CLINICAL TRIAL WITH TRINURIDE

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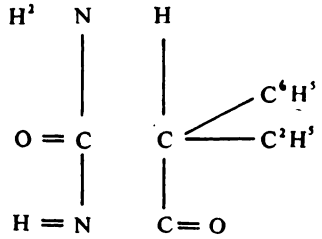
SPIELMAN and his colleagues (1948) were initially responsible for demonstrating the anti-convulsant action of the acetylurea derivatives. However, it was not until several years later that comprehensive studies were carried out by Professor Frommel in Geneva (1953).

Frommel and his associates carried out extensive laboratory experiments on animals to demonstrate the anti-convulsant action of phenylethylacetylurea (P.E.A.U.). His work also included investigation into the toxicity of the drug.

As this drug is at present little known in Great Britain, the following brief introduction to its structure and pharmacology may be of interest. The compound belongs to the acetylurea derivatives, one of which, phenylacetylurea, has already been shown to have marked anti-convulsant properties. This compound, however has proved too toxic for general use. Phenylethylacetylurea has the following structural formula, which resembles that of phenobarbitone.



Though by itself the drug has shown considerable anti-convulsant properties its effects were enhanced by combining it with other anti-convulsants. Originally a combination with phenylacetylurea was prepared. However, owing to the toxicity of this latter drug, a combination with diphenylhydantoin was adopted. In addition phenobarbitone has been incorporated into the compounds.

Thus in Great Britain the compound known as trinuride has been introduced. This has the following combinations:

Phenylethylacetylurea	0·20 gm.
Diphenylhydantoin	0·04 gm.
Phenobarbitone	0·015 gm.
Excipient	0·4 gm.

It is with this compound that we have undertaken the clinical trial now described.

Of previous clinical trials with P.E.A.U., one of the first was that carried out by Walther (1951). This study was primarily prompted by the investigation of toxicity and only 6 out of 10 cases were epileptics. Much more comprehensive

work was carried out by Sorel and de Smedt at Louvain (1953). They showed clinically that one-third of their cases improved considerably, one-third were slightly improved whilst the remainder showed no change.

To us these results were of considerable interest, as 31 of these cases were regarded as oligophrenics and had in the majority shown resistance to previous forms of treatment. More recently Sorel (1957) has compared the action of trinuride with several well-known anti-convulsants. Conspicuous results were also obtained by von Soyter and J. Fässler (1956) of the Steinen Children's Sanatorium in Raphaelstein.

Clinical Trial

The discovery of a drug which will control or abolish the convulsions of grand mal epilepsy is always of paramount importance to those who care for the epileptic patient. Apart from the control of the convulsion, the drug must exert little or no side effects. It should therefore permit the epileptic patient to undertake his daily routine with the minimum of inconvenience.

It is with these thoughts in mind that we have carried out the following clinical trial using trinuride. We feel that though of recent years there have been a number of new anti-convulsants placed on the market, there is still scope for further investigation into drug therapy for the control of epilepsy.

We have also aimed at the observation of any toxic effect which may be produced over the period of use of the drug. Another factor which we stress is the observation of any change in the behaviour state of the patient, a factor of considerable importance to those who actively nurse the patient.

Unfortunately the EEG examination was not available for the patients within this trial group. We have therefore based our results purely on clinical observations.

The material used consisted of 32 resident patients of Botleys Park Hospital, all of whom were certified mental defectives. They consisted of an adult group of 27 patients, aged from 16 to 51 years, and a smaller group of 5 children, aged from 6 to 13 years. The I.Q. ranged from 30 to 70+. Previously all the patients used were under treatment with phenytoin, primidone and phenobarbitone, either alone or in combination.

Method

As we have stated, all the patients used in this trial were already undergoing drug therapy. Thus it was necessary to employ the well-known addition, substitution and withdrawal technique. The following scheme was therefore employed for our adult patients.

First week	One tablet of trinuride was added to the existing drug.
Second week	Two tablets of trinuride (one morning and evening) was commenced and if the patient was already on phenytoin, this was reduced by 1½ grains per day.
Third week	The trinuride was increased to 3 tablets per day (1 t.d.s.). The phenytoin remaining was stopped.
Fourth week	The trinuride was increased to 4 tablets per day (2 tablets b.d.). Further reduction of phenobarbitone and any other anti-convulsant above.
Fifth week	Trinuride increased to 5 tablets per day (2 morning and evening and one midday). Phenobarbitone stopped.
Sixth week	Increased if necessary to 6 tablets per day (2 t.d.s.).

We must emphasize that it is important that this process of transition should not be hurried.

We attempted to control our cases using trinuride alone, but in 3 cases a little additional phenobarbitone and in one case phenytoin had to be given. It should of course be remembered that 4 tablets of trinuride contain approximately 1 grain of phenobarbitone.

With our children we employed a similar substitution scheme but did not increase the trinuride to more than 3 tablets per day. It is to be noted that all the children concerned were more than 5 years. The makers recommend that for children under 5 years not more than one tablet daily should be given.

The trial took place under hospital conditions and lasted for a period of six months. We feel that this is the minimum period for the assessment of any anti-convulsant.

Mindful that we wished primarily to observe the action of the drug on grand mal epilepsy we have used the following schemes. Three distinct categories have been created based on the number of grand mal attacks over an equivalent 6 monthly period before and during the course of the trial.

Thus we classify as "improved" the patient who shows a decrease of more than 25 per cent. in the number of convulsions. They were recorded as "worse" if the convulsions had increased by more than 25 per cent. No change occurs in the intervening group who have neither more nor less than 25 per cent. ni the number of convulsions.

The following, therefore, are the tabulated results showing effect of trinuride on grand mal epilepsy amongst our adult male and female groups.

Grand Mal Convulsions	Number of Cases	Percentage
Worse	7	26
No change	10	37
Improved	10	37
Total	27	100

Nine of the above had concomitant petit mal epilepsy. With this condition, unless clinically there is very marked improvement, we think that it would be unwise to venture much comment without the evidence of EEG. All that we can say regarding petit mal is that we found no evidence of any marked change in any of our cases.

Close observation was made to observe any behaviour change. It was noticeable that during the initial period of transition some of our cases became very restless. We supposed that this was due in part to the reduction of barbiturate intake and also to a certain degree of excitation caused by the P.E.A.U., a fact first noticed by Sorel and de Smedt (1953). Final assessment of our adults shows that 2 cases demonstrated marked improvement in behaviour and conduct. Twenty-two showed no appreciable change whilst 3 cases were worse.

During the course of the trial, one of our adults unfortunately died; the cause of death was not related to the trinuride—post-mortem examination showed a cerebral tumour. We have not included this patient in our results as he died before a period of assessment could be made.

The drug was also tried on a case of epiloia with chronic cardio-vascular disease, but had to be discontinued because of deterioration of the patient's physical state before any assessment could be made. Having knowledge of this patient's previous condition, we do not feel justified in holding the

trinuride responsible for his deterioration. These two cases have accordingly not been included in the results tabulated above.

The results observed in the group of children are tabulated below.

Age	No. of Convulsions Before Trial (Gm. per Month)	No. of Convulsions During Trial (Gm. per Month)	Remarks
10	4	9	Marked behaviour
13	7	12	change
9	10	4	Lethargy
9	2	7	Lethargy
6	2	2	No change

The behaviour change noted in the first two children related to an exaggeration of the uncontrolled impulsively aimless behaviour so common amongst certain epileptic children. In these two cases, this behaviour became so severe that treatment had to be discontinued. This type of change had been noted by Krauss (1957). Finally, there was no significant relationship between results and the I.Q. rating of the patients.

Toxic and Side Effects

As this drug combination has not as yet been widely investigated in this country, we thought it advisable to carry out the following scheme of laboratory investigation.

1. *Blood Count.* Red and white cell count, haemoglobin estimation by the alkaline haematin method and a differential white cell count.

2. *Liver Function Tests.* Total serum proteins were estimated by the Biuret method and fractionation was carried out by electrophoresis in a barbitone buffer at pH 8·6, zinc sulphate flocculation test by the method of Kunkel. The formal gel test.

3. *Urinalysis.* Routine examination of the urine was by Benedict qualitative method for copper reducing substances, salicylsulphonic acid test for protein and examination of the centrifuged deposit.

4. *Amino Acid and Indole Excretion Patterns.* These were assessed by the two-dimensional paper chromatograph technique on urine.

5. *Blood Urea.* This was estimated by the urease-nesslerisation method.

These investigations with the exception of the blood urea were all carried out before the start of the clinical trials. Then, after commencement, urine analysis was carried out weekly. At monthly intervals, blood counts were performed and at three-monthly intervals a complete examination as detailed above performed. This was again repeated at the end of the trial.

Results

(a) *Haemopoietic System.* There was no evidence of any deleterious effects of trinuride on this system.

(b) *Liver Function.* The tests employed did not reveal any changes in liver function as a result of trinuride therapy. The excretion patterns of amino acids and indoles showed no significant changes.

(c) *Urinary System.* Apart from occasional traces of glucose, which occurred in five cases, the only other abnormality detected was protein. Eleven of our cases showed a trace of albumin at some time. In only 2 of these cases did it persist for subsequent examination. However in spite of continuation of

treatment, they had all cleared up at the termination of the trial. The results of the blood urea revealed that in no case was the amount present in excess of the upper limit of normality.

In general, we observed no purely clinical side-effects such as exanthema or gastric intolerance.

Discussion

On analysis of the results of this trial, it will be evident that trinuride possesses marked anti-convulsant properties especially related to grand mal epilepsy. Thus we found that 37 per cent. of our cases of grand mal epilepsy were improved. This conclusion is enhanced when we consider that another 37 per cent. showed no change and that these cases had all previously been controlled, as far as possible, by other anti-convulsants. The inference is that trinuride is an efficient anti-convulsant in comparison with others in general use today.

We have been unable to observe any marked improvement in general behaviour and mental state such as observed by Ruggeri and de Sanctis (1952). This may in part be due to the type of patients we had used in the trial. It must be remembered that they were all mental defectives, some with I.Q.s of less than 30, at which level improvement, unless dramatic, cannot readily be obtained or assessed.

We feel that the true value of this compound may well be best shown in the study of the epileptic found among neurological out-patients. Here the stimulating effect of the P.E.A.U. may help to counteract the depressive side-effects of the barbiturates.

In considering the results which we obtained with the children, it is obvious that our numbers are too small to be of significant value. However, we do feel that these poor results were possibly due to increased excitation during the transition period. This excitability has already been mentioned in relation to our adults. We feel however that the children, having been for the most part under treatment for epilepsy for a shorter period than the adults, may be more prone to the effects of a stimulating drug. Thus from our experience we would recommend that in children great care should be taken during the transition period not to remove too much barbiturate until the child is well established.

In general our impressions are that though this is not an easy drug to control during the transition period, when this is passed it is remarkably free from troubles.

From the results of our laboratory investigations, it can be seen that both the haemopoietic system and the function of the liver are unaffected. However, in dealing with the urinary system we did observe traces of albuminuria. We do not wish to ignore such a finding, but in spite of continuation of treatment this condition was only transitory and at the end of the trial all cases were free from proteinuria. Further, no blood urea was shown to be above the level of normality. The appearance of a trace of glucose seems to be of no significance, as the amounts were small and did not persist. It is however of interest to note that Frommel (1957) has detected a similar substance in his laboratory animals which were undergoing investigation with trinuride. Additional evidence against any toxic action in the kidney is revealed in the case that died. Here histological examination of the kidneys showed no evidence of toxic damage. Thus it may well be that our findings are of little significance.

Our final conclusion is that trinuride is a compound with considerable

anti-convulsant properties when used in the treatment of grand mal epilepsy. It is well worthy of further trial.

Summary

In this paper, a clinical trial was carried out using the compound trinuride.

Twenty-seven adults and five children all suffering from grand mal epilepsy were given the drug for a period of 6 months.

The results showed 37 per cent. improved; 37 per cent. no change; 26 per cent. worse in adult cases.

The results with the children were poor and are detailed in the text. Full investigation of any toxic properties were undertaken. The only evidence of any disturbance was the appearance of some transient trace of albuminuria.

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