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Use of clobazam for the treatment of refractory complex partial seizures

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Clobazam (CLB) add-on therapy was attempted in 183 patients with intractable complex partial seizures in whom conventional benzodiazepines had been successfully discontinued before initiation of CLB. Although complete remission was initially achieved in 61, tolerance developed in almost half (49.2%) within the first 3 months, whereas 23 out of 31 patients (74.2%) who remained seizure free for the first 3 months continued to be so over the next 3 months. CLB add-on therapy proved to be significantly more effective when concurrent GTC occurred more often than yearly. In the current series, no frank psychotic episodes were elicited among the 61 patients who achieved complete suppression of long-standing complex partial seizures, which was in agreement with previous studies. From these results, we believe that CLB is an effective, safe, and inexpensive medication for add-on therapy in difficult to treat focal epilepsies, especially without concurrent use of conventional benzodiazepine compounds.

Key words: clobazam; add-on therapy; complex partial seizures.

INTRODUCTION

Clobazam (CLB), a 1,5-benzodiazepine, has been proven effective as an intermittent or short-term add-on drug for individual patients with refractory partial epilepsy since Gastaut and Low[1] first suggested its efficacy three decades ago, however, controversy remains regarding its long-term effectiveness[2,3]. Some authors have postulated that sedation and withdrawal effects together with the development of tolerance, as with all benzodiazepines used for treating epilepsy, may limit its usefulness, though CLB has an excellent safety record[4]. On the other hand, others such as Remy[5] have asserted that even though tolerance might develop, this aspect has been overemphasized in view of the fact that a long-term benefit figure of 28% could be expected without tolerance. For the past decade, CLB has been especially emphasized as a drug useful for the treatment of intractable CPS[6,7]. After a long 20-year delay, CLB recently become available in Japan. As a result, we hope to re-assess its efficacy with special attention to intractable complex partial seizures, as well as determine which clinical factors may predict favorable or poor response to CLB therapy.

SUBJECTS AND METHODS

The study subjects were 183 outpatients with intractable complex partial seizures (CPS) that occurred more often than monthly (Table 1) and remained intractable despite maximum drug therapy with all of the standard antiepileptic drugs available in Japan. All were treated with clobazam by the second and the last author from June 2000 to August 2001. Drug dosages were initiated in a range of 5–10 mg and titrated maximally to 20 mg, according to previous studies in Japan[8]. All conventional benzodiazepine compounds, if taken regularly, were discontinued before initiation of clobazam.

In Table 2, basic patient demographic data are presented. Each subject was fully advised and provided written informed consent. The main parameter for

Table 1: Seizure frequency (complex partial seizures).

Monthly	77 (42.1%)
Weekly	92 (50.3%)
Daily	14 (7.7%)
Total	183 (100%)

Table 2: Subjects ($n = 183$).

Sex (male/female)	84/99
Age (years)	33.7 (9.9)
Onset (years)	14.4 (9.2)
Duration of illness (years)	26.2 (41.9)
Seizures	
SPS, limbic	42/183
SPS, simple motor	11/183
GTC, more than yearly	39/183
GTC, less than yearly	63/183
Epileptic syndromes	
Frontal lobe epilepsy	8/183
Temporal lobe epilepsy	
With HS	23/183
Without HS	69/183
Occipital lobe epilepsy	5/183
Other partial epilepsies	77/183
Others	1/183
Effective dosage	6.6 (2.6)
Maximum dosage	10.3 (4.8)

Figures in parenthesis: SD.

efficacy was the change of CPS frequency, and patients who experienced a seizure frequency reduction of more than 50% were considered to be responders. Seizure frequency was classified as: daily, weekly, monthly, yearly, less than yearly, or no seizure, and patients were judged as improved or worsened as a function of this classification. We counted generalized tonic–clonic seizures (GTC) as occurring concurrently only when they appeared more often than once a year. Auras typically reported by patients with temporal lobe epilepsy such as epigastric discomfort, anxiety, illusion of familiarity, and experiential phenomena were categorized as limbic aura. Only those seizure types occurring in more than 20 patients were analyzed.

Each patient was examined and assessed every 2 or 4 weeks during the observation period. We determined the blood levels of co-medicated antiepileptic drugs before as well as during each examination after the initiation of clobazam. Seizure frequencies were assessed at 1, 3, and 6 months after the beginning of therapy. The treatment was withdrawn prematurely when intolerable side effects or intercurrent serious medical illness emerged newly, the seizure symptoms worsened to an intolerable extent, and/or the patient or a family member decided to discontinue the therapy. Patients for whom the treatment was withdrawn prematurely before the first assessment of seizure frequency were considered as drop-out cases. Adverse events were obtained by open questioning, and recorded at the initial interview and at each subsequent visit.

Statistical analyses were performed using χ^2-tests with Yates' modification for small numbers and Mann–Whitney's *U*-test. All tests of hypotheses were two-sided. Results were considered statistically significant at a risk level of 0.05.

RESULTS

1. Drop-outs. Table 3 summarizes the reasons for treatment withdrawal. There were 21 patients who dropped out of the study within 1 month of the initiation of clobazam.
2. Adverse events (Table 4). Eleven adverse events were reported spontaneously. Somnolence was by far the most frequent complaint (37.7%), with gait disturbance (12.0%) and irritability (4.9%) also relatively often reported. All other adverse events including psychiatric symptoms such as emotional instability and depression were only sporadically described. Notably, frank psychosis was never observed, even in patients who had had a long history of drug-resistant CPS and became seizure free with clobazam therapy ($n = 61$).
3. Interactions between clobazam and co-medicated antiepileptic drugs (Table 5). Only those antiepileptic drugs prescribed to more than 20 patients were analyzed. Blood levels were measured during the pre-study period and 2 or 4 weeks after the initiation of clobazam. Among four standard antiepileptic drugs, only the levels

Table 3: Premature withdrawals.

Reason	
Adverse reaction	38% (8)
Patient decision	52% (11)
Worsening of seizures	10% (2)

Table 4: Adverse events.

Somnolence	69 (37.7%)
Emotional instability	1 (0.5%)
Irritability	9 (4.9%)
Concentration difficulty	1 (0.5%)
Depression	1 (0.5%)
Tremor	1 (0.5%)
Vertigo	1 (0.5%)
Gait disturbance	22 (12.0%)
Nausea	1 (0.5%)
Loss of appetite	1 (0.5%)
Diarrhea	1 (0.5%)
Total	86 (47.0%)

Table 5: Changes in blood levels of co-medicated AEDs.

	Before	2/4 weeks later	*P*-value
Carbamazepine ($n = 100$)	9.1 (2.7)	9.5 (3.0)	$0.038 < 0.05$
Phenytoin ($n = 78$)	18.4 (5.0)	18.9 (5.3)	N.S.
Zonisamide ($n = 26$)	21.1 (10.4)	22.1 (10.1)	N.S.
Phenobarbital ($n = 41$)	20.9 (8.0)	21.2 (9.6)	N.S.

Table 6: Efficacy of treatment ($n = 183$).

	1-month later	3 months later	6 months later
Worsened	9 (4.9%)	9 (4.9%)	12 (6.6%)
No change	72 (39.3%)	70 (38.3%)	56 (30.6%)
Improved	81 (44.3%)	68 (37.2%)	55 (30.1%)
Drop-outs	21 (11.5%)	36 (19.7%)	60 (32.8%)

of carbamazepine were found to significantly increase.

4. Efficacy of treatment. Following assessments 1 month after the initiation of therapy, improvement of seizure frequency was recorded for 44.3% of the patients treated with clobazam and complete seizure remission was achieved in 37.7%. The number of patients who achieved improvement decreased steadily during the observation period (44.3%, 1 month later; 37.2%, 3 months later; 30.1%, 6 months later) (Table 6), as did the responder rates (50.3%, 1 month later; 40.4%, 3 months later; 32.8%, 6 months later). However, once complete remission had been achieved for more than 3 months, seizure recurred in only one fourth of the patients (25.8%) over the next 3 months (Table 7). Among the seizure-free patients, development of tolerance decreased steadily as the duration of remission extended (37.7%, 1 month later; 50.8%, 3 months later; 74.2%, 6 months later) (Table 7).
5. Factors influencing remission (Table 8). Excluding drop-out cases, we compared patients who achieved complete remission 1 month after the initiation of therapy ($n = 61$) with those who did not ($n = 101$). Sex, age at first examination, age of epilepsy onset, duration of illness, combined seizure types, and effective as well as maximum dosage of the prescribed clobazam were compared. There were no statistically significant differences between the groups, except for concurrent generalized tonic–clonic seizures ($P = 0.009$) and maximum dosage of clobazam ($P = 0.004$).

DISCUSSION

Previous case control studies have provided conflicting results regarding the interaction between clobazam and standard antiepileptic drugs (AED). While Sennoune *et al.*[9] denied any interaction, Yagi *et al.*[8] and Cocks *et al.*[10] suggested a significant elevation of the blood levels of carbamazepine and valproate. Further, acute phenytoin and carbamazepine intoxications have been sporadically reported after initiation of CLB therapy[11,12]. Our study results suggested that the blood level of carbamazepine is elevated after the initiation of CLB. Some adverse events such as gait disturbance could be related to this, therefore, attention should be paid to the possible emergence of acute intoxication of the co-medicated AEDs, especially carbamazepine.

Table 7: Complete remission and development of tolerance.

	Seizure free	Seizure continued	Dropped-out
1-month later	61/183 (37.7%)	101/183 (55.2%)	21/183 (11.5%)
3 months later	31/61 (50.8%)	24/61 (39.3%)	6/61 (9.8%)
6 months later	23/31 (74.2%)	7/31 (22.6%)	1/31 (3.2%)

Table 8: Factors influencing remission.

	Seizure free ($n = 61$)	Seizure continued ($n = 101$)	*P*-value
Sex (male/female)	29/32	47/54	N.S.
Age (years)	33.8 (10.5)	33.2 (9.6)	N.S.
Onset (years)	14.8 (7.9)	14.1 (9.4)	N.S.
Duration of illness (years)	19.1 (12.0)	19.1 (9.7)	N.S.
Seizures			
SPS, limbic	16/61	21/101	N.S.
GTC (more than yearly)	18/61	13/101	0.009
Effective dosage	7.1 (2.5)	6.4 (2.7)	N.S.
Maximum dosage	9.1 (3.9)	11.4 (5.1)	0.004

Figures in parenthesis: SD.

The effectiveness of CLB toward the function of epilepsy as well as seizure types has been discussed in detail[1,2,7,8,13,14], however, there is a lack of studies that have considered specific combinations of seizure types in view of differential effectiveness. Within the current series of patients with intractable CPS, CLB add-on therapy proved to be significantly more effective when concurrent GTC occurred more often than yearly. This suggests that those who suffered from drug-resistant CPS without secondary generalization from the beginning or whose secondary generalization could be alleviated or nearly alleviated with standard AEDs, were less likely to benefit from the add-on therapy.

Potent AEDs, which include phenytoin and zonisamide as well as other newly developed drugs such as vigabatrin, will cause alternative psychosis in a substantial number of patients following successful suppression of enduring intractable CPS[15]. In the current series, in agreement with previous ones[1,2,4], no frank psychotic episodes were reported among the 61 patients who achieved complete suppression of long-standing CPS. Occurrences of acute frank psychosis inevitably limit drug therapy administered to the patients in question, which eventually forces them to consider surgical intervention. However, since patients with a history of psychosis prior to surgery are susceptible to postoperative recurrence[16], such an adverse event may limit surgical intervention as well. Therefore, lack of alternative psychosis occurrence supports the use of add-on CLB as a meaningful step for intractable CPS prior to referral for neurosurgery.

The rate of responser in the current study agreed well with that of previous reports (42–65%)[17–20]. In contrast to the relatively uniform rates of responder in these various studies, the percentage of seizure-free patients varied widely (7.2% by Montenegro *et al.*[19] vs. 19% by Koeppen *et al.*[21]). Our result (23/183 = 12.6%) fell between those in spite of the relatively low maximum dosage. As Montenegro *et al.*[19] pointed out, this dispersion could be explained by the follow-up period (Montenegro *et al.*[19], 16.7 months; the current study, 6 months; Koeppen *et al.*[21], 3 months). Further, we believe that discontinuation of conventional benzodiazepines in advance of CLB add-on therapy might also contribute to the rather high remission rate seen in the current study.

In agreement with previous reports[1,2,22–25], tolerance developed in our series of patients. Indeed, the efficacy of CLB therapy was totally or at least partially lost in half of the once remitted patients 3 months after initiation. However, most of those other authors also agreed that, once complete remission had been maintained for a certain period, differently from 1,4-benzodiazepines[26], a seizure-free state tended to persist in a certain proportion of patients. In our series, the recurrence rate also decreased gradually after the initiation of CLB therapy.

In view of the rarity of severe adverse events encountered in our study, including upsetting psychotic episodes[1,27], we believe that CLB add-on therapy is a useful alternative for patients with intractable CPS.

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