Immediate Changes of the Electroencephalograms after Intravenous Injection of Clonazepam and Their Relation to Its Effect on Clinical Fits in Children with Minor Seizures

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IINUMA, K., TAMAHASHI, S., OTOMO, H., ONUMA, A. and TAKAMATSU, N. *Immediate Changes of the Electroencephalograms after Intravenous Injection of Clonazepam and Their Relation to Its Effect on Clinical Fits in Children with Minor Seizures.* Tohoku J. exp. Med., 1978, 125 (3), 223-231 — Immediate EEG changes after intravenous administration of clonazepam and a correlation between the EEG changes and the effect of oral administration of the drug were studied in 21 children with minor seizures whose interictal EEG showed a paroxysmal abnormality. In 13 cases of infantile spasms whose EEG showed hypsarhythmia, paroxysmal discharges were completely or remarkably suppressed in 4 cases, partially suppressed in 3 cases, but not improved in 6 cases. Suppression bursts pattern was less improved. In 5 cases of Lennox syndrome, paroxysmal discharges were markedly improved in 3 cases. In a case of petit mal absence, paroxysmal discharges were completely suppressed. In all 5 cases whose EEGs were completely improved, paroxysmal discharges reappeared 7 to 30 min after the intravenous injection. In 2 out of the 5 cases, paroxysmal discharges became severer at reappearance than before the injection. Among 12 cases whose EEG showed an improvement after the intravenous injection, their clinical seizures were improved in 9 cases, but the clinical effect was mostly transient. In the majority of the cases whose EEGs were not improved, no clinical effect was observed. There was a highly significant correlation between immediate EEG changes and clinical effect of clonazepam ($p < 0.02$ by the chi-square test). — clonazepam; EEG; minor seizures

The anticonvulsive properties of a benzodiazepine derivative, clonazepam (5-(o-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepine-2-one; CZP) have been demonstrated in human pharmacological studies (Gastaut et al. 1971). It has been reported that effect of CZP is favorable in most forms of epilepsy (Birket-Smith and Mikkelsen 1972), especially in Lennox syndrome and/or infantile spasms (Dumermuth and Kovacs 1973; Martin and Hirt 1973). It has also been shown that CZP is a very effective drug in controlling status epilepticus (Gastaut et al. 1971).

There is, however, a certain diversity of opinion as for its effects on EEG,

TABLE 1. *Results of EEG changes and clinical effects of clonazepam in 21 patients with minor seizures*

Case No.	Age (years-months) Sex	Diagnosis	EEG before CZP i.v.	EEG after CZP i.v.	Effects of orally given CZP on clinical seizures
1	0-2 M	I.S.	Periodic irregular sp-w-b	Sz. activities partially suppressed	Unchanged
2	0-3 F	I.S., chronic subdural effusion	Diffuse low voltage, multifocal sp-w, suppression bursts, lack of sleep spindles	Unchanged sz. activities, but attenuation of background activity, sleep spindles incompletely appeared	Unchanged
3	0-4 M	I.S., microcephalus	Periodic type of hypsarhythmia	Unchanged	Unchanged
	0-5 F	I.S., chronic subdural effusion	Periodic type of hypsarhythmia	Unchanged	Unchanged
6	0-6 F	I.S.	Hypsarhythmia	Sz. activities completely suppressed for 6 min	Completely controlled, recurred 4 weeks later
	0-6 F	I.S., homocystinuria	Hypsarhythmia	Unchanged	Not given
	0-7 M	I.S.	Hypsarhythmia	Sz. activities remarkably suppressed, only focal spikes in bilateral C for 9 min, spindles apparent	Adequately controlled, recurred 17 days later
8	0-8 M	I.S.	Periodic type of hypsarhythmia	Sz. activities remarkably suppressed for 7 min, but severer at reappearance	Significantly controlled
9	0-9 M	I.S., tuberosus sclerosis	Asymmetric hypsarhythmia	Sz. activities completely suppressed for 30 min, LVF induced	Completely controlled, recurred 4 weeks later
10	0-9 M	I.S.	Hypsarhythmia	Unchanged	Unchanged
11	0-10 F	I.S., microcephalus	Periodic type of hypsarhythmia	Unchanged	Adequately controlled

TABLE I. (Continued)

Case No.	Age (years-months) Sex	Diagnosis	EEG before CZP i.v.	EEG after CZP i.v.	Effects of orally given CZP on clinical seizures
12	1-1 M	I.S.	Hypsarhythmia, lack of spindles in rt. hemisphere	Sz. activities slightly decreased, sleep spindles apparent even in rt. hemisphere	No clinical sz. were observed both before and after drug therapy
13	1-9 M	I.S.	Hypsarhythmia, regional fast in lt. T	Sz. activities unchanged, slow waves slightly decreased, regional fast waves more marked	Worse in frequency of clinical sz.
14	1-10 F	I.S., microcephalus	Hypsarhythmia	Sz. activities partially suppressed for 10 min	Completely controlled, recurred 2 weeks later
15	2-2 M	I.S., transformed to Lennox	Poly-sp-w-b, HVS	Sz. activities unchanged, HVS suppressed	Completely controlled
16	4-0 F	Lennox	Diffuse slow-sp-w, MVF	Sz. activities completely suppressed for 13 min, but severer at reappearance, 16-18 Hz MVS induced	Completely controlled, recurred 10 days later
17	4-10 F	Lennox	Poly-sp-w-b, sp-w-b	Sz. activities partially suppressed for 30 min.	Significantly controlled
18	5-4 F	Lennox	Sp-w-b, focal sp, sp-w	Sz. activities completely suppressed for 14 min, 20 Hz MVS induced	Not given because of no clinical sz.
19	9-7 M	Lennox	Diffuse slow sp-w, irregular sp-w, lack of spindles	Sz. activities remarkably decreased, sleep spindles apparent	Adequately controlled, recurred 1 month later
20	7-10 M	Absence status	Diffuse 3 Hz sp-w complex	Sz. activities completely suppressed for 4 min, MVF induced	Completely controlled, recurred 9 weeks later
21	0-4 F	Abortive sz., microcephalus	Sporadic sp-w	Unchanged	Unchanged

Abbreviations are as follows: CZP, clonazepam; i.v., intravenous injection; M, male; F, female; I.S., infantile spasms; Sp-w-b, Spike-wave bursts; poly-sp-b, poly-spike bursts; sz., seizure or seizures; lt., left; rt., right; C, central; T, temporal; MVF, middle voltage fast activity.

particularly on interictal EEG findings (Bianchi Saus et al. 1973; Hökkinen 1973; Groh and Rosenmayr 1974). Literature dealing with the effects of CZP on EEG particularly in children is scanty (Bianchi Saus et al. 1973; Groh and Rosenmayr 1974). The present study was undertaken to evaluate the effect of intravenous injection of CZP on EEG and its relation to clinical effect of oral CZP in children with minor seizures.

SUBJECTS AND METHODS

Twenty-one children, 11 boys and 10 girls, with minor seizures ranging from 2 months to 9 years of ages, were subjected to the present study in the ward of Tohoku University Hospital. The types of seizures and numbers of cases were as follows: infantile spasms in 14 cases, Lennox syndrome in 5, petit mal status in 1, and unclassified abortive seizure in 1.

The etiology for seizures could be clarified in 8 cases. These included 6 patients with microcephalus, two of which were accompanied with chronic subdural effusion confirmed by the computerized tomography and craniotomy, one with tuberous sclerosis, and one with homocystinuria with 5,10-methylene-tetrahydrofolate reductase defect (Narisawa et al. 1977).

Electroencephalograms were recorded during sleep stage, using a 13-channel electroencephalograph (Toshiba EEG 23-A, Tokyo, Japan). CZP was available in ampules of 1 mg/ml, to which 1 to 4 ml of solvent was added. Doses between 0.04 and 0.06 mg per kg of body weight were intravenously injected slowly over a period of 1 to 3 min. EEG was continuously observed before, during and for about 30 min after the injection of CZP. Each EEG tracing was examined as to whether there are changes in the seizure discharges, induction of the fast waves, depression or activation of focal elements, and/or activation of other findings such as sleep spindles.

After an intravenous administration test, each patient, except for Cases 6 and 18, was orally given 0.05 to 0.12 mg per kg of body weight per day of CZP. Most of the patients were given CZP alone until this drug was proved unsatisfactory, except for Cases 16, 19, 20 and 21. The frequency and character of the seizures were observed before and after the treatment of CZP. The effectiveness of the medication was judged to be: (1) complete; (2) adequately improved, with more than 75% reduction in frequency; (3) significantly improved, with more than 50% reduction in frequency; (4) little or not improved; or (5) worse. The judgement was made after at least 4 weeks of medication.

RESULTS

Results of the immediate changes of EEG after the intravenous administration of CZP in relation to clinical seizure pattern and dominant EEG pattern are presented in Table 1 and summarized in Table 2. Examples of the changes are shown in Figs. 1 and 2.

Eight cases showed a complete or remarkable suppression of seizure activities in EEG, but all the cases showed a reappearance of seizure activities within 6 to 30 min after the injection. In 2 out of the 8 cases, seizure activities at reappearance were severer than before the injection of CZP. Four cases showed a partial suppression of seizure activities. Two of the 4 cases showed a reappearance of seizure activities within 5 to 20 min after the injection. Nine cases showed unchanged seizure activities by the intravenous injection of CZP.

Effect of oral treatment of CZP on the clinical seizures are as follows. Six cases

TABLE 2. Correlation between improvement of EEG after intravenous administration of clonazepam and clinical seizure type

Clinical sz. type	Dominant EEG		Improvement of sz. activities after clonazepam i.v.		
			Complete or remarkable	Partial	Not significant
Infantile spasms	Hypsarhythmia	7	2	2	3
	Periodic hypsarhythmia	5	1	1	3
	Asymmetric hypsarhythmia	1			
	Other form	1			1
	Total	14	4	3	7
Lennox syndrome	Diffuse slow spike-wave	2	2		
	Poly-sp-w-c	3	1	1	1
	Total	5	3	1	1
Absence	3 Hz sp-w-c	1	1		
Abortive	Sporadic sp-w	1			1
Total		21	8	4	9

Fig. 1. Electroencephalograms of Case 7.

Spike discharges were scarcely observed in C₃-P₃ and C₄-P₄ leads 1 min after the injection of CZP. Paroxysmal poly-spike-wave complexes reappeared 9 min after the injection.

showed a good result with a complete cessation of clinical seizures, but a reappearance of seizures was seen in 5 of the cases. Three cases were adequately controlled and 2 were under a significant control. Seven cases showed poor or no effect. In one case, the seizures got worse than before CZP therapy.

Fig. 2. Electroencephalograms of Case 16.

Paroxysmal discharges were completely suppressed and 16–18 Hz fast activities appeared 1 min after the injection of CZP. Paroxysmal discharges reappeared 13 min after the injection.

TABLE 3. Correlation between immediate EEG changes after intravenous injection and clinical effectiveness of clonazepam

Effect on clinical sz.	Suppression of seizure activities by CZP i.v. in EEG							
	Complete (Reapp.)		Remarkable (Reapp.)		Partial (Reapp.)		Unchanged	Total
Complete (Recurrent)	4 (4)	(4)			1 (1)	(1)	1	6 (5)
Adequate (Recurrent)			2 (2)	(2)				3 (2)
Significant			1	(1)	1	(1)		2
Poor, no or worse					2*		6†	8
Total	4	(4)	3	(3)	4	(2)	8	19
Not orally treated	1	(1)					1	2

Chi-square=21.13, DF=9, $p<0.02$. Reapp, reappeared.

* In one case, no clinical seizures were observed both before and after drug therapy, but EEG was not improved by oral treatment.

† Clinical seizure became worse in one case.

Correlation between EEG changes after the intravenous injection and the effect of oral treatment of CZP on clinical seizures is shown in Table 3. Among 12 cases whose EEG showed an improvement after intravenous injection of CZP, an improvement of clinical seizures was observed in 9 cases, although the seizures recurred in 7 of the 9 cases. In 9 cases whose EEG showed no change after

intravenous injection of CZP, the oral treatment was not or poorly effective in 6 cases, including a case in which clinical seizures became even worse than before therapy, and beneficial effect on seizures was observed only in 2 cases. There is thus a highly significant correlation between the electroencephalographic improvement by intravenous injection of CZP and the clinical effect of CZP treatment ($p < 0.02$ by the chi-squared test).

Sleep spindles were found to be more apparent in 4 cases after intravenous injection of CZP.

In 3 cases, 20 or 25 Hz fast activity (almost 20 to 50 μ V) was induced after the intravenous injection. An example is shown in Fig. 2. Appearance of the fast activity was diffuse, neither focal nor lateralized.

DISCUSSION

CZP is a new anticonvulsant for the treatment of epilepsy, especially of minor seizures (Hanson and Menkes 1972) such as Lennox syndrome and/or infantile spasms (Martin and Hirt 1973; Dumermuth and Kovacs, 1973; Vassella et al. 1973; Carson and Gilden 1975) and typical absence (Martin and Hirt 1973; Groh and Rosenmayr 1973; Dreifuss et al. 1975; Mikkelsen et al. 1976).

Intravenously administered CZP has been shown to suppress 3 per second spike-wave activities in typical absence (Gastaut et al. 1971; Martin and Hirt 1973; Groh and Rosenmayr 1974), slow spike-wave in Lennox syndrome, (Martin and Hirt 1973; Groh and Rosenmayr 1974), poly-spike-waves in grand mal (Gastaut et al. 1971; Martin and Hirt 1973), and the recruiting rhythm in tonic seizures (Gastaut et al. 1971).

Bianchi Saus et al. (1973) reported that intravenous injection of CZP showed a stronger effect on generalized EEG abnormalities than on focal abnormalities and no effect on hypsarhythmia. Häkkinen (1973) found that in a case of 25 years old patient with Lennox syndrome, the discharges disappeared after the injection of 2 mg of CZP, and there was a tonic fits, with generalized high amplitude and high frequency discharges lasting 4 seconds about 5 min after the completion of the slow injection. Rosenmayr and Groh (1973) reported that in 37 cases with generalized spike-wave discharges, 18 were normalized, 10 were remarkably improved, and 9 were unchanged. According to these previous literatures, EEG changes after intravenous injection of CZP were most remarkable in generalized spike-wave pattern. The present study also showed that generalized spike-wave discharges were most remarkably improved, but hypsarhythmia was not so remarkably improved. In the EEG features of Lennox syndrome, diffuse slow spike-wave pattern was more improved than poly-spike-wave pattern. As for hypsarhythmia, typical hypsarhythmia was more improved than periodic hypsarhythmia by intravenous injection of CZP (Table 2). Thus, EEG of diffuse or generalized seizure discharges may be most sensitive to intravenous administration of CZP. EEG of focal or periodic pattern was rather insensitive to intravenous administration of CZP.

Martin and Hirt (1973) reported that regression of the hypersarhythmia was observed after intravenous injection of CZP. In our 2 cases, the appearance of epileptic discharges became more frequent 7 to 13 min after injection of CZP. Effect of intravenous injection of CZP on EEG was temporary and it may be supposed that CZP rather activates epileptic activities after transient suppression.

Binachi Saus et al. (1973) mentioned that the intravenous injection of CZP was useful as a prognostic test of the future results of oral treatment. Groh and Rosenmayr (1974) reported that there was a highly significant correlation between these two variables: the greater the EEG normalization on intravenous administration of CZP, the better, as a general rule, were the prospects for successful long-term treatment with this drug. In the present study, a high correlation between EEG changes and the effect on clinical seizure control was also found (Table 3). These results indicate that CZP i.v. test is useful to predict the effectiveness of oral therapy.

It was reported that CZP administered intravenously or orally produces an increase in low-voltage fast activity in a high percentage of patients (Martin and Hirt 1973; Rosenmayr and Groh 1973; Fazio et al. 1975). In our study, an increase in fast activity after the injection was observed only in 4 of 21 cases. Laguna and Korein (1972) reported that the appearance of low voltage fast activity was a commoner effect of intravenous injection of diazepam, one of derivatives of benzodiazepine, and that it was less prominent on the side with focal brain damage.

Lombroso (1966) claimed that diazepam-induced low voltage fast activity was similar to that following injection of short acting barbiturate and might have lateralizing value (Lombroso and Erba 1970). In the present study, CZP-induced fast activity did not point out the focus of brain damage, even in a case having localized epileptic activity. CZP i.v. test may not have lateralizing value in minor seizures.

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