Drug Treatment of Disease

DRUGS IN TREATMENT OF EPILEPSY

BY

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This paper is concerned solely with the medical treatment of epilepsy. To conform with the intention of this series of articles the word "medical" is used in its narrowest sense—pharmacological—and "epilepsy" in its widest—to include recurring discrete disorder of sensation, behaviour, or consciousness of any sort due to cerebral disturbances, whatever the prime cause. The treatment is of fits of all kinds, whether symptomatic of brain disease (for example, trauma), of disease elsewhere (for example, vascular disease), or of unknown origin (idiopathic). It would be wise to consider this against the wider, and perhaps more important, aspects of epilepsy which were presented as a symposium in this *Journal* on March 22, 1958.

Kinds of Epilepsy

For pharmacological as well as other reasons the precise form of epilepsy must be recognized on clinical grounds and, if in doubt, with the help of the electroencephalogram, because, for instance, drugs which may benefit one form of petit mal due to local brain damage may aggravate the other form with the characteristic spike-and-wave discharge in the electroencephalogram. For our present purpose epilepsy is divided into:

The general epilepsies:

Grand mal.

Petit mal.

Focal epilepsies.

Grand mal is a pure tonic-clonic fit, which is the same whatever the cause. Petit mal includes the brief, frequent, stereotyped "absences" of childhood and myoclonic jerking. And the focal epilepsies include all other attacks however diverse or elaborate. Treatment of grand mal and focal attacks is so similar that they will be considered together, and the word anticonvulsant will be used generically whether or not an actual convulsion occurs in the attack.

Even after full investigation and medical or surgical treatment of the cause of the fits, medical treatment of the fits themselves is subservient to management of the patient's attitude, his life, and its background. Indeed, continuation of medical treatment may become inevitable because continuing stress in the life perpetuates epilepsy in a predisposed person.

Types of Drug

The most successful anticonvulsants for practical use in the ambulant patient can be listed thus:

(a) Barbiturates, especially phenobarbitone and methylphenobarbitone.

(b) Hydantoins—phenytoin ("epanutin") and methoin ("mesontoin").

(c) Primidone ("mysoline").

(d) Diones—troxidone ("tridione") and paramethadione ("paradione").

(e) Others, especially acetazolamide ("diamox"), phensuximide ("milontin"), and phenacemide ("phenurone").

Though they derive from different chemical sources it is remarkable how closely similar the basic molecular formula of each group of the better anticonvulsants is.

Time of Administration

The average time of effective concentration after ingestion of an anticonvulsant is from six to eight hours, but the time of administration must be judged by the time of occurrence of fits. Some people always have them by day, some always by night, and the peak period is within an hour or so of rising. Therefore, the day's dose may be given on retiring, on rising, or spaced through the day. When fits are more frequent at the menstrual period a much larger dose may be given in that week.

Barbiturates

Occasionally, bromides have been given as a last desperate attempt to stop fits when all else had failed. But they are mentioned first to dismiss them with the comment that, though they stopped many fits, they did the epileptic person much harm in turning him into a handicapped, retarded dullard with bromism.

The first drug of choice remains phenobarbitone. This shares with aspirin and alcohol the stigma of abuse, but it remains an excellent anticonvulsant. It is safe, of very low toxicity, with little tendency to sensitivity. Do not, however, discount as neurotic the occasional patient who complains bitterly of sleepiness on a tiny dose, for some cannot tolerate it and many become depressed with it, though most become used to it after a few weeks.

It is always wise to begin treatment with phenobarbitone, $\frac{1}{2}$ gr. (32 mg.) once or twice in the day, but not to use much more than this in the first instance. Children, who will require a smaller dose according to their size, may be very tolerant of it, but sometimes become irritable and difficult while taking it. If so, stop it, for they will not mend. If fits continue in spite of a reasonably small dose of phenobarbitone, do not push it, for the patient will probably become retarded or depressed, and his distress and difficulty in continuing his pattern of life will bring more fits. Instead, go on to the hydantoins.

Phemitone ("prominal"), which is methylphenobarbitone, is converted to phenobarbitone in the stomach. Its anticonvulsant dose is double that of phenobarbitone, and though its pharmacological effect should be the same, patients who are sleepy with phenobarbitone may be content with phemitone (1–3 gr. (65–200 mg.) in a dose). It is worth trying. Long-acting phenobarbitone in an "enseal" is also advised for the same purpose.

Initial sensitivity to phenobarbitone or phemitone is unusual, but the physician is occasionally surprised to see a rash which, developing years after beginning treatment, disappears on withdrawing the barbiturate.

The effects of overdosage are subtle and serious, for the sensitive patient becomes intellectually retarded, slothful, sleepy, and sometimes very depressed. These symptoms are serious because they are insidious, not recognized for what they are, and greatly handicap the epileptic in pursuing his way in life. They should be avoided, even at the cost of an occasional fit; their continuation may lead to a vicious spiral downward, with a return of fits. Never, therefore, push barbiturates or have recourse to the amphetamines to try to offset these effects. Instead, limit the dose of phenobarbitone to the patient's toleration, and add another non-sedative anticonvulsant, of which the hydantoins are the best.

Hydantoins

When phenobarbitone has been given to an adult up to a total of three $\frac{1}{4}$ -gr. (32-mg.) doses in the day and further treatment is needed, add phenytoin sodium (diphenyl hydantoin sodium, epanutin) 0.1 g. twice or three times a day. It may be given in a larger dose at morning or evening if fits are diurnal or nocturnal only. It is a wise generalization that the margin between the effective anti-convulsant and toxic amount is small, so that the hydantoins must be given in fairly large doses, 0.3 g. daily being usual. Most adults will develop toxic effects if they take 0.4 g. daily for a few weeks, for the substance slowly accumulates, and it may be necessary to give 0.3 g. and 0.4 g. on alternate days to control fits without toxicity.

Sensitivity results in a rash with pyrexia and transient adenitis just like German measles or measles, but can be controlled by an antihistaminic such as promethazine hydrochloride, given for 10 days. The drug may also cause the unique hyperplasia of the gums, especially in children, macrocytosis, or rarely macrocytic anaemia, gastric disturbances, and most commonly ataxia, incoordination, and diplopia. It is wise to give patients having phenytoin crude vitamin B as "bemax" or "marmite"; to encourage dental hygiene; and to reduce treatment for two days from time to time if the patient becomes unsteady. Indigestion is relieved by giving the drug with meals, or with sodium bicarbonate. More serious, though rare, complications such as exfoliative dermatitis call for its immediate withdrawal, but there is no need to carry out repeated blood counts.

Methoin (mesontoin, or methyl-phenyl-ethyl-hydantoinate) has the same dose and similar therapeutic effect. It does not cause gum hypertrophy, but may make the patient drowsy, and is more likely to cause blood changes than is phenytoin sodium. It can be given as an alternative when gingivitis is troublesome.

It is so useful to give the hydantoins and phenobarbitone together that they can be obtained in the same capsule—phenobarbitone 0.05 g. and phenytoin sodium 0.1 g., to be given two or three times a day.

Primidone

Primidone (mysoline) has been successful in major epilepsy where other anticonvulsants have failed. It is not often toxic, but it has a sedative action, particularly when given with phenobarbitone, so that I never use these two substances together. Primidone is still much more expensive than the anticonvulsants already mentioned, so it is sensible to use phenobarbitone and phenytoin before trying it. Begin with very small doses indeed, gradually increasing from half a 0.25-g. tablet to three or more a day, because some people tolerate it very badly, are drowsy, ataxic, and may have vertigo and vomiting.

Once established, treatment with primidone seems uneventful. It can, with benefit, be combined with phenytoin, particularly in major epilepsy, but it is unlikely to be so successful with focal attacks, or minor attacks of any kind.

Treatment of Petit Mal

True petit mal is much more difficult to treat successfully than are other forms of epilepsy. Fortunately, however, unless the short attacks are very frequent, they may be no more than a nuisance, and a child may live in reasonable adjustment to them. In consequence, if attacks are resistant to treatment or the patient intolerant of it, it may be expedient to cease, letting the child continue otherwise normally, as an alternative to a drugged life.

The substances so far mentioned are usually of little value in treating true petit mal, though some brief "absences" may really be unrecognized focal attacks, and so respond to phenobarbitone or phenytoin. In general,

sedatives make true petit mal worse, and stimulants improve it. In addition, children with petit mal are apt to become aggressive, surly, and unsocial with phenobarbitone, and so have more attacks. Conversely, amphetamine, dextroamphetamine, and caffeine may greatly benefit patients with petit mal and improve their behaviour. It is important in view of the specificity of treatment to be guided by the electroencephalogram as well as by the characteristics of the attacks.

Diones

Troxidone (tridione) is sometimes drastically successful in controlling petit mal. When it is successful it seems to work in quite a small dose, and increasing the dose does not improve the therapeutic response. Adults or large children can take three or four 0.3-g. tablets a day, smaller children three or more 0.15-g. tablets according to size.

Many patients have toxic responses, but fortunately these are usually not serious. Most commonly there is glaring vision, when objects glow and sparkle in bright light, while hiccups or nausea also occur; but these symptoms do not often call for withdrawal of the drug. Rashes may be seen initially but often subside; occasionally blood dyscrasias occur—aplastic anaemia and granulopenia. It is much more important to watch the child's health than to do frequent blood counts, because harmless fluctuations in the count may be encountered and a sudden aplasia missed. I give special attention to details of health and do not do serial blood counts, and so far have been able to regulate treatment without harm to the child. If troxidone is moderately successful, see if paramethadione (paradione) in the same dose is better, otherwise stop treatment.

Other Drugs

Amphetamine.—Amphetamine sulphate, methylamphetamine, or dextroamphetamine, 5 mg., may be effective in true petit mal. They may reduce attacks and improve the child's behaviour. They should be tried if petit mal is frequent, and children tolerate them well. Methylamphetamine has the fewest side-effects. Caffeine citrate 5 gr. (0.32 g.) may help children benefited by amphetamine.

Acetazolamide (diamox) has recently been given with other anticonvulsants because, as well as being a diuretic, it is a carbonic anhydrase inhibitor and lowers blood pH. Reports have varied, and results are often disappointing, but occasionally the addition of acetazolamide (0.25 g. once or twice a day) to existing anticonvulsants has been followed by striking improvement. There are minor toxic effects, and rare serious ones. Acetazolamide is expensive, but a short trial of its effects will quickly establish its value in any one case.

Phenacemide (phenurone) 0.5 g. one to three times a day has serious toxic effects. This is a great pity, because it is a most effective agent in all forms of epilepsy. Frequently, there is improvement in the refractory case, to be followed by anorexia, nausea, liver damage, or blood disorder. It also causes psychosis. It should, I think, be used only as a last resort when attacks are out of control and the patient is under close observation.

Among other substances, *phensuximide* (milontin) 0.5 g. three to four times a day is the most well tried. It is effective in petit mal epilepsy, and can be tried after the substances already mentioned.

A final note of warning. If several drugs have been tried, and more than two are being used, the patient is probably suffering more than he is gaining by them.

Status epilepticus remains a very dangerous complication which must be brought under control as soon as possible. Paraldehyde (5 ml. intramuscularly) repeated every two or three hours until attacks have stopped is probably still the safest drug. Intravenous anaesthesia can also be used, but an anaesthetist with positive-pressure apparatus should be available.