THE USE OF 'TRINURIDE' (PHENYLETHYLACETYLUREA) IN THE TREATMENT OF EPILEPSY

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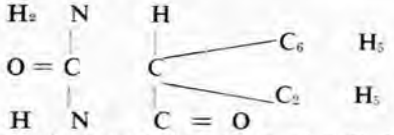
Favourable results in the treatment of epilepsy with 'trinuride' were first reported by Frommel *et al.*[1] Sorel and de Smedt,[2] and Furtado.[3] These workers found this preparation to have an effective anticonvulsant action over a wide range of clinical forms of epilepsy. As there have been few accounts in the current British literature on the observations of the anticonvulsant action of 'trinuride' on epilepsy, we feel that our observations on 21 patients treated with this drug over the past 2 years are worth recording.

Pharmacology

The important ingredient of 'trinuride', which is reputed to have a useful adjuvant or even specific activity, is phenylethylacetylurea. The elaboration of this active principle was derived from a chemically related substance, phenylacetylurea, better known as 'phenurone'. This compound had previously found wide application particularly in the USA, but later was found to have serious toxic side-effects on the haemopoietic, hepatic, and renal functions. Phenylacetylurea possesses the following structural formula:



It contains the basic chemical skeleton of 3 C, 2 O and 1 N, which is found in the closed-ring ureides such as phenobarbitone; the hydantoins, e.g. 'epanutin'; the oxazolidines, e.g. 'tridione'; as well as in the pyrimidine-diones, e.g. 'mysoline' and in the succinimides used in the treatment of *petit mal* epilepsy.

One tablet of 'trinuride' contains: phenylethylacetylurea, 0·200 g.; diphenylhydantoin, 0·040 g.; phenobarbitone, 0·015 g.

MATERIAL AND METHODS

'Trinuride' was given to 21 patients attending the Epilepsy Clinic of the Western Infirmary for periods of 6 - 24 months. All the patients were observed and treated by one of the physicians of the clinic and the majority were seen by one of us (J.B.G.). Each case record included a full history, a complete clinical and neurological examination, and pertinent laboratory studies, although liver- and renal-function studies were not performed as a routine measure. Electro-encephalographic evaluation was performed in every case before and during therapy with 'trinuride'. For the purpose of neurosurgical assessment, 4 patients had sphenoidal EEG recordings. In 3 of these arteriography was subsequently carried out and in 1 an air encephalogram was performed. No case was subjected to temporal lobectomy. One of the patients, case 16, showed an arteriovenous malformation, but the lesion was inoperable. The series comprises 13 male and 8 female patients ranging in age from 19 years to 55 years. The average age for the group was 35·2 years. In 13 patients seizures had been present for more than 5 years and in 8 for 1 - 5 years.

Every patient in this series was judged to be suffering from severe intractable epilepsy, although none of the patients was demented. The incidence of seizures among the group was high (see Table I) and the attacks had not been diminished in frequency and severity by various combinations and permutations of standard anticonvulsant drugs.

Twelve patients suffered from *grand mal* epilepsy; 1 of these had *petit mal* in addition. All had tonic-clonic fits of which the patients had no knowledge. The EEG invariably showed generalized paroxysmal dysrhythmia and in some instances spike activity was recorded at random. Nine of the patients were judged to be suffering from focal epilepsy. In this group the striking feature common to all cases was a disturbance in the normal pattern of behaviour, with concomitant disturbance of affect. These patients have been said to have psychomotor epilepsy, epileptic equivalents, or temporal lobe epilepsy. In addition 5 of these patients were subject to recurrent major convulsions.

The process of substitution of 'trinuride' for previous forms of medication was gradual and effected over a period of 4 - 5 weeks. We generally observed the following routine:

1st week. The existing medication was left unchanged, but to this 1 'trinuride' tablet was added.

2nd week. Two 'trinuride' tablets daily were commenced and the original therapy halved.

3rd week. The 'trinuride' was increased to 1 tablet 3 times a day with further reduction of phenobaritone or any other anticonvulsant the patient may have been taking.

4th week. 'Trinuride' was increased to 4 tablets a day — 2 morning and evening, with a corresponding reduction in other anticonvulsants. (The dosage thereafter was adjusted to individual needs and tolerance.)

This trial took place on ambulant patients who regularly attended the neurological clinic, though several were initially admitted to hospital for special neuroradiological investigations and commencement of therapy.

We did not attempt to control our cases using 'trinuride' alone and, in some, phenobarbitone, 'epanutin' and 'mysoline' were retained but at a greatly reduced level of dosage. The daily dosage of 'trinuride' in each individual

TABLE I. OBSERVATIONS ON 21 PATIENTS TREATED WITH 'TRINURIDE'

Case	Sex	Age	Nature of attacks	Duration of epilepsy: More than 5 years	Duration of epilepsy: Less than 5 years	Average monthly no. of major attacks before 'trinuride' therapy*	Average monthly no. of major attacks on 'trinuride' therapy	Daily no. of 'trinuride' tablets	Results
1	F	24	Temporal lobe		+	—	—	3	Markedly improved
2	M	39	Temporal lobe	+		8	5	3	Markedly improved
3	M	31	*Grand mal*	+		6	3	4	Improved
4	F	26	Temporal lobe		+	5	8	4	Worse
5	M	19	*Grand* and *petit mal*		+	5	Discont.	3	Worse
6	M	41	Temporal lobe	+		—	—	4	No change
7	M	23	*Grand mal*		+	5	1	5	Markedly improved
8	M	25	*Grand mal*		+	5	2	4	Markedly improved
9	F	37	Temporal lobe	+		4·5	0	4	Markedly improved
10	M	44	Temporal lobe	+		—	—	3	Markedly improved
11	M	43	*Grand mal*	+		10	9	4	No change
12	M	51	*Grand mal*	+		5	Discont.	4	Worse
13	M	29	*Grand mal*		+	5	6	4	No change
14	F	27	Temporal lobe		+	—	—	3	Markedly improved
15	F	55	*Grand mal*	+		5	1·5	4	Markedly improved
16	M	29	Temporal (A-V lobe anomaly)	+		2	0·5	5	Markedly improved
17	M	36	*Grand mal*		+	7	1·5	4	Markedly improved
18	F	27	Temporal lobe	+		4	1	4	Markedly improved
19	F	49	*Grand mal*	+		5	3	4	Improved
20	M	40	*Grand mal*	+		5	3·5	3	Improved
21	F	49	*Grand mal*	+		5	2	4	Improved

* Based on the average monthly number of attacks during the 6 months preceding commencement of 'trinuride' therapy.

case is given in Table I. It is important to mention that a daily dose of 4 'trinuride' tablets contains 1 gr. of phenobarbitone.

RESULTS

We assessed the 2 groups of general and focal epilepsy separately. In observing the results of treatment we employed 4 categories:

1. *Markedly improved:* Between 75 and 100% reduction in frequency of attacks.
2. *Improved:* Between 25 and 50% reduction in frequency of attacks.
3. *No change:* The same frequency of attacks or only a slight percentage improvement.
4. *Worse:* Increased frequency of attacks.

Thus in the group of generalized epilepsy the analysis was: 4 markedly improved; 4 improved; 2 no change observed; and 2 worse.

In the patients manifesting temporal lobe attacks, the improvement was most satisfactory. Seven patients were markedly improved with considerable lessening in psychic and psychomotor auras and general improvement in behaviour. This designation of marked improvement also applied to the major convulsions to which these cases were subject.

One patient showed no change and one became worse, with agressive outbursts and increased major attacks.

Side-effects

These have been carefully studied by Sharpe, Dutton, and Mirrey.[4] In a series of 32 in-patient mentally defective epileptics, they made routine blood counts, liver-function studies, urinary analysis, and blood-urea estimations. They stated that 'trinuride' had no deleterious effect on the haemopoietic system. Liver-function tests did not reveal any gross changes, and the urine, apart from traces of glucose and albumin, was normal.

We did not observe any clinical side-effects although routine laboratory studies were not regularly performed. Slight excitability, however, occurred in 2 patients, insomnia was complained of by another, and 1 patient with temporal lobe epilepsy became psychotic. Two other patients exhibited ataxia and incoordination which disappeared on lowering the dose of 'trinuride'.

DISCUSSION

Analysis of the results of this study show that 'trinuride' possesses marked anticonvulsant properties effective in *grand mal* and particularly in temporal lobe epilepsy. Thus we found that 8 of the 12 patients with severe generalized epilepsy were improved. Even more gratifying improvement was noted in the behaviour patterns and severity of major convulsions among the group manifesting temporal lobe disturbances.

Similar observations on general behaviour and mental state have been recorded by Ruggeri,[5] but were not seen by Sharpe, Dutton, and Mirrey.[4] This may have been due to the fact that these patients were certified mentally defective with very low IQ's. We feel that this drug is certainly worth further study since it appears to have considerable anticonvulsant properties when used in the treatment of clinical epilepsy.

CONCLUSION

'Trinuride' was given to 21 adult epileptic patients attending the Neurological Clinic of the Western Infirmary. Eight patients with generalized epilepsy were improved with the medication. In 6 out of 8 patients with severe temporal-lobe seizures there was a most gratifying response. Providing that the drug is carefully administered in the transition period, it is easy to handle and remarkably free from complications. There were few side-effects in this limited series.

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