The Turkish Journal of Pediatrics
Volume 20 / Nos. 3-4 / July-October 1978 / pp. 91 - 99

The Effect of Clonazepam on Myoclonic Seizures in Infancy and Childhood*

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It has been generally accepted that myoclonic seizures present a heterogenous group as far as etiology, pathophysiology, and EEG are concerned.[1-8] Gibbs and Gibbs[9] have used the term hypsarrhytmia for the EEG changes seen in patients with infantile spasm. Gibbs et al.[2] have also shown that these patients displayed age related changes in EEG as is the case with normal children.

The best results in controlling the seizures have been obtained with ketogenic diet[4, 8, 10-16] ACTH or cortisone also have positive effects, although recurrence is frequent.[17-20] These treatments have no positive effect on mental and motor retardation and it has also been shown that these drugs do cause changes in EEG patterns when administered for other conditions.[21]

In recent years the mechanisms which influence the cerebrospinal fluid levels of neurotransmitters, but their CSF levels and their metabolites have been the subjects of various investigations.[22-24] Drugs which belong to the benzodiazepin group increase serotonin levels by lowering the brain serotonin turnover.[25-26] It has been reported that clonazepam which is chlorinated derivative of nitrazepam has been found to be effective in controlling myoclonic seizures. Therapeutic dose has been found to be 13-72 ng/ml of serum. The half-life of clonzepam varies between 22-33 hours. There is a linear relatinoship between oral administration and serum levels.[27]

The purpose of study was to investigate the role of clonazepam (Rivotril) in myoclonic seizures.

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Method

Fifty-four patients with myoclonic epilepsy diagnosed in Hacettepe University Children's Hospital between May 1975 and May 1976, were studied in two groups: the first group was made up of 29 patients who had never taken any anticonvulsants, the second group was made up of 37 patients who were on various anticonvulsants prior to the study. All these patients were placed on clonazepam. Later on 14 of the 29 and 12 of the 37 patients dropped out of the project. Therefore the single drug group was reduced to 15 (4 girls and 11 boys) and the combination drug group was reduced to 25 (7 girls and 18 boys).

The mean age for the single drug group was 3 years 11 months and it was 2 years 11 months for the combination drug group. Thirteen in the first group and seventeen in the second were diagnosed to be mentally retarded. The possible etiologies for the seizures were: 11 due to birth trauma, 7 due to infections, 3 due to the trauma, 2 due to prematurity, 1 due to degenerative central nervous system disease (methachromatic leucodystrophy). (Table I).

TABLE I

POSSIBLE ETIOLOGY FOR THE DISEASE

Birth trauma	11
Infection	
Encephalitis	6
Varicella	1
Trauma	3
Phenyketonuria	1
Prematurity	2
Vaginal bleeding in mother	1
Methachromatic leucodystrophy	1
Unknown	14

The starting age of the seizures in 50 % of the patients was 12 months and under. In the single drug group, nine out of 15; in the combination drug group, 12 out of 25 patients had had seizures for less than one year.

Drug administration: Clonazepam which is a derivative of chlorinated benzodiazepin was administered with a starting dose of 0,05 mg/kg and this was increased up to 0,3 mg/kg if necessary.

Procedure: All the patients were given physical and neurological examination. The following biochemical tests were performed before the

drug administration was started: Serum calcium, phosphorus, alkaline phosphatase, fasting blood sugar (glucose), blood and urine amino acids paper chromatography, skull X-rays, and EEG.

After these initial examinations each patient was asked to return for a control visit in the first, second, third and sixth months. During these visits the neurological examination was repeated and the frequency of the seizures was recorded.

The results were categorized in three groups. I: Patients with 100 % to 75 % reduction in seizures were considered to have good results, II. 75 % to 50 % reduction of seizures was fair or medium recovery, III. any improvement with less than 50 % reduction was considered to be ineffective. The second and third categories were combined in calculating the data.

Results

Out of the total 40 patients 19 had good results eight had medium recovery and 13 failed to respond to the treatment. Eight patients out of the 15 in the single drug group reached good results and four had medium recovery. In the other group where clonazepam was used in combination with other anticonvulsants, 11 out of the total 25 patients had good results and four had medium recovery. (Table II).

TABLE II

THERAPEUTIC EFFECTS OF CLONAZEPAN ON 40 PATIENTS

	Good (75-100 %)	Medium recovery (50-75 %)	Ineffective
Clonazepam (Single)	8	4	3
Clonazepam (In Combination)	11	4	10

Clonazepam seemed to be more effective on the children whose seizures started after six months of age in both groups. (Table III).

When duration of the disease was considered, clonazepam was found most effective in patients the onset of whose disease occurred more than one year prior the study. There was no difference between the two groups. (Table IV) Clonazepam was also more effective in the idiopathic group when it was taken on its own and in symptomatic groups when it was taken in combination with other drugs. (Table V).

TABLE III

THE DISTRIBUTION OF THE NUMBER OF RECOVERIES ACCORDING TO THE ONSET OF THE DISEASE

	0 - 6 months		6 months	
	No. of the patients	Good (75-100 %)	No. of the patients	Good (75-100 %)
Clonazepam (Single)	9	4	6	4
Clonazepam (In Combination)	12	4	13	7

TABLE IV

THE DISTRIBUTION OF THE NUMBER OF RECOVERIES ACCORDING TO THE DURATION OR THE DISEASE

	0 - 1 year		> 1 year	
	No. of the patients	Good (75-100 %)	No. of the patients	Good (75-100 %)
Clonazepam (Single)	9	3	6	5
Clonazepam (In Combination)	12	4	13	7

TABLE V

THE RELATIONSHIP BETWEEN ETIOLOGY AND TREATMENT

	Symptomatic		Idiopthic	
	No. of the patients	Good (75-100 %)	No. of the patients	Good (75-100 %)
Clonazepam (Single)	11	4	4	4
Clonazepam (In Combination)	14	8	11	3

Clonazepam was shown to be effective in the group with fewer seizures as compared to the group with frequent seizures. (Table VI) no relation was observed between recovery and the age of patients.

TABLE VI

NUMBER OF RECOVERIES DURING SIX MONTHS OF THE TREATMENT

	Number of the seizures per day	No. of the patients	1st month	2nd month	3rd month	6th month
Clonazepam (Single)	1 - 10 seizures	8	6	4	5	6
	< 10 seizures	7	1	2	2	2
Clonazepam (In Combination)	1 - 10 seizures	13	10	7	8	8
	< 10 seizures	12	8	5	3	3

Discussion

Clonazepam is reported to be effective in temporal lobe epilepsy,[28,29] focal epilepsy, grand mal epilepsy,[30] and status epilepticus.[31] Within the mixed epileptic group clonezepam was found to be more effective on myoclonic and petit mal epilepsies, however, Barnetti[32] has shown that it has no positive effect in myoclonic seizures.

Carson and Gilden[33] used only clonazepam on eight patients. Out of the eight, five had total recovery, one had better than 50 % recovery, our results were more favorable.

Although the results of Barnetti's[32] study indicated that age, sex and duration of illness had no effect on the outcome, we found in our study that seizures which started after the age of six months and diseases with longer than one year duration responded better to clonazepam. This could be explained by the fact that these patients had less brain damage.

Maslan[28] reported eight out of 14 and Vassella[34] reported six out of 37 patients developed some resistance to the drug. In our study 10 patients developed resistance and two of them improved when the drug dose was increased. We have found that there was no difference between three month and six month check-ups. Bang[35] et al have shown that there is no statistically significant difference in the effectiveness of the drug with passage of time.

The heterogeneous character of the myoclonic seizures makes it difficult to compare the result of various studies. Most of the studies involved all of the minor motor epilepsies.

The work of Fazio[36] et al consisted of the summary of the previous series, reported the efficiency of the medication to be excellent in 52, good in 19 and insufficient in 36 of 102 patients with myoclonic seizures. Hanson and Menkes,[37] Vassella[34] et al., Carson and Gilden[33] had similar results in their study. The results of our study also confirmed the above findings. In a study similar to ours Martin and Hirt[38] reported full recovery in 24 out of 53 patients. Worse results were obtained with infantile spasm similar results in our study were obtained with one group of infants under the age of six months.

In summing up the results, clonazepam was found to be a highly effective anticonvulsant in the treatment of myoclonic seizures. The effectiveness of the drug was equally demonstrated by the group of children who had not taken any anticonvulants before clonazepam was used as the only drug and also with the group of children who took clonazepam in combination with other drugs.

Summary

This study was undertaken to investigate the effect of clonazepam on myoclonic seizures. The drug was administered to two groups of patients: first group consisted of patients who had never taken any anticonvulsants, second group consisted of patients who had been treated with one or more anticonvulsant with no success.

The effect of clonazepam was investigated in relation with the onset of the disease, the duration, and the frequency of the seizures, the effect of clonazepam was found to be more pronounced with patients whose seizures started after the age of six months and in the patients whose disease started more than one year prior to the study and in those with fewer attacks.

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