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EFFECTIVENESS OF CLOBAZAM AS ADD-ON THERAPY IN CHILDREN WITH REFRACTORY FOCAL EPILEPSY

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ABSTRACT - The objective of this study was to evaluate the safety and efficacy of clobazam in children with refractory focal epilepsy. We investigated 100 consecutive patients concerning etiology of epilepsy, previously used antiepileptic drugs, seizure frequency and adverse events. Clobazam was introduced as add-on therapy in patients with previous failure of at least two monotherapies. Mean age was eight years-old and 39 patients were girls. Clobazam mean dosage was 23.6 mg/day. Mean use of clobazam was 18.6 months. Twenty-two patients had adverse events. Twenty-six patients became seizure-free, 11 had an improvement of >75% and in 58 there was no modification in seizure frequency. Five patients had an increase in seizure frequency. Clobazam efficacy lasted for more than one year in 42% of the seizure-free patients. Clobazam seems to be safe and effective in the treatment of focal epilepsy in childhood and should be considered in patients with refractory seizures.

KEY WORDS: clobazam, focal epilepsy, childhood.

Eficácia do clobazam como terapia adjuvante em crianças com epilepsia focal refratária

RESUMO - O objetivo deste estudo foi avaliar a segurança e eficácia do clobazam em crianças com epilepsia focal refratária. Nós investigamos 100 pacientes consecutivos em relação à etiologia da epilepsia, uso prévio de drogas anti-epilépticas, freqüência de crises e eventos adversos. Clobazam foi introduzido como terapia adjuvante em pacientes que não responderam a pelo menos duas monoterapias. A idade média foi 8 anos e 39 pacientes eram do sexo feminino. A dose média de clobazam foi 23,6 mg/dia. O uso médio de clobazam foi por 18,6 meses. Vinte e dois pacientes tiveram eventos adversos. Vinte e seis pacientes tornaram-se livres de crises, 11 tiveram melhora > 75% e em 58 não houve modificação na freqüência de crises. Cinco pacientes tiveram aumento na freqüência de crises. A eficácia do clobazam permaneceu por mais de um ano em 42% dos pacientes sem crises. Clobazam parece ser seguro e eficaz no tratamento de epilepsia focal na infância e deve ser considerado em pacientes com crises refratárias.

PALAVRAS-CHAVE: clobazam, epilepsia focal, infância.

In childhood, most epileptic syndromes are benign. Nevertheless, there is a group of severe epilepsy syndromes with refractory seizures that do not respond well to the usual antiepileptic drugs (AEDs).

Clobazam, a 1,5-benzodiazepine with good efficacy and tolerance, is considered an excellent option as add-on therapy for adults with refractory epilepsy[1-9]. Only a few studies have systematically investigated the efficacy and safety of clobazam in children[10-13].

The objective of this study was to evaluate the safety and efficacy of clobazam as add-on therapy in children with refractory partial epilepsy.

METHOD

This was a retrospective study, conducted at the pediatric epilepsy clinic of our university hospital. We evaluated 100 consecutive patients who met all the inclusion criteria, from June 2003 to February 2004. Patients were interviewed by one of the authors according to a semi-structured questionnaire that included the etiology of epilepsy, previously used AED, seizure frequency and adverse events. We collected data from the patients' routine visits and clinical files. The protocol and the informed consent were approved by the ethical committee of our university hospital.

Inclusion criteria were: age between six months and 18 years-old; diagnosis of focal epilepsy according to the

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International League Against Epilepsy syndrome classification[14]; previous failure of at least two monotherapies; use of clobazam as add-on therapy; signature of informed consent by parents or legal guardian.

Exclusion criteria were: diagnosis of generalized epilepsy or epileptic encephalopathy even if the patient also presented with focal seizures; progressive metabolic disorders or brain tumors.

Patients underwent interictal electroencephalographic (EEG) routine recordings using the International 10–20 System for electrode placement. Long term EEG monitoring was performed when appropriate.

Introduction of clobazam – Clobazam was introduced as add-on therapy (starting with 5 mg/day) in patients with previous failure of at least two monotherapies. The titration rate was according to clinical response, but the interval of increasing doses was no shorter than one week. The dose escalation was 5 mg for each step. The initial dose was 5 mg/day at bedtime, up to 60 mg/day, twice a day. Clobazam was prescribed on a minimally effective, up to the maximum, tolerated dose basis. Clobazam's dose was decreased or the drug was stopped if the patient presented with an adverse event.

Analysis of the data – For analysis of the results, patients were divided in four groups according to seizure control: a) seizure free; b) > 75% of seizure reduction; c) no improvement; and d) increase in seizure frequency.

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

We performed an analysis curve, using the method of Kaplan and Meier, for retention of clobazam during the 18-month period.

Adverse events were analyzed according to the clobazam dosage and number of AEDs. We also analyzed adverse events in relation to the age of the patients. For both analyses we used the t-student test with the level of significance of 0.05.

RESULTS

Ages ranged from one year to 18 years old (mean = eight years old). Thirty-nine patients were girls. All patients, except one, were using at least one AED when clobazam was introduced: 40 with carbamazepine, 24 with valproate, 19 phenytoin, 12 phenobarbital, 11 lamotrigine, eight topiramate, seven oxcarbazepine, and one vigabatrin.

The Table shows the characteristics of the patients. Sixty-five patients had a symptomatic epilepsy syndrome. In 35 patients the etiology of seizures could not be established. An EEG showed epileptiform abnormalities in 85% of the patients.

Doses ranged from 5 to 60 mg/day (mean = 23.6 mg/day), and patients used clobazam for a period ranging from 0.5 to 78 months (mean = 18.6 months). Clobazam was discontinued when the maximum tolerated dose was reached without seizure improvement or due to adverse events.

Twenty-two patients presented adverse events: somnolence in nine, irritability in nine, headache in two, and allergic reaction, vomiting and ataxia in one patient each. In 11 patients the adverse events were mild or transitory; however, in 11 patients clobazam was withdrawn due to the severity of the adverse events, primarily irritability.

The mean dosage used by patients presenting adverse events was 21.542 mg of clobazam, as opposed to 24.276 mg in those without adverse events (p= 0.435). The mean number of AEDs used by patients presenting adverse events was 2.292, as opposed to 2.237 in patients without adverse events (p=0.635).

When adverse events were analyzed according to age, our data showed that irritability occurred main-

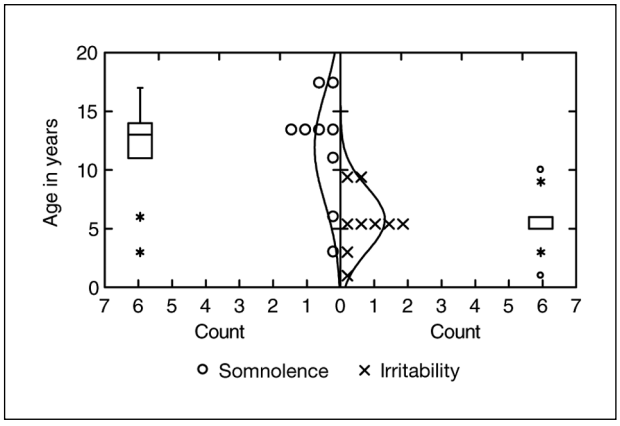

Fig 1. Somnolence versus irritability according to age.

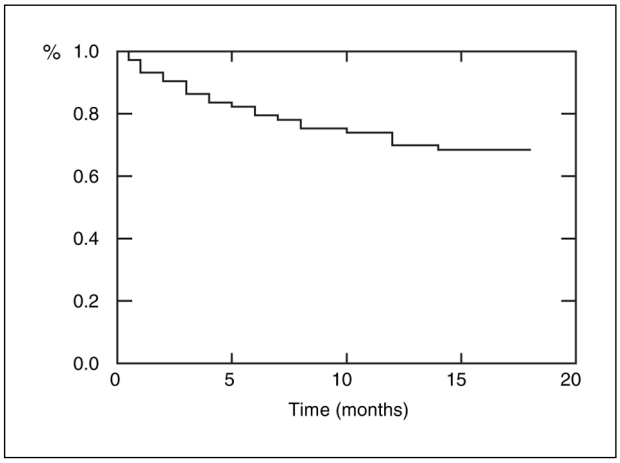

Fig 2. Survival curve plot of 72 patients over the 18-month follow-up period, showing the percentage of patients with retention of clobazam as a fraction of time.

Table. Characteristics of the patients.

ID	Age/ gender	Neurologic examination	Neuroimaging	AED associated with clobazam	Clobazam dose (mg)	Use of clobazam (months)	Interruption of clobazam	Reason for clobazam withdrawl
1	14/F	Strabismus	Gliosis	TPM	30	62	No	–
2	17/F	Normal	Normal	DPH	40	20	No	–
3	16/M	Normal	FCD	CBZ	40	18	No	–
4	16/F	Strabismus	HA	CBZ	30	28	No	–
5	11/M	Normal	Porencephalic cyst	CBZ	40	18	No	–
6	6/F	Developmental delay	Normal		15	12	Yes	LE
7	7/M	Normal	FCD	LTG-TPM	60	46	No	–
8	13/M	Normal	Temporal lobe atrophy	CBZ	30	8	Yes	Poor compliance
9	12/M	Blindness + developmental delay	Septo-optic dysplasia	DPH	20	14	Yes	LE
10	8/F	Developmental delay	Porencephalic cyst	DPH-PB-OXC	25	78	No	–
11	5/M	Developmental delay	Normal	VA	30	32	No	–
12	18/M	Developmental delay	Normal	LTG	60	18	No	–
13	14/F	Normal	HA	LTG-CBZ	30	12	No	–
14	14/M	Normal	Normal	CBZ-TPM	20	13	No	–
15	6/F	Language impairment	Diffuse atrophy + agenesis corpus callosum	CBZ	10	19	No	–
16	6/M	Normal	FCD	DPH	20	12	No	–
17	15/M	Normal	Low grade tumor	DPH	30	11	No	–
18	4/M	Normal	Normal	PB	60	7	Yes	LE
19	14/M	Normal	HA	VA	20	24	No	–
20	1/M	Speach delay	Normal	CBZ-VA	10	17	No	–
21	4/F	Normal	Normal	OXC-VA	15	6	Yes	LE
22	6/F	Developmental delay	Subcortical laminar heterotopia	LTG-VA	20	15	No	–
23	13/M	Normal	FCD	VA	50	20	No	–
24	14/M	Normal	HA	OXC-PB	20	18	No	–
25	1/F	Developmental delay	Normal	CBZ	15	24	No	–
26	11/F	Normal	FCD	VA	20	4	No	–
27	15/M	Normal	Low grade tumor + HA	CBZ-TPM	50	18	No	–
28	2/F	Developmental delay	Tuberous sclerosis	CBZ	20	48	No	–
29	4/M	Normal	FCD	CBZ-DPH	10	34	No	–
30	11/F	Developmental delay	Gliosis	CBZ	30	30	No	–
31	7/M	Normal	Normal	PB-CBZ	25	31	No	–
32	5/F	Developmental delay	HA	VA-TPM	5	1	Yes	AE
33	4/M	Normal	Normal	DPH-PB	30	12	No	–
34	3/M	Normal	Normal	CBZ–DPH	30	10	No	–
35	1/M	Normal	Normal	DPH	7,5	12	Yes	AE
36	7/M	Normal	HA	VA	20	29	No	–
37	17/F	Normal	Nomal	CBZ	30	36	Yes	AE
38	8/F	Developmental delay	Normal	DPH	25	11	No	–
39	10/F	Normal	FCD	CBZ	20	36	No	–
40	4/M	Language disturbance	Diffuse atrophy	PB	40	22	No	–
41	6/F	Normal	FCD + HA	VA	5	1	Yes	AE
42	13/F	Normal	FCD	DPH	40	18	No	–
43	10/M	Lower limb diplegia	Normal	LTG	50	7	No	–
44	7/M	Normal	Normal	CBZ-TPM	40	6	No	–
45	3/M	Developmental delay	Tuberous sclerosis	VA	10	12	Yes	AE
46	8/F	Normal	Cavernoma	VA-LTG	10	6	No	–
47	9/M	Normal	Normal	CBZ	20	7	No	–
48	4/F	Normal	FCD + HA	CBZ	15	36	No	–

Table. Continued.

49	11/M	Normal	FCD	OXC	20	29	No	–
50	9/M	Normal	FCD	CBZ	10	18	Yes	AE
51	10/M	Normal	FCD	TPM	30	6	Yes	AE
52	10/M	Hemiparesis	FCD	VA	20	36	No	–
53	15/M	Normal	Normal	VGB	60	4	No	–
54	4/F	Normal	FCD	CBZ-LTG	5	4	Yes	AE
55	15/F	Normal	HA	OXC	30	24	No	–
56	10/M	Developmental delay	Normal	CBZ	30	22	No	–
57	13/M	Developmental delay	Tuberous sclerosis	CBZ	40	8	Yes	LE
58	10/F	Ataxia	Cerebellar atrophy	LTG	10	18	No	–
59	9/F	Normal	Normal	DPH	10	12	No	–
60	1/M	Developmental delay	Tuberous sclerosis	CBZ	10	36	Yes	AE
61	15/F	Normal	HA	LTG-VA	50	24	No	–
62	8/F	Normal	Focal atrophy	CBZ	15	30	No	–
63	17/M	Normal	FCD	OXC	50	3	Yes	LE
64	5/M	Normal	Normal	LTG	25	12	No	–
65	13/M	Normal	HA	CBZ	30	41	No	–
66	7/F	Developmental delay	Focal atrophy	CBZ	20	10	Yes	LE
67	4/M	Developmental delay	Brain atrophy	PB	20	43	No	–
68	4/M	Developmental delay	Normal	VA	40	36	No	–
69	6/M	Developmental delay	Normal	PB	–	2	Yes	LE
70	2/F	Developmental delay	Normal	VA	25	39	No	–
71	3/F	Developmental delay	Epidermal cyst	VA	20	24	No	–
72	2/F	Normal	Cerebral calcification	CBZ	10	6	No	–
73	8M/F	Normal	Vascular insult	PB	5	1	Yes	LE
74	2/M	Normal	FCD + HA	TPM-DPH	25	11	No	–
75	8/F	Developmental delay	Normal	LTG	20	9	No	–
76	3/F	Normal	FCD	OXC	20	29	No	–
77	6/M	Developmental delay	Normal	VA	15	5	Yes	LE
78	6/F	Strabismus	Normal	CBZ	15	18	No	–
79	2/M	Speech delay	Normal	VA	5	24	No	–
80	2/M	Developmental delay	Normal	VA	10	27	No	–
81	11/M	Developmental delay	Schizencephaly	CBZ-PB	10	13	No	–
82	6/F	Developmental delay	Normal	VA	5	3	Yes	AE
83	9/M	Developmental delay	Diffuse atrophy	VA	10	4	Yes	LE
84	9/F	Developmental delay	Normal	CBZ	15	3	Yes	Poor compliance
85	3/F	Developmental delay	Agenesis of corpus callosum	LTG-DPH	40	12	No	–
86	16/M	Normal	FCD	DPH	20	2	Yes	LE
87	1/M	Developmental delay	Porencephalyc cyst	DPH	5	0,5	Yes	AE
88	16/M	Normal	HA	CBZ	55	22	No	–
89	13/M	Developmental delay	Vascular insult	VA	20	39	No	–
90	1/F	Normal	Periventricular nodular heterotopia	DPH	5	5	No	–
91	3/M	Developmental delay	Normal	DPH-CBZ	20	21	No	–
92	5/M	Hemiparesis	FCD	VA-PB	20	9	No	–
93	12/M	Normal	FCD	CBZ	20	24	No	–
94	4/M	Developmental delay	Focal atrophy	VA-PB	10	6	No	–
95	3/M	Developmental delay	Encephalocele	CBZ	20	43	No	–
96	6/M	Developmental delay	Normal	CBZ	10	5	No	–
97	9/F	Tetraparesis	Subcortical atrophy	CBZ-DPH	30	19	No	–
98	7/M	Normal	Normal	CBZ	20	16	No	–
99	12/M	Normal	FCD	CBZ	10	1	Yes	–
100	12/M	Normal	FCD	DPH	30	48	No	–

FCD, focal cortical dysplasia; HA, hippocampal atrophy; TPM, topiramate; DPH, phenytoin; CBZ, carbamazepine; LTG, lamotrigine; PB, phenobarbital; OXC, oxcarbazepine; VA, valproate; VGB, vigabatrin; AE, adverse event; LE, lack of efficacy.

ly in pre-school age children (mean age = 5.7y) while somnolence occurred mainly in adolescents (mean age = 11.8y, p=0.005, Fig 1).

Twenty-six patients became seizure-free, 11 had >75% of seizure reduction and in 58 there was no modification in seizure frequency after introduction of clobazam. Five patients presented an increase in seizure frequency. It is important to note that in 42% of the seizure-free patients and in 36% of the patients with >75% seizure reduction, clobazam efficacy lasted for more than one year.

The Kaplan-Meier survival analysis revealed a retention rate of clobazam at 18 months (Fig 2).

Seizure-free patients – Twenty-six patients became seizure-free after introduction of clobazam as add-on therapy. Twenty-one patients had symptomatic epilepsy - eight focal cortical dysplasia, three focal atrophy, three hippocampal atrophy, two schizencephaly; and porencephalic cyst, diffuse atrophy, calcification, polymicrogyria, and vascular lesion in one patient each. Five patients had probable symptomatic epilepsy syndrome.

Patients with lower seizure frequency showed a sustained response to the treatment (p=0.021). Seizures were controlled for more than one year in 11 patients with weekly or monthly seizures, and only in one patient with daily seizures.

DISCUSSION

Clobazam has an important antiepileptic effect and is less expensive than the new AEDs, but still has not been considered as a first-line drug in the treatment of epilepsy[3]. In children, clobazam has equivalent efficacy to carbamazepine and phenytoin in monotherapy[10]. Clobazam has also been used for severe epileptic encephalopathies of childhood, such as Lennox-Gastaut syndrome, severe myoclonic epilepsy of infancy and electrical *status epilepticus* of sleep[15-18].

The definition of refractory epilepsy remains controversial; however, the chances of seizure control after the failure of two drugs are not good[19,20]. In spite of this, 26% of the patients became seizure free after the introduction of clobazam and, in 42% of them, seizure control lasted for more than one year.

The retention of clobazam over a period of 18 months was more than 60% (Fig 2). Retention rate is a good marker for the comparative roles of efficacy and tolerability of AEDs. A recent review showed that clobazam is the only AED with a consistency of data in clinical practice[21].

The major drawback of our 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 proof of efficacy of a drug, add-on trials enable the study drug and co-therapy to be adjusted as needed, which mimics clinical practice. Moreover, they are accepted by regulatory agencies and enable a longer study duration[22]. Clobazam was withdrawn in 11 patients due to adverse events, mainly irritability and somnolence. It seems to be a safe drug, however, and its cognitive and behavioral effects are comparable to those of standard monotherapy in school-aged children[23]. Similar to adults, in whom somnolence is the main adverse effect associated with clobazam, in our study, adolescents who had an adverse event presented mainly somnolence. As opposed to adults and adolescents, behavioral disturbances are frequently seen in children[13], and this is in keeping with our data as irritability was the main finding seen in small children. Although 22% of the patients presented adverse events, when there was an improvement in seizure control most families accepted mild or transitory side effects.

Like most AEDs, increasing clobazam dose is usually ineffective when seizure control relapses[24]. However, after a previous period in which it has been effective, clobazam may keep its antiepileptic effect when used intermittently[25].

Although tolerance to clobazam may occur, sustained responders have been identified. It is estimated that 28% of patients will have a long-term benefit without tolerance[24]. Patients with a short duration of epilepsy and higher serum levels of clobazam tend to maintain their seizure control for longer periods[2,26]. Unfortunately, we could not assess clobazam serum levels; however, we could identify sustained responders to clobazam as those with a lower seizure frequency. This is a small sample and larger series should be assessed in order to confirm our findings.

We conclude that clobazam seems to be safe and effective as add-on therapy for children with refractory partial epilepsy.

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