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VALUE OF PRIMIDONE IN EPILEPSY

BY

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Since the introduction of primidone ("mysoline"; 5-phenyl-5-ethylhexahydropyrimidine-4: 6-dione) as an anticonvulsant drug some two years ago, two papers have appeared on its use in the treatment of epilepsy. A report of its initial trial at the David Lewis Epileptic Colony was given by Handley and Stewart (1952). Of the 40 patients treated all of whom had had prolonged treatment with other drugs, 12 had complete abolition of all types of attack over the six-months period of trial, and a further 11 showed a reduction of two-thirds or more. Butter (1953) recorded his results also from a special hospital for epileptics, where 58 patients had been treated. Again all had had extensive previous treatment. During 15 months only 3% had their fits abolished, but 50% derived some benefit. The results in both these reports must be regarded as very promising in view of the type of case treated. The present paper records our experience in the treatment of both symptomatic and idiopathic epileptics from the routine out-patient practice of a neurological clinic.

Case Material

Seventy patients of whom detailed records were available are considered here, though a further 12 have been treated; 43 were male and 27 female, and their ages ranged from 4½ to 60 years. Twelve had post-traumatic epilepsy—four from closed head injuries and eight from brain wounds; 10 had symptomatic epilepsy from proved brain lesions such as neoplasm or vascular accident; the remaining 48 cases were regarded as idiopathic. In Table I the cases are grouped according to the predominant type of fit or fits that they had. However, all those listed as having focal fits did have

TABLE I.—Results of Primidone Treatment in Different Types of Epilepsy

Group	Much Improved	Im-proved	No Change	Worse	Total	Treatment Abandoned
1. Grand mal only	11	14	2	2	29	2
2. Grand mal and petit mal	1	5	2	0	8	0
3. Psychomotor attacks	0	2	2	0	4	0
4. Grand mal and psychomotor	4	2	2	1	9	1
5. Petit mal only	2	2	3	1	8	2
6. Focal attacks	2	4	1	0	7	0
Total	20	29	12	4	65	5

an occasional grand mal with the focal attack as an aura. The 31 patients in group 1 had mainly grand mal—10 with a definite aura; 8 (group 2) had both petit and grand mal; 4 (group 3) had psychomotor epilepsy; 10 (group 4) had psychomotor and grand-mal attacks; 10 (group 5) had petit mal only; 7 (group 6) had focal attacks—2 motor, 3 sensory, and 2 visceral.

Dosage.—This varied from 1.5 to 0.375 g. a day. At first a routine of three or four 0.25-g. tablets a day was used, but later an initial dosage of half a tablet thrice daily was adopted, as this produced less drowsiness. It was noted in some early cases that the substitution of primidone for phenobarbitone and sodium hydantoin produced a modification of the attacks, but not always an actual reduction. As a result hydantoin was tried in conjunction with primidone, and the combination appeared to be more effective. In general, therefore, our initial dosage scheme has become primidone, 0.125 g. (2 gr.) and hydantoin, 0.05 g. (½ gr.) each thrice daily, and this is adjusted in the light of clinical response. A combination of primidone and barbiturates, though occasionally used, has often proved unduly soporific. Primidone alone, however, has been used in 15 cases, with definite improvement in seven.

In five cases toxic symptoms caused the drug to be abandoned in from 10 days to two months of the start of treatment. Of the remaining 65, 12 were treated for less than six months, 23 for six to 12 months, 16 for 12 to 18 months, and 14 for 18 to 24 months. All had had previous treatment, usually for some years, with barbiturates, hydantoin, and sometimes troxidone; and it was because fits continued despite this that primidone was tried.

Results

The results of treatment in each of the six types of attack are shown in Table 1. Those whose attacks were abolished or so reduced as to be negligible so far as their ordinary activities were concerned were regarded as *much improved*; when attacks were reduced by 50% or more they were regarded as *improved*. Reduction was assessed by comparison with the frequency during the year previous to starting primidone. Only those whose actual attacks were increased were labelled "worse," other toxic effects of the drug being considered separately. It will be seen that the best results were obtained in the grand mal and grand mal and psychomotor groups. There are, however, aspects of the drug's action which do not emerge from these figures alone. In groups 1 and 4 there was sometimes a striking improvement in general social behaviour—irritability and perverseness being noticeably reduced. Relatives often remarked on this, and it is important in assessing the drug's value as a remedy in epilepsy rather than solely as an anticonvulsant. In three of the four cases of group 5 who showed improvement, this was unexpectedly delayed. In one, for instance, there had been no improvement after three months and treatment was to be abandoned at the next visit two months later. However, by then attacks were beginning to lessen, and nine months after the onset of treatment they had been completely abolished.

TABLE II.—*Results of Primidone Treatment in Traumatic, Symptomatic, and Idiopathic Epilepsies*

Type of Epilepsy	Much Improved	Im-proved	No Change	Worse	Total	Treatment Abandoned
Traumatic ..	4	7	0	0	11	1
Symptomatic ..	0	5	4	1	10	0
Idiopathic ..	16	17	8	3	44	4

In Table II the results are compared in the idiopathic, traumatic, and symptomatic cases. There is no significant difference between the traumatic and idiopathic. Of the symptomatic ones, five (two improved, two no change, one worse) had a presumed progressive organic cause) so that their poorer response was to be expected. These also weight the overall results in Table I.

In Table I cases are grouped on a clinical basis. However, since the electroencephalogram (E.E.G.) pattern appears to correlate more highly than the clinical description of the attack with response to the oxazolinediones, results are given in relation to E.E.G. records in Table III for the

TABLE III.—*Clinical Results of Primidone Treatment in Relation to Varying Electroencephalogram Patterns*

E.E.G. Pattern	Much Improved	Improved	No Change	Worse	Total
3 cps. wave and spike ..	3	2	1	1	7
2-4 cps. bilateral paroxysm ..	2	1	1	0	4
Generalized dysrhythmia ..	2	2	1	0	5
Localized or focal spikes:					
atypical wave and spike ..	9	14	6	3	32
Bilateral theta paroxysm ..	4	9	3	0	16
Normal record ..	0	1	0	0	1
Total ..	20	29	12	4	65

65 patients who continued treatment. There does not seem to be any great difference in the clinical response of the varying E.E.G. patterns.

Those cases with localized or focal spike discharges and atypical wave and spike rhythms most often had these abnormalities in leads from the temporal regions. Clinically, also, they showed a high incidence of psychomotor attacks and the milder conduct disorders sometimes associated with epilepsy. In general, therefore, they represent what have recently tended to be described as "the temporal lobe epilepsies." The record of some improvement in 23 out of the 32 cases is therefore of special interest.

When alterations in seizures are considered in detail in a given case an interesting point emerges. In grand mal attacks with an aura, the grand-mal element may be controlled while the aura continues or even becomes aggravated. In one patient a series of brief sensory attacks in one arm usually lead up to a grand-mal convulsion. For the first few weeks of treatment the sensory attacks became prolonged, so that for some 12 hours a continuous sensation occurred, similar to the previous attacks, but no grand mal developed and the sensation slowly cleared. Addition of hydantoin curtailed this aura, and some months later there were no grand-mal attacks and only occasional brief sensory attacks. A similar effect was noted in three other patients. In one the prolongation of an abnormal sensation was so unpleasant that she refused to continue the drug.

Toxic Effects

In general primidone seems singularly free from toxic effects, and when they occur they are usually mild and transient.

Routine blood counts and urine tests were done in the first 15 patients, but as they showed no abnormality they were abandoned for subsequent cases. Thirty-six patients complained spontaneously of drowsiness at the start of treatment. A further 22 mentioned this in reply to questions. It usually cleared in a week or two, but 12 patients

were still troubled by it months later. A few also described mild confusion and inability to concentrate. In three this was so marked as to constitute a mild confusional psychosis, and in all three of them paranoid trends appeared. In two the drug was abandoned because of this and in the third it was restarted in a smaller dose, with benefit. Two patients had an urticarial rash soon after starting the drug; blood counts were normal and the rash did not reappear when the drug was begun again after an interval. Transient nausea, giddiness, and ataxia occurred in four cases, and, in one, treatment had to be given up. In two vomiting was troublesome: one refused to continue the drug because of this, the other continued with a smaller dose after an interval, with no return of sickness.

Two patients who omitted the drug abruptly and without medical advice developed marked increase in their grand-mal attacks—in one amounting to a mild status epilepticus. It seems best to curtail primidone gradually if possible. In this respect it may be similar to the barbiturates and hydantoins, and unlike troxidone, which does not carry this risk of provoking status epilepticus if stopped suddenly.

Apart from the five cases in which treatment was given up early for the reasons mentioned above, in four it was omitted after three to six months because the fits seemed to be worse; and in a further ten, after a trial of six to nine months, as there was no improvement.

Conclusions

Primidone seems to be of some value in all types of epilepsy. However, the impression is gained that it is less useful in petit mal than in grand mal, while the proportion of psychomotor cases which are improved is especially gratifying, since this type is usually resistant to other anticonvulsants. It may be that it will find a special application here; though more prolonged experience is required, because temporary improvement from any change of drug has so often been misleading in the past.

Apart from its anticonvulsant action, it seems to benefit the milder behaviour disorders, those angularities of conduct from which some epileptics seem to suffer. The relatively high incidence of these in the "temporal lobe epilepsies" suggests that neuronal circuits in this region may be especially implicated and that the drug may act specifically on these. Its evident though mild soporific effect, since this is shared with other anticonvulsants, cannot wholly account for the benefit.

The results reported here are the more striking because this series is a highly selected one, most cases having failed to respond adequately to all the usual anticonvulsants. However, the absence of any serious toxic effects suggests that primidone should be given adequate trial as the drug of first choice in the routine treatment of epileptics.

Summary

Results of primidone treatment in 70 cases of epilepsy whose response to other anticonvulsants had been unsatisfactory are given—48 were idiopathic, 12 traumatic, and 10 symptomatic. Thirty-one had grand mal, eight mixed grand and petit mal, 10 petit mal only, 14 psychomotor attacks with or without grand mal, and seven focal attacks. Forty-nine cases showed improvement, and this occurred in all types of attack. In view of the usually poor response of psychomotor attacks to anticonvulsants, some improvement in eight out of 13 patients who continued treatment is of special interest. Toxic effects are usually mild and transient. In five cases they caused early cessation of treatment, in two probably unnecessarily.

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