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Trial of Amino-oxyacetic Acid, an Anticonvulsant

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ALTHOUGH the overall outlook for control of seizures in children is satisfactory, there remains a small number of patients resistant to all forms of drug therapy. It is toward this group that any new forms of therapy will first be directed.

The present trial of a new anticonvulsant was carried out on children, and was stimulated by the desire to determine whether the drug under investigation had any effect on the syndrome of infantile massive spasms with mental deterioration. This is a well-defined clinical entity consisting of a generalized muscular jerk with flexion of the trunk and limbs, lasting only a matter of seconds and beginning usually in the first year of life. The characteristic electroencephalographic (EEG) pattern associated with these massive spasms has been called "hypsarrhythmia", and the spells themselves have been variously termed "massive myoclonic jerks", "jack-knife", "salaam", and "lightning" spasms. In perhaps half the cases the cause is diffuse cerebral damage from perinatal birth trauma or anoxia, whereas in the remainder the cause is thought to be developmental or idiopathic in origin. In some instances the spasms can be controlled by the use of corticosteroids, but in the great majority mental deterioration occurs even though the spasms are stopped. For this reason, it is a matter of some concern to find a form of medication which prevents this unfortunate outcome.

There is another group of children with seizure disorders in which some degree of mental deterioration may occur. In this group also, control of the seizures is difficult. These children tend to be rather older than those with massive spasms and present with akinetic or myoclonic minor motor seizures. There is no characteristic EEG pattern associated with these seizures.

ABSTRACT

It has been shown experimentally that the drug amino-oxyacetic acid (AOA) can raise the level of gamma aminobutyric acid (GABA) in the brain. Since GABA is a powerful neuronal inhibitor it seemed worth while to assess the value of AOA as an anticonvulsant.

This drug was given to 23 infants and children, all but one of whom were resistant to usual anticonvulsant medication. The types of seizure patterns were classed as major (including focal) and minor (akinetic, myoclonic and hypsarrhythmic) and the patients were followed for up to one year. Of eight children with major seizures, five were improved; of eight with minor seizures, three were improved; and of six with hypsarrhythmia, none were improved. One patient with phenylketonuria and minor seizures was improved.

It is concluded that this approach to anticonvulsant therapy is worth pursuing and that the drug may also find some use in the treatment of phenylketonuria and of seizures due to vitamin B_6 dependency.

PHARMACOLOGY

In 1950 it was found that gamma aminobutyric acid (GABA) was present in considerable quantities in mammalian brain, and it was later observed that extracts from mammalian central nervous systems could modify the effects of stimuli on the neurones of crayfish.[1] Subsequent experiments showed that this effect was due mainly to the GABA content of mammalian brain.

Animal experiments showed that GABA protects against convulsions induced by thiosemicarbazide and isoniazid, and that these convulsions are associated with a decrease in the amount of GABA which

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Since this paper was submitted, the Upjohn Company has suspended manufacture of the drug U-7524. Despite the fact that this drug may not be available commercially in the future, the authors feel that the results obtained in children are of sufficient interest to justify recording.

can be extracted from the animal's brain. GABA applied directly to the cortex has also been reported to arrest electrically or chemically induced convulsions in dogs. In addition, animal experiments have shown that when GABA is administered orally or parenterally, it fails to cross the blood-brain barrier and its entry into the spinal fluid is also limited, so that an increased concentration in the brain cannot be expected.

The drug presently under investigation, amino-oxyacetic acid (U-7524), offers an alternative approach to increasing cerebral concentrations of GABA. The most generally accepted theory of GABA metabolism (Fig. 1) is that it is formed by the decarboxylation of glutamic acid. It undergoes transamination in combination with alphaketoglutaric acid to succinic-semialdehyde plus glutamic acid in a reaction which involves a transaminase, using pyridoxal phosphate as a co-enzyme. Amino-oxyacetic acid (AOA) competes with GABA for the transaminase by acting as a preferential substrate and, as it has an affinity some 3000 times greater, it effectively prevents the breakdown of GABA. The administration of AOA in animals produces an increase of up to five times in the intracerebral concentration of GABA.[2, 3] Peak levels are not reached for six to eight hours after ingestion but may remain above normal for 24 hours.

Animal toxicity experiments have failed to show any consistently induced side effects and, in particular, liver function tests were all within the normal range after administration of this drug.[3]

Drug trials on humans were carried out with convict volunteers.[3] When doses of up to 200 mg. daily were used, conflicting results were obtained. In some, a syndrome of nausea, with or without vomiting, but with dizziness and fatigue—the whole effect being that of a hangover—was produced; in others, however, the dose could be increased to 400 mg. daily without any clinical side effects. Laboratory investigations were negative, though slight changes in the liver function tests (a rise in serum transaminase or cephalin flocculation) were reported in a few subjects.

PRESENT SERIES

Twenty-three patients (13 boys and 10 girls) have been treated and followed up for periods up

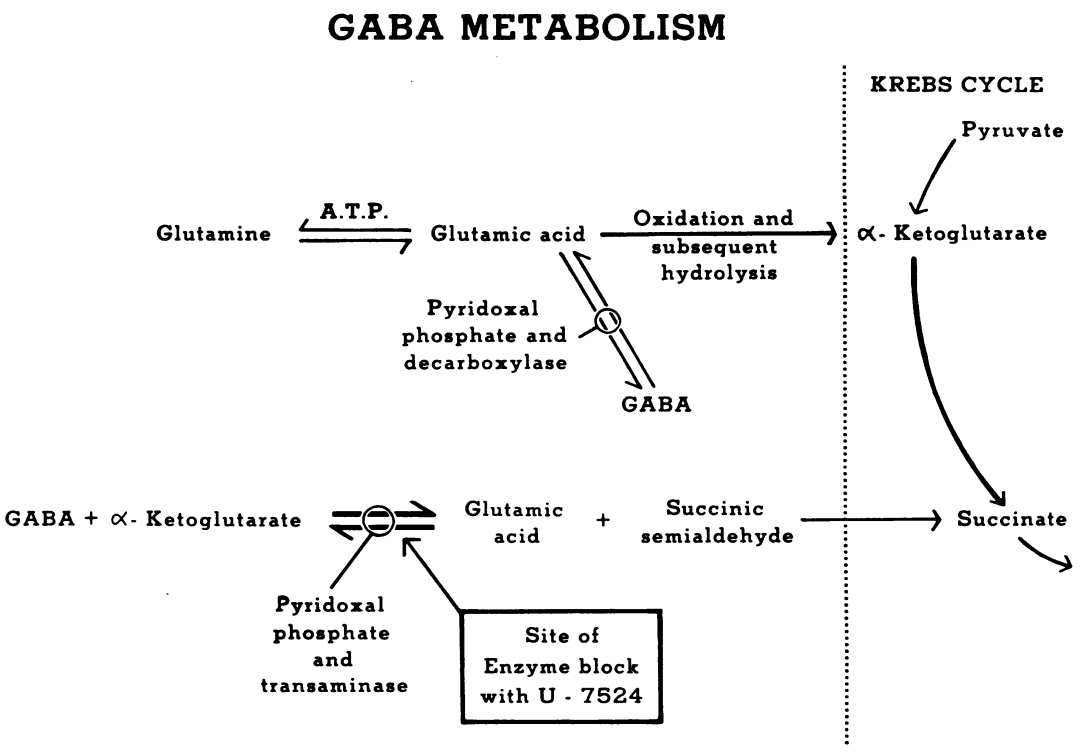

Fig. 1

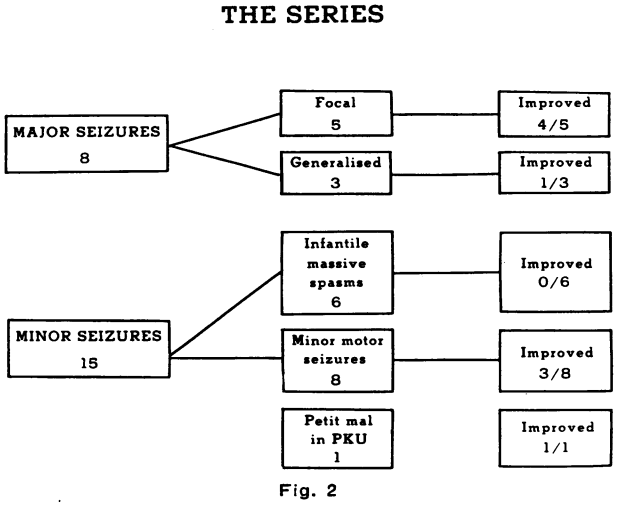

Fig. 2

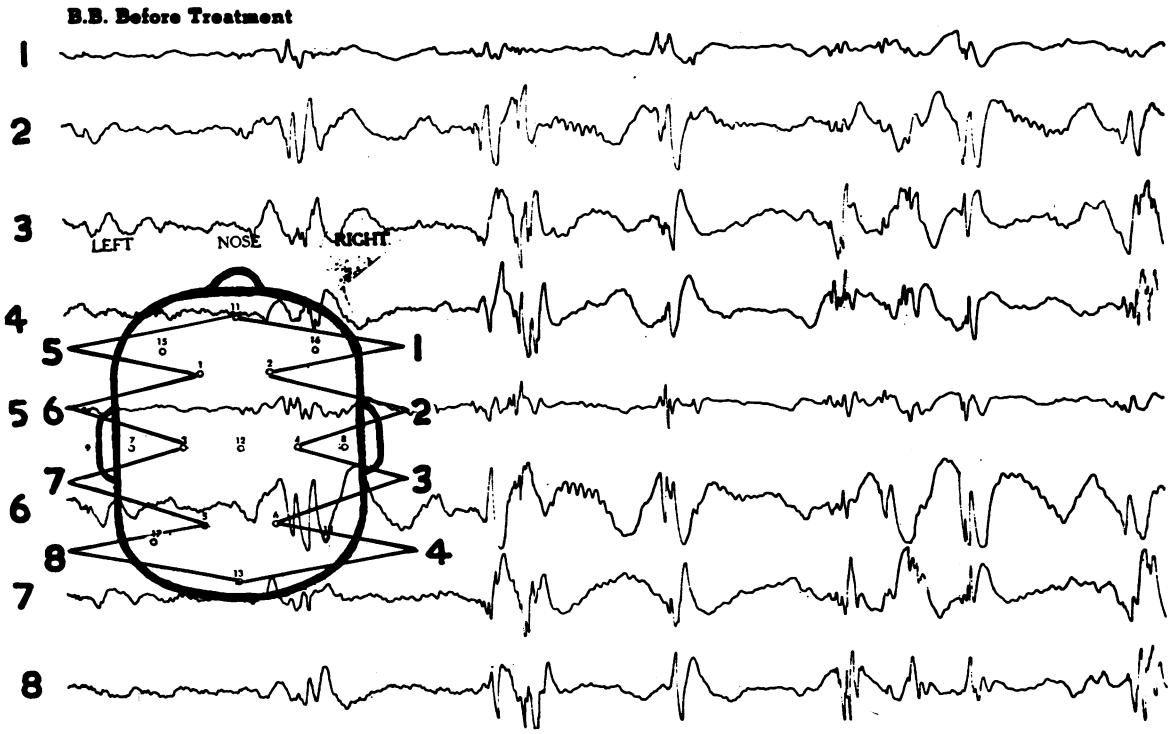

Fig. 3

to one year. Their ages ranged from six months to 13 years. All except one, an infant with massive spasms, had previously had extensive therapy with the usual anticonvulsants.

The first 13 patients were admitted to hospital and, before being given the drug, had complete blood counts, urinalysis, liver function tests, electrocardiograms (EKG) and electroencephalograms (EEG). Any medication which the patient was already receiving was continued and AOA was added in a dose of approximately 1 mg./lb. body weight. The laboratory tests were repeated after five and then after 10 days of treatment, and, depending on the response, the patients were then followed up as outpatients or the drug was discontinued.

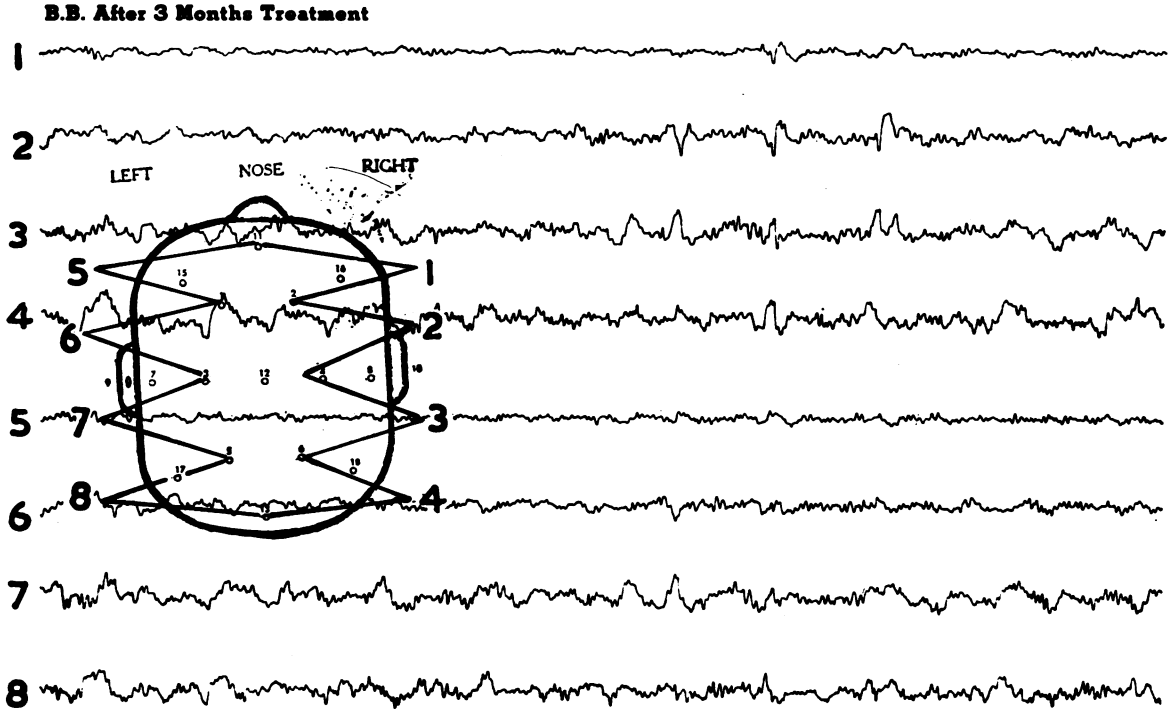

Fig. 4

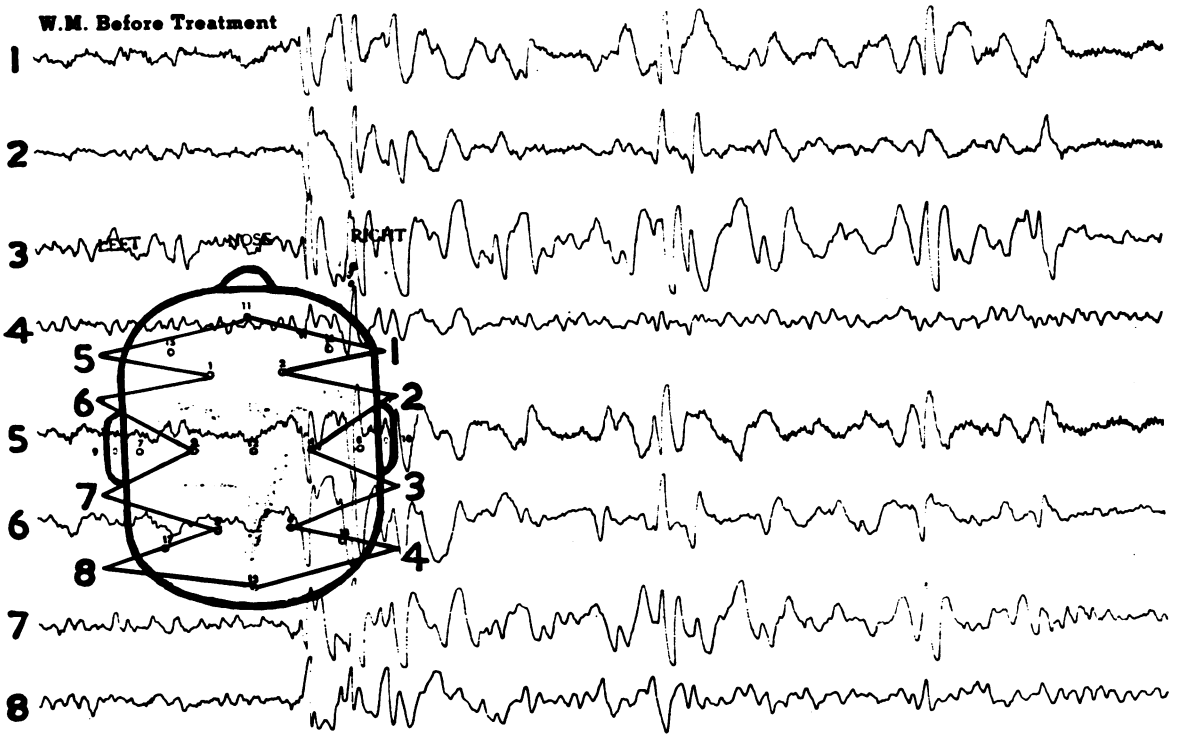

Fig. 5

The remaining 10 patients were managed entirely on an outpatient basis, and follow-up tests were carried out after about three and six months of treatment.

RESULTS

The results of this investigation are summarized in Fig. 2.

Major seizures: There were eight subjects in this group, three of whom had minor seizures in addition to major ones. In five of the eight the seizures were focal. Birth trauma and postnatal head injury were considered to be possible etiological factors in some of the patients; the remainder were idiopathic.

Of the five with focal major seizures, four have been markedly improved for periods of up to eight months. One patient, after initial improvement, showed a return of the attacks, suggesting the development of tolerance to the drug.

Of the three with generalized major seizures, one has been seizure-free after treatment whereas two were unimproved.

Minor seizures: Of the 15 patients with minor seizures, six had infantile massive spasms and none of these were improved.

Of the eight with other forms of minor seizures, three were improved but one of these has shown signs of increasing tolerance to the drug. There was no evidence that any particular clinical form of minor seizure was susceptible to this therapy, nor was there any correlation with EEG pattern.

The remaining patient had phenylketonuria with simple staring spells, and responded to treatment.

CASE REPORTS

CASE 1, B.B., aged 2½ years. No seizures were noted in this patient until the age of 21 months when he began having brief akinetic "drop" attacks numbering at least 40 daily. Coincidentally he became slow mentally and lost the speech he had already acquired. Treatment was given with phenobarbital, primidone and trimethadione (Trimedone) without effect. He was started on AOA, 25 mg. daily, and within 24 hours the seizures ceased. None have occurred in the ensuing nine months.

The EEG before treatment with AOA (Fig. 3) was grossly abnormal, with continuous epileptogenic activity; after three months of therapy (Fig. 4) it was markedly improved. Other laboratory tests showed no changes.

CASE 2, W.M., aged 13 years. This boy had a mild right infantile hemiplegia and subsequently fractured his skull when seven years of age. Soon after the injury he began to have frequent major seizures which gradually decreased in frequency, being replaced by akinetic attacks, up to 20 daily. He had received treatment with phenobarbital, diphenyl hydantoin sodium (Dilantin), primidone, amphetamine and reserpine (Serpasil) with no benefit. He was treated with AOA 75 mg. daily, and after two weeks' treatment the seizures stopped. None have been noted in the ensuing 10 months.

EEGs in 1956, 1958 and 1961 (Fig. 5) were abnormal and exhibited much epileptogenic activity. After 17 days' treatment with AOA the EEG (Fig. 6) showed considerable improvement and four months later (Fig.

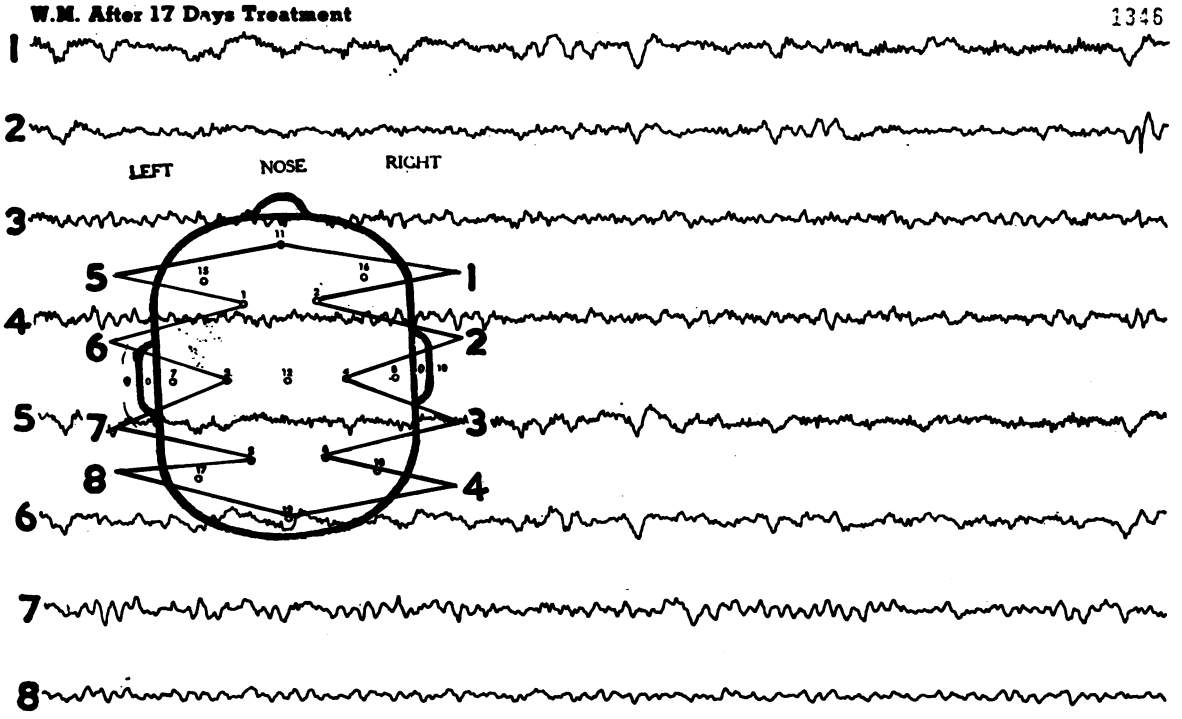

Fig. 6

7) was within normal limits. Laboratory investigations were otherwise normal apart from a single alkaline phosphatase level of 35 units, four months after treatment started.

SIDE EFFECTS

In two infants excessive drowsiness occurred and was attributed to overdosage. Other minor effects included irritability in one case and nausea in another.

No effect was noted on the kidneys or bone marrow, as judged by routine urinalyses and blood counts. In six of the 23 patients the liver function tests showed some deviation from normal, as indicated by a slight transient rise in the serum transaminase or alkaline phosphatase levels. In addition,

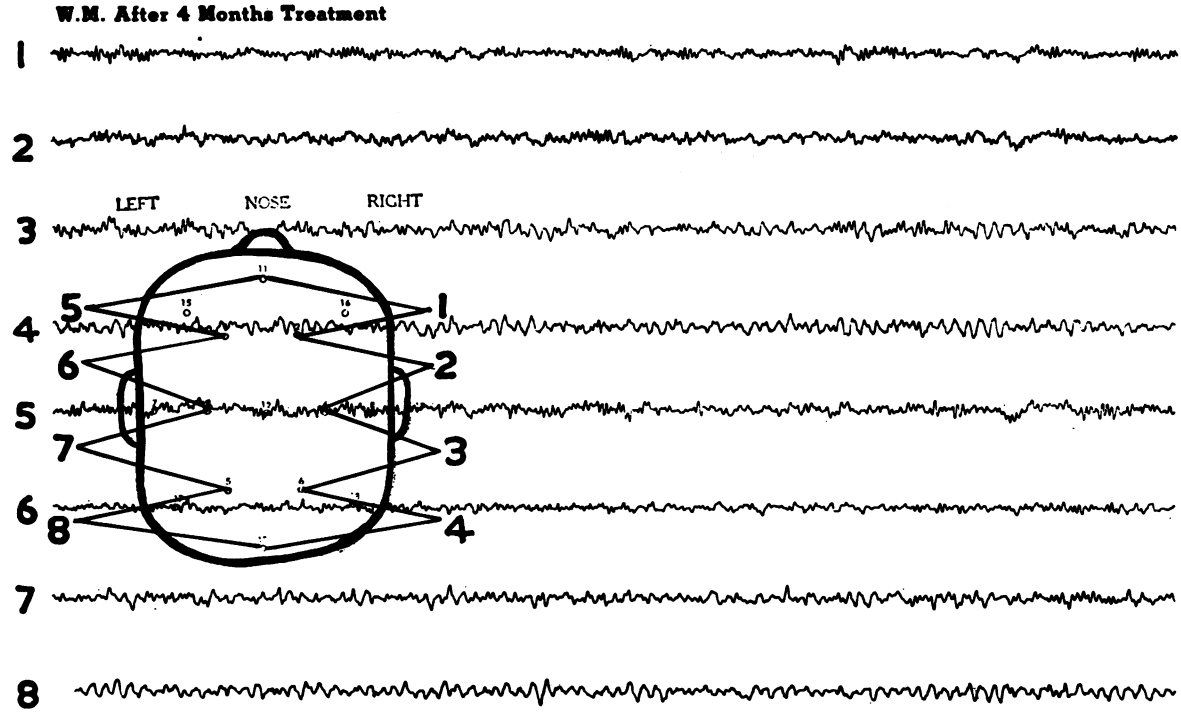

Fig. 7

a further patient had a persistent rise in the serum transaminase only, and another patient had a similar persistent rise in the alkaline phosphatase only. No other abnormal findings or clinical changes have occurred in these two patients.

More extensive liver function tests have included serum cholesterol, bromsulphalein retention tests, electrophoretic serum protein patterns and studies on the blood coagulation mechanisms. All these investigations have been normal, and this finding, together with the absence of any clinical evidence of liver toxicity, would suggest that the abnormal liver function tests noted do not afford evidence of liver damage.

DISCUSSION

Any drug which helps to control seizures in patients resistant to the usual forms of medication is clearly of value. However, the importance of amino-oxyacetic acid lies as much in its presumed metabolic effects as in its present practical application, for it offers a new therapeutic approach to the control of seizures. If drugs of this type prove to be of value, some insight into the biochemical changes accompanying seizures may be obtained.

Two further possible uses for this drug should be mentioned. There is some evidence that there is a reduction in the GABA level in the brain of subjects with phenylketonuria[4] because the formation of GABA from glutamic acid is inhibited by certain phenylalanine derivatives, including o- and p-hydroxyphenylacetic acid. One patient in this series had phenylketonuria, and despite apparently good dietary control the serum phenylalanine levels had fluctuated up to 15 mg. % over a period of two years. Control of her minor spells was achieved with AOA. Since the outlook in cases of phenylketonuria, even when patients are treated from early infancy and are well controlled, is that the children may not—and probably do not—achieve their full intellectual potential, it is worth while considering the use of any agent which might lead to higher levels of GABA in the brain.

Secondly, there are theoretical reasons for believing that AOA might have a place in the treatment of vitamin B_6-dependent convulsions. Vitamin B_6 is a co-enzyme in numerous reactions, one of which is the decarboxylation of glutamic acid to GABA. Since convulsions can be produced experimentally by lowering the brain GABA content, it would seem reasonable that this group of metabolic convulsive disorders may respond if the brain level of GABA is raised. Consequently those resistant to vitamin B_6 might respond to AOA. As yet there has been no opportunity to test this hypothesis.

Two clinical observations can be made. Experimental work in cats suggested that diphenyl hydantoin sodium (Dilantin) might potentiate the effect of AOA.[5] In the present series there were nine patients in whom the AOA was added to existing Dilantin medication; of these, six were improved and three showed no change.

The early trials with the drug indicated that an initially good response might gradually wear off, and this was the case with two of the patients in the series. In one of these there was a further response when the dose of AOA was increased, but this was temporary. This response may indicate that tolerance to this drug may develop.

It has been suggested in this communication that the anticonvulsive effect of the drug is due to a rise in the GABA level in the brain. However, this may not be so. Experimental work has shown that the maximal anticonvulsive effect of AOA does not coincide with the time when GABA levels in the brain are at their highest, and since the drug also leads to a rise in the glutamine levels in the brain, this latter phenomenon might account for the anticonvulsive effects.[6] Further, hydroxylamine, which also leads to an increase in the brain level of GABA, does not protect animals against thiosemicarbazide-induced seizures, which would be expected if the higher levels of GABA were the important mechanism. Some reservations about the precise mode of action of AOA are therefore justified.

CONCLUSION

A trial has been conducted in 23 children using a new anticonvulsive agent, amino-oxyacetic acid. The results suggest that this new type of therapeutic approach has something to offer and is worth pursuing.

SUMMARY

A new anticonvulsive agent, amino-oxyacetic acid (AOA), is described. It is believed to enhance cerebral levels of gamma aminobutyric acid (GABA) by acting as a preferential substrate and thus blocking normal GABA breakdown.

The drug has been used with 23 children, all but one of whom were resistant to the usual forms of medication.

Eight children had major seizures and five were improved; 14 had minor seizures and three were improved. One patient with phenylketonuria and minor seizures was improved.

Minor changes in liver function tests were noted in eight patients; these are not thought to indicate liver damage. Tolerance to the drug during the period of administration was noted in two patients.

Other possible uses for the drug are discussed.

Thanks are due Dr. E. L. Masson of The Upjohn Company of Canada for supplies of amino-oxyacetic acid (U-7524), and our colleagues at the Hospital for Sick Children for permission to treat their patients with the drug.

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