the minimum effective dose up to the maximum tolerated dose.

## Analysis of the data

For analysis of the results, patients were divided in five groups according to seizure control: a) seizure-free; b) 75% of improvement in seizure control, c) > 50% of improvement, d) no improvement, and e) data not available.

In the group of patients with improvement in seizure control, we also assessed the duration of this improvement according to four categories: a) more than one year of improvement, b) six months to one year, c) three months to six months, and d) less than three months of improvement.

We performed an analysis curve using the method of Kaplan and Meier, for retention of clobazam during a period of 36 months. Statistical analysis was performed using the chi-square test.

## RESULTS

For the 100 consecutive patients with TLE and MRI signs of HS, 58 were women; ages ranging from 16-76 years (mean age 41.3 years). The duration of epilepsy ranged from 3-61 years (mean=29.07 years).

The first seizure symptoms were indicative of TLE in all patients, that is, epigastric aura, fear, déjà-vu, jamais-vu, etc. Seventy-seven patients had at least one secondary generalized seizure.

From the 100 patients with MRI signs of HS, all had hippocampal atrophy and 91 had hippocampal hyperintense signal on T2 sequences. An average of nine (range 2 - 26) EEGs was performed for each patient.

Every patient used at least two different monotherapies (mean=2.27), up to seven, and a mean of 2.45 polytherapies, up to 10, before the introduction of clobazam.

## Patients exposed to clobazam

Seventy-eight patients met the inclusion criteria (51 women), ages ranging from 16 to 76 years old (mean=42.2). Mean monthly seizure frequency before the use of clobazam was 9.62 (range 1-110/months, median 5). Thirty-four (43.5%) patients had MRI signs of HS on the left side, 25 (32%) on the right side and 19 (24.5%) on both sides. Antiepileptic drugs associated with clobazam were carbamazepine (n=69), phenytoin (n=13), oxcarbazepine (n=5) and valproate (n=1).

Seventy-seven patients had at least one abnormal EEG. Interictal epileptiform abnormalities at anterior and basal medial temporal (electrodes F7, F8, T1, T2, T3, T4) were present in 73 (93.5%). Four (6.5%) patients presented only nonepileptiform abnormalities in the temporal regions. Only one patient presented six normal EEGs.

Doses ranged from 5 to 60 mg/day (mean=22.6 mg/day), and patients used clobazam for a period ranging from one month to eight years (mean=29 months). Eight patients had a follow up period less than three months, and four patients used clobazam for a period less than three months because the drug was withdrawn due to adverse events. Clobazam was discontinued when

**Table: Adverse events when clobazam was added**

Adverse event	Number of patients
Somnolence	29 (37%)
Dizziness	11 (14%)
Diplopia	8 (10%)
Irritability	5 (6.5%)
Headache, agitation	3 (4%)
Depression	2 (2.5%)
Nausea, vomit, slurred speech, ataxia, malaise, memory abnormalities, toe hypoesthesia	1 (1.2%)

Note: some patients presented more than one adverse event.

the maximum tolerated dose was reached without seizure improvement.

Forty-four (56.4%) patients had adverse events. Somnolence, dizziness and diplopia were the most frequent (Table). Fourteen (18%) patients discontinued the medication due to either adverse events (n=9), lack of efficacy (n=3) or both (n=2). Most patients in whom clobazam was withdrawn had multiple adverse events, which were somnolence (n=5), dizziness (n=5), headache (n=3), ataxia (n=1), nausea/vomiting (n=1), depression (n=1) and diplopia (n=1). Clobazam was withdrawn due to adverse events in two seizure-free patients.

Sixteen (20.5%) patients were seizure-free, 20 (25.5%) had more than 75% reduction in seizures, eight (10%) had more than 50% reduction in seizures, 20 (26%) were nonresponders to clobazam. We could not determine seizure frequency on follow up in 14 (18%) patients, either because patients did not fill out seizure calendars or because this information was not available in the charts. However, we had information about MRI, EEG and clinical findings, AED used, adverse events and when clobazam was discontinued in these 14 patients.

Among the 44 patients in whom seizure control improved after the introduction of clobazam, the improvement lasted for more than one year in 30 (68%) patients, six months to one year in ten (23%), three to six months in two (4.5%) and less than three months in two (4.5%).

The analysis curve using the method of Kaplan and Meier showed 40% retention of clobazam during the period of 36 months.

### Seizure-free patients

All patients who became seizure-free after clobazam introduction were using carbamazepine (doses ranging from 1000 to 1600 mg, mean=1292 mg/day) when clobazam was introduced. Clobazam doses ranged from 10 to 40 mg/day (mean=21.6). Nine patients had left HS, three right HS and four bilateral HS. The percentage of seizure-free patients was not influenced by whether HS was unilateral or bilateral ( $p>0.05$ ).

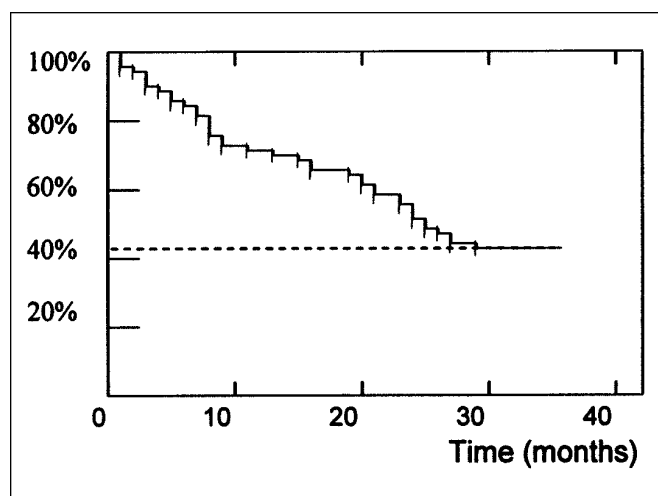
Nine patients presented adverse events (somnolence in eight, dizziness in four, irritability in one and diplopia in one). In two patients clobazam was withdrawn due to adverse events.

### DISCUSSION

Temporal lobe epilepsy is the most common type of epilepsy in adults and one of the most frequent causes of medically intractable epilepsy, particularly when associated with HS.<sup>3</sup> Patients likely to become refractory may be identified based on the number of seizures before therapy or inadequate response to initial treatment with AEDs.<sup>16</sup> Although our patients were not uniform in the number of AEDs used before clobazam, the chances of seizure control after two drugs fail are not good.<sup>2,3,16</sup>

It is known that MRI signs of HS are not necessarily a marker for refractory epilepsy, and it may occur in benign forms of TLE or even asymptomatic relatives.<sup>17-19</sup> However, HS is the most common finding in patients with refractory TLE who undergo surgery.<sup>3</sup> The overall seizure-free rates with medical treatment of TLE range from 11 to 42%.<sup>20-22</sup>

When different monotherapies do not result in seizure control, treatment requires combination of more than one AED,



**Figure:** Survival curve plot over a period of 36 months, showing percentage of patients with retention of clobazam as a fraction of time.

which may be associated with more frequent and severe side effects. New AEDs have been developed in order to provide better seizure control and keep adverse events within acceptable limits. The new AEDs are more expensive than conventional agents and price is their major problem; therefore cost should be taken into consideration in drug selection.<sup>23,24</sup> Clobazam is much less expensive than the newer AEDs.

The major drawback of this study is the fact that the information was assessed retrospectively and there is no control group. Retrospective studies always include the possibility of bias that cannot be controlled or accounted for. Although randomized controlled trials are considered the best test of efficacy of a drug, double-blind studies do not enable drug adjustment as needed and the follow-up period is usually short (less than 12 weeks).

Pharmacokinetic interactions are difficult to control in add-on trials. In addition they provide no evidence for activity of the test drug in monotherapy and overestimate the toxicity of the test drug. However, add-on trials have some merits and mimic clinical practice. Moreover, they are universally accepted by regulatory agencies and enables longer study duration.<sup>25</sup>

Although it is believed that the main drawback to clobazam, and other benzodiazepines, is the occurrence of tolerance,<sup>26</sup> our data shows that it has been overestimated. Almost half (46%) of the patients in our study were either seizure-free or had more than 75% reduction in seizure frequency, and this benefit was sustained for more than one year in 68% of them.

Sedation or somnolence was the most frequent adverse event reported, followed by dizziness and diplopia. Although almost 50% of patients presented adverse events, they were usually mild and did not lead to interruption of medication in most cases.

Clobazam can increase the serum levels of carbamazepine or its epoxide metabolites<sup>27</sup> and it was not always possible to distinguish clobazam related adverse events from those secondary to its interaction with other AED.

Although information about the response to clobazam was not available for 18% of the patients, we had the data about adverse

events and clobazam discontinuation. Therefore, these patients could be included in the survival analysis.

The retention of clobazam over a period of 36 months was more than 40% (Figure). Retention rate in drug trials has been considered a good marker for the comparative roles of efficacy and tolerability. That is in agreement with a recent review of long-term studies using the nonstandard AEDs in the management of chronic refractory epilepsy, which states that only clobazam has shown a consistency of data in clinical practice.<sup>28</sup>

It is important to note that our study provides information about a single type of epilepsy associated with unequivocal neuroimaging markers. Our data suggest that clobazam should be considered as add-on therapy in the treatment of TLE associated with MRI signs of HS.

## REFERENCES

- Karceski S, Morrell M, Carpenter D. The expert consensus guideline series. Treatment of epilepsy. *Epilepsy Behav* 2001;2: A1-A50.
- Brodie M J, Dichter M A. Drug therapy: antiepileptic drugs. *N Engl J Med* 1996;334:168-175.
- Wiebe S, Blume WT, Girvin JP, Eliasziw M. Effectiveness and efficiency of surgery for temporal lobe epilepsy study group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001;345:311-318.
- Engel J Jr. Finally, a randomized, controlled trial of epilepsy surgery. *N Engl J Med* 2001;354:365-367.
- Barcs G, Halasz P. Effectiveness and tolerance of clobazam in temporal lobe epilepsy. *Acta Neurol Scand* 1996;93:88-93.
- Heller AJ, Ring HA, Reynolds H-M. Factors relating to dramatic response to clobazam in refractory epilepsy. *Epilepsy Res* 1998;2:276-280.
- Montenegro MA, Cendes F, Noronha AL, et al. Efficacy of clobazam as add-on therapy in patients with refractory partial epilepsy. *Epilepsia* 2001;42:539-542.
- Canadian Clobazam Cooperative Group. Clobazam in treatment of refractory epilepsy: the Canadian experience. A retrospective study. *Epilepsia* 1991;32:407-416.
- 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.
- Koeppen D, Baruzzi A, Capozza M, et al. Clobazam in therapy-resistant patients with partial epilepsy: a double-blind placebo-controlled crossover study. *Epilepsia* 1987;28:495-506.
- Robertson MM. The place of clobazam in the treatment of epilepsy: an update. *Hum Psychopharmacol* 1995;10:S43-S63.
- Satishchandra P, Varadarajalu R, Rajaram P. Long-term use of clobazam in the management of intractable epilepsy: a prospective study. *Neurology (India)* 1998;46:284-287.
- Schmidt D, Rohde M, Wolf P, Roeder-Wanner U. Clobazam for refractory focal epilepsy. A controlled trial. *Arch Neurol* 1986;43:824-826.
- Canadian Study Group for Childhood Epilepsy. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. *Epilepsia* 1998;39:952-959.
- Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389-399.
- Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314-319.
- Kobayashi E, Li LM, Lopes-Cendes I, Cendes F. Magnetic resonance imaging evidence of hippocampal sclerosis in asymptomatic, first-degree relatives of patients with familial mesial temporal lobe epilepsy. *Arch Neurol* 2002;59:1891-1894.
- Kobayashi E, Lopes-Cendes I, Guerreiro CA, et al. Seizure outcome and hippocampal atrophy in familial mesial temporal lobe epilepsy. *Neurology* 2001;56:166-172.
- Andrade-Valença LP, Valença MM, Ribeiro LT, et al. Clinical and neuroimaging features of good and poor seizure control in patients with mesial temporal lobe epilepsy and hippocampal atrophy. *Epilepsia* 2003;44:807-814.
- Semah F, Picot MC, Adam C, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;51:1256-1262.
- Stephen LJ, Kwan P, Brodie MJ. Does the cause of localization-related epilepsy influence the response to antiepileptic drug treatment? *Epilepsia* 2001;42(3):357-362.
- Kim W-J, Park S-C, Lee S-J, et al. The prognosis for control of seizures with medication in patients with MRI evidence for mesial temporal sclerosis. *Epilepsia* 1999;40(3):290-293.
- Perucca E. Drug Treatment. In: Shorvon S, Dreifuss F, Fish D, Thomas D (Eds). *The Treatment of Epilepsy*. London: Blackwell Science, 1996:152-168.
- Meinardi H. Why phenobarbital? *Epicaded News* 1993;1:7-8.
- Schmidt D. *Drug Trials in Epilepsy. A Physicians Guide*. London: Martin Dunite, 1998.
- Singh A, Guberman AH, Boisvert D. Clobazam as long-term epilepsy treatment: sustained responders versus those developing tolerance. *Epilepsia* 1995;36:798-803.
- Shorvon SD. Benzodiazepines. Clobazam. In: Levy RH, Mattson RH, Meldrum BS, (Eds). *Antiepileptic Drugs*. 4th ed. New York: Raven Press Ltd., 1995:763-777.
- Satishchandra P, Trimble MR. On being seizure-free. *Epilepsy Behav* 2001;2:4-7.