Efficacy of clobazam monotherapy in three cases of symptomatic localization-related epilepsy in children

Clobazam is approved in many countries as an additional antiepileptic drug for the management of intractable epilepsy. However, a number of reports have also described its use as first-line therapy in this indication. In this article, we describe three cases involving children (aged 2–12 years) with symptomatic localization-related and intractable epilepsy who responded to low dosage (0.2–0.4 mg/kg/day) clobazam monotherapy. For periods of 3.1–4.4 years, the treatment was well-tolerated and improved electroencephalogram findings with complete disappearance of clinical convulsions. Thus, low-dose clobazam appears to be a useful treatment option in these difficult-to-manage cases of intractable epilepsy.

KEYWORDS: children ▪ clobazam ▪ electroencephalogram ▪ localization-related epilepsy ▪ monotherapy ▪ *N*-desmethyl clobazam

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Clobazam, a 1,5-benzodiazepine anti-epileptic drug (AED), was initially developed at the Institute of Medical Pharmacology Roussel-Maestretti, Milano, Italy, in 1966 as an anti-anxiety agent. However, clobazam is now used as an additional AED for intractable epilepsy in more than 90 countries, since Gastaut and Low first reported its use in this indication in 1979 [1]. Clobazam has generally proven effective against refractory and intractable epilepsies [2,3]. Moreover, various reports have described the efficacy of clobazam for Lennox–Gastaut syndrome and severe myoclonic epilepsy in infancy [4,5].

Clobazam was introduced to Japan in May 2000. In this article we report three cases of symptomatic localization-related and intractable epilepsy for which clobazam monotherapy was effective. We investigated three patients, aged 2–12 years, who were treated at the Kitasato University Hospital, Kanagawa, Japan, for more than 3 years. Each patient underwent diagnostic electroencephalography and cranial computed tomography (CT) or magnetic resonance imaging (MRI). In each case, we examined the electroencephalograms every 6 months after changing to clobazam monotherapy and, at the same time, measured blood concentrations of clobazam and its major metabolite *N*-desmethyl clobazam (NCLB). We also reviewed the available evidence on the efficacy and safety of clobazam monotherapy in children.

Case reports

Case 1

A 4-year-old girl with symptomatic localization-related epilepsy related to an abnormality in chromosome 4 had a tonic type of cerebral palsy and severe mental retardation. From the first day after birth she was observed to be pedaling, and had tonic convulsions of the left arm along with apnea. We noted abnormal cranial CT and electroencephalography findings and, therefore, initially treated her with phenobarbital. We later used valproic acid and subsequently introduced clobazam due to repeated secondary generalized seizures. After changing to clobazam monotherapy (because of the occurrence of pancytopenia, a likely adverse effect of valproic acid), her seizures disappeared. Cranial MRI at age 14 months (Figure 1A) revealed hypotrophy of the corpus callosum and brain atrophy. A T_1-weighted image (T1WI) revealed that atrophy of the gyri of the whole cerebrum had spread, and the posterior corner of the right cerebral ventricle had become larger. It presented as periventricular leukomalacia. Interictal electroencephalography at the time of polytherapy revealed sharps and spikes in the centroposterial area on the right side with irregular slow waves (Figure 2A). Blood concentrations of both clobazam and NCLB (Table 1) were almost the same as those reported in a previous study [2]. After changing to clobazam monotherapy, these paroxysmal discharges disappeared (Figure 2B). The patient has had no seizures and no adverse effects for 3 years. Although we noted a slight decrease in blood concentrations of clobazam and NCLB, her electroencephalography findings have shown no paroxysmal discharges.

Case 2

A 2-year-old boy suffered hypoxic encephalopathy after severe neonatal asphyxia and had

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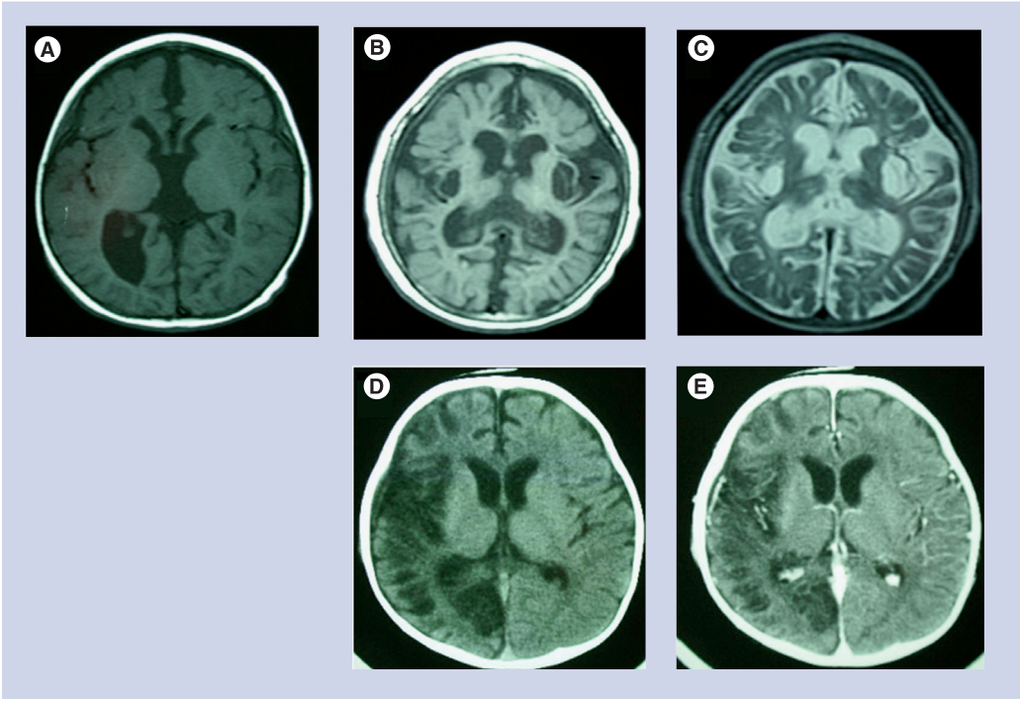

Figure 1. Cranial magnetic resonance images and computed tomography of each case. **(A)** A T1-weighted image (T1WI) of Case 1 revealed brain atrophy in the spread of the gyri and expansion of the posterior corner of the right cerebral ventricle. There is atrophy of the whole cerebrum with hypotrophy of the gray matter. **(B)** A low-intensity area on a T1WI and **(C)** a high-intensity area on a T2-weighted image (T2WI) in the bilateral basal nuclei were noted in Case 2. **(D)** Plane computed tomography of Case 3 revealed right cerebral hemiatrophy, especially in the low-intensity area supported by the right middle and posterior cerebral arteries; **(E)** on enhanced computed tomography, the spherical corpus callosum did not appear to be injured.

exhibited partial seizures with apnea since birth. He also had cerebral palsy and was severely mentally retarded. From the abnormal cranial MRI and electroencephalography findings, we diagnosed him as having symptomatic localization-related epilepsy and started him on carbamazepine therapy. The patient later experienced a few partial and secondary generalized seizures. We initially treated him with valproic acid followed by clobazam. Since changing to clobazam monotherapy, he has not had another seizure. Cranial MRI at age 18 months showed atrophy of the whole cerebrum and hypotrophy of the gray matter with dilatation of the sylvian fissure. We noted low-intensity areas on a T1WI (Figure 1B), and high-intensity areas on a T_2-weighted image (T2WI) in the bilateral basal nuclei (Figure 1C). These are usually recognized as phenomena caused by an hypoxic change in the neonatal period.

While undergoing polytherapy, interictal electroencephalography during a drug-induced deep sleep revealed sharps, spikes and irregular spikes and waves discharged on both sides centroposteriorly, with a continuous abnormal background of diffuse high-voltage slow activity (Figure 2C). The NCLB concentration in the blood (Table 1) was significantly lower than that reported previously [2]. After changing to clobazam monotherapy, the paroxysmal discharge disappeared without spikes and waves in the central area (Figure 2D). After 3 years, we measured almost the same clobazam and NCLB concentrations in the blood, and similar findings on the electroencephalogram. However, the clinical manifestations had improved. The patient is currently bedridden because of severe intellectual impairment and motor paralysis, but has had no post-therapeutic clinical seizures.

Case 3

A 12-year-old boy had symptomatic West syndrome due to a right acute subdural hematoma with onset at 18 months of age. We started medication with vitamin B_6 and adrenocorticotropic hormone (ACTH; corticotropin). The infantile spasms disappeared; however, we recognized that partial seizures with a left-sided predominance coexisted with generalized seizures, with the eyeballs fluctuating to the left. We introduced clobazam with valproic acid and nitrazepam continuously for

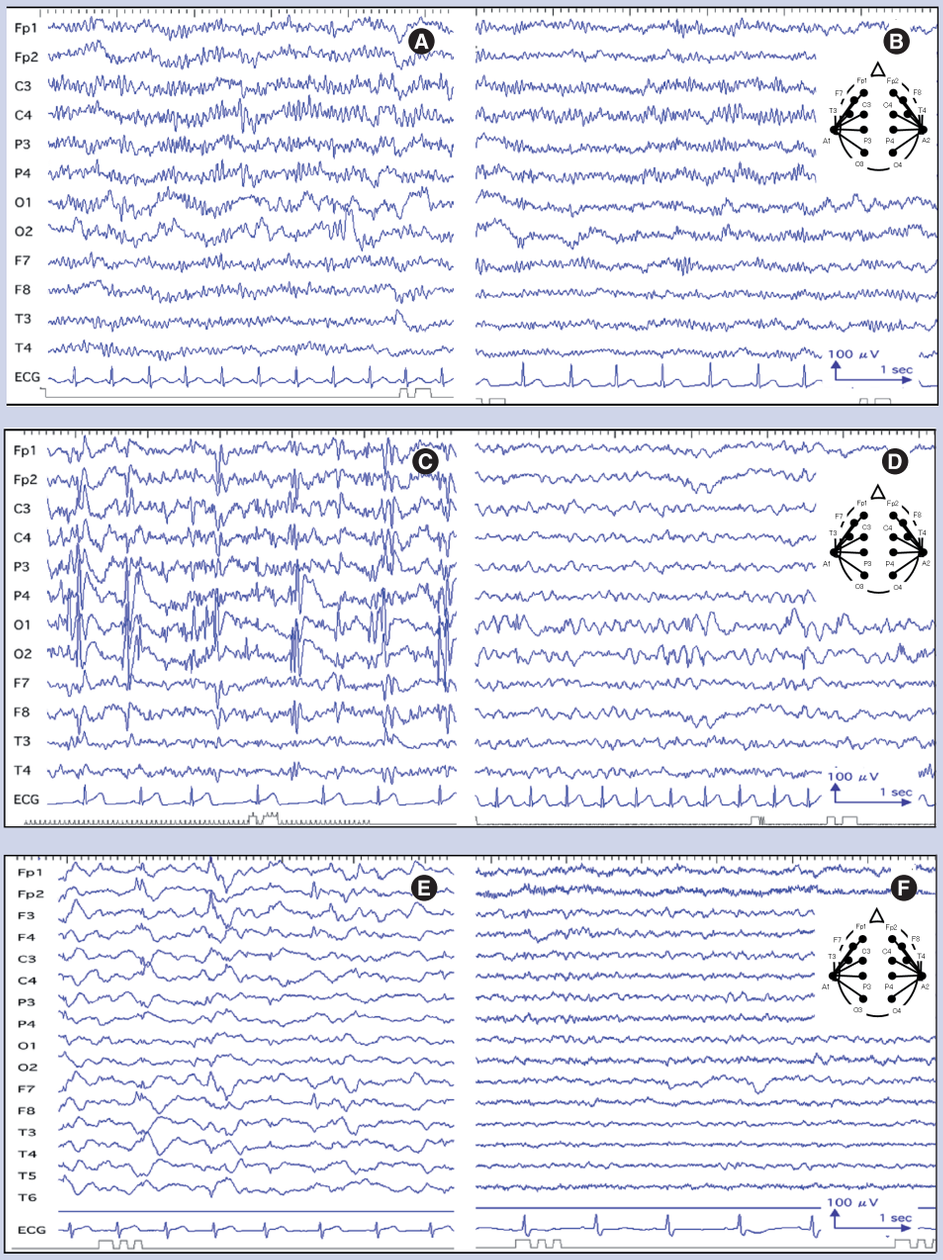

Figure 2. Interictal electroencephalograms while undergoing polytherapy and after changing to clobazam monotherapy. **(A)** Paroxysmal discharges in the centroposterior area were dominant on the right side in Case 1. **(C)** Paroxysmal discharges were noted bilaterally and centroposteriorly in Case 2, and **(E)** predominantly in the right Fp, F and C areas in Case 3**. (B,F)** These paroxysmal findings disappeared and/or **(D)** decreased after changing to clobazam monotherapy.

the intractable complex partial seizures. With the introduction of clobazam, the frequency of seizures decreased.

We observed a few myocloni 1 day after changing to clobazam monotherapy. However, the patient has had no epileptic seizures. Cranial CT revealed right cerebral hemiatrophy (Figure 1D & 1E), especially in the low-intensity area supported by the right middle and posterior cerebral arteries. The spherical corpus callosum did not appear injured in the enhanced CT. Interictal electroencephalography while undergoing polytherapy showed sharps and spikes predominantly in the right Fp, F and C, with an irregular high-voltage slow activity (Figure 2E).

After changing to clobazam monotherapy, these paroxysmal findings disappeared (Figure 2F). The concentration of NCLB in the blood (Table 1)

Table 1. Blood concentrations of clobazam and *N*-desmethyl clobazam in the three patients.

Case No.	Dosage (mg/kg/day)	Clobazam (ng/ml)	NCLB (ng/ml)
1	0.4	410	1783
2	0.2	349	236
3	0.2	198	232

NCLB: N-*desmethyl clobazam.*

tended to be lower than that reported previously [2]. The patient has had no seizures or adverse effects during the last 3 years. Although we noted slight decreases in the blood concentrations of clobazam and NCLB, the electroencephalography findings did not reveal any paroxysmal discharges.

Discussion

Clobazam is approved as an additional AED, mainly for intractable epilepsy [2,3,6–9]. There are, however, various reports describing its potential as a first-choice medication [10–13]. In this regard, the efficacy of clobazam for the Lennox–Gastaut syndrome and severe myoclonic epilepsy in infancy has recently been reported [4,5]. Generally, the usual daily dosage is approximately 20–40 mg/day in adults [2,3,6–8,10] and 0.5–1.5 mg/kg/day in children [8,9]. For long-term therapy, it has been shown that a high dosage of clobazam is not more effective than a low dosage. The effects of a low dosage of clobazam appear from 6 weeks to 12 months after starting treatment [11]. In the present study, even though a low dosage was used (0.2–0.4 mg/kg/day), clobazam was clinically effective for 3.1–4.4 years. We evaluated the effect of clobazam by the disappearance of clinical seizures and the improvement of electroencephalography findings. We also measured the blood concentrations of clobazam and its major metabolite NCLB [14] in all three cases (**Table 1**). Sennoune *et al.* found that clobazam and NCLB blood concentrations are approximately 450 ± 250 ng/ml and 1300 ± 730 ng/ml, respectively [10]. Moreover, Kinoshita *et al.* showed that even low dosages of clobazam are effective in patients who have higher NCLB concentrations [15]. In the present study, clobazam blood concentrations were on the low side. However, we considered clobazam therapy to be effective because, even though the dosages used were at the lower limits, relatively higher NCLB blood concentrations were recorded.

Electroencephalography findings after clobazam therapy have previously been reported to improve [6], and this was confirmed in the present study since paroxysmal discharges disappeared after changing to clobazam monotherapy in all cases. Moreover, we observed either no seizures or a decrease of seizures during more than 3 years of follow-up, and we also noted a significant improvement in electroencephalography findings every 6 months. These findings support the therapeutic efficacy of clobazam. Blood concentrations of clobazam measured every 6 months tended to be the same or gradually decreased with time as the children got older and gained weight.

Tolerance has been cited as the most important problem of clobazam therapy. In 1994, Remy proposed that while tolerance may develop, this aspect may have been overemphasized [6]. The Canadian Clobazam Cooperative Group reported tolerance as a factor leading to the discontinuation of clobazam in only 9% of cases [8]. Therefore, we initiated treatment with low-dosage clobazam, in consideration of tolerance, and continued with that dosage as long as it was effective.

The only adverse effects noted in the present study were temporary sleepiness and dizziness in two cases. This may have been due to the fact that NCLB blood concentrations were maintained at low levels. Generally, NCLB has a significant influence on both the therapeutic and adverse effects of clobazam [16] and, in view of this, we initiated clobazam monotherapy at a low dosage. Physicians should be especially careful when NCLB blood concentrations are high because the frequency of the mutant allele of cytochrome P450 (CYP)2C19, which is involved in the metabolism of NCLB, varies significantly in Asian populations [17].

As it has been shown that polytherapy with conventional agents offers little hope of complete or improved control when monotherapy has failed [13], an alternative approach is to consider clobazam monotherapy [9,10,13]. In children, clobazam has been used to prevent febrile seizures and to treat various types of intractable epilepsies [11]. In the three cases described here, clobazam monotherapy produced an improvement in electroencephalography findings and complete

disappearance of clinical convulsions for 3 years. Thus, we believe that clobazam monotherapy is effective for epilepsies in children, and it may be particularly safe and effective if low dosages are used, since this obviates the risk of high NCLB blood concentrations.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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