Current Practice

PRACTICAL NEUROLOGY

Drug Treatment of Epilepsy in Childhood

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As in adults, the management of epilepsy in children has been vastly improved by the development of a range of effective drugs. In children, however, not only are there marked clinical differences in the seizure disorders which influence the choice of drugs, but also the use of drugs may present special problems, especially in younger age groups.

The Individual Fit

The need to treat a fit depends in part on whether or not there is evidence that major fits are themselves potentially damaging. Though the matter is unresolved, our patients should be given the benefit of any doubt, and all fits which have gone on long enough for an anxious parent to obtain the help of a doctor should be treated. These will have rarely lasted less than 15-20 minutes.

The aim of treatment must be to give a predictably effective dose of a drug by a predictably effective route. Though on theoretical grounds it may be an advantage to choose a drug that the patient is not already having, the dosage will have to be sufficient to achieve satisfactory therapeutic levels, and the route of administration chosen to be swiftly effective.

Undoubtedly the speediest route is by intravenous administration, but there are certain practical difficulties. Restraining a jerking young patient in the home long enough to give a potentially dangerous intravenous injection is sometimes difficult, whilst the risk of laryngospasm debar the domiciliary use of intravenous barbiturates. Though paraldehyde can be given very slowly intravenously, it is very sclerosant and immiscible with saline. For both barbiturates and paraldehyde intramuscular use is preferred, but it must be remembered that in a prolonged fit, in which there is pyrexia, dehydration, and circulatory embarrassment, absorption from an intramuscular site may be relatively slow. Certain poorly absorbed drugs such as phenytoin may be absorbed just as rapidly from the gastrointestinal tract as from an intramuscular site and are best given intravenously if administered in an emergency.

The rectal route, which provides a relatively large surface area with a generous venous plexus for absorption, may be usefully exploited in many patients. Paraldehyde, freshly mixed with either arachis or olive oil, can be painlessly administered in a dose similar to that used parenterally. Barbiturates or diazepam mixed with saline may also be given by this route.

If the situation is complicated by hyperpyrexia, active cooling may be supplemented by pethidine compound injection (pethidine, promethazine, and promazine).

Drugs Used

Paraldehyde (0.1 ml./kg.) (dosage referred to body weight) is still perhaps the most widely used in hospital, since it is relatively free of respiratory depressant action and will control most

prolonged fits, but it may be necessary to repeat the dosage in 15-20 minutes. Unfortunately this drug is not entirely stable, and ideally it must be kept cool and in the dark. Moreover, it must be used with a glass syringe, since it interacts with many plastics, and one cannot encourage or condone its administration from a disposable syringe, however zealously expeditious, before the barrel wilts.

Phenobarbitone Sodium.—Being stable, this drug is more valuable for domiciliary use, and can be given in a single injection of 6 mg./kg. Unfortunately, if the patient is already having barbiturates, phenobarbitone may not be so effective in controlling the fit, and the risk of respiratory depression may be greater.

Diazepam has recently been exploited as a safe and potent anticonvulsant for the treatment of status epilepticus. With 5 mg. in 1 ml. solution, given intravenously in a dosage of 0.1 mg./kg., the dosage can be titrated against control of the fit with little risk of respiratory depression. Unfortunately, it has been my experience that if the patient is already having the drug, or if he has had it recently, it is much less effective; but it can be given in much higher dosage if necessary. In view of its known hypotensive effect great care should be exercised, and the blood pressure should be monitored in its use if other anticonvulsants, especially barbiturates, have already been given.

If the foregoing drugs in the dosages recommended are ineffective within 10 minutes arrangements should be made for prompt transfer to hospital. If the child has stopped fitting before he reaches there, this is reason for self-congratulation: if not, then the facilities of a casualty department or inpatient unit are probably going to be essential.

Febrile Convulsions

Though the nature of "febrile convulsions" is in dispute, it is recognized that in early childhood, particularly between the ages of 1 and 4 years, some children tend to have major fits at the onset of non-specific febrile illness, often of the upper respiratory tract. Fits are usually brief and symmetrical and have a familial tendency.

Ounsted and his colleagues,¹ suggesting that certain chronic seizure disorders might be a sequel of prolonged major fits in early childhood, have indicated a generic relationship between such prolonged seizures and febrile convulsions. The implication of Ounsted's work is that measures should not only be taken to curtail the duration of an actual fit irrespective of its cause, but also that prophylactic measures should be adopted in those children who have shown an early tendency to convulse in association with a non-specific infection.

It is my policy to recommend antipyretics (aspirin 10 mg./kg. or paracetamol 25 mg./kg.) 4-hourly for 3 doses per 24 hr.,

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with direct efforts to keep the child cool during infective illness, and if the child has had two or more fits previously I recommend the addition of regular prophylaxis with full doses of the best-tolerated anticonvulsant (phenobarbitone or phenytoin). While the administration of anticonvulsants may not prevent the recurrence of "febrile convulsions," it serves to insure against status epilepticus. Intermittently administered anticonvulsants are ineffective, perhaps because their maximum therapeutic level is not achieved quickly enough.

Infantile Spasms

Infantile spasms, also known as salaam or lightning spasms, are a form of epilepsy occurring usually in the first two years of life. They are associated with slowing of mental development, and, though the spasms may arrest spontaneously between the ages of 2 and 3 years, most of the children remain mentally handicapped, with a high proportion showing autistic features. The name "hypsarrhythmia" has been applied to the grossly disorganized E.E.G. accompanying the disorder. The condition is symptomatic of a miscellany of diseases—metabolic disorders such as phenylketonuria, congenital malformations such as agenesis of the corpus callosum, hereditary disorders such as tuberous sclerosis, perinatal brain damage, and as an encephalopathic complication of immunization with triple vaccine. The mechanism of the seizure disorder is unknown, and it is unusual for it to be complicated by major fits. Conventional anticonvulsants are unhelpful, but A.C.T.H. and steroids have been shown to be usually very effective in controlling spasms, and they often induce a lasting remission.² Unfortunately, though the control of spasm can be quite dramatic, the influence on subsequent mental development is less impressive. Nevertheless, there is evidence suggesting that when the spasms develop in infants without previous developmental abnormalities (structural or biochemical) the long-term mental development is better in treated than in untreated patients.

Though the relative therapeutic merits of A.C.T.H. and oral steroids in this syndrome have not yet been clearly delineated, it is the usual practice to give a large dosage of one or the other. Some workers recommend short courses of A.C.T.H.—40 units daily for two weeks, repeating if necessary—while others administer a somewhat lower dosage for six to eight weeks. Elsewhere oral steroids in a dosage of 5 mg./kg./day are administered for as long as three months without any decisive evidence that one scheme is superior in the long term to another.

Other acute and subacute encephalopathies besides infantile spasms may be controlled by steroids alone, and they are occasionally helpful in the treatment of status epilepticus. Undoubtedly, but for the side-effects of prolonged administration, A.C.T.H. and steroids would have a much wider use in the management of epilepsy in childhood. The mode of action is unknown, and is in enigmatic contrast with the use of steroids to induce seizures experimentally in animals.

Because of the potentially dangerous side-effects which may occur, the decision to use A.C.T.H. or steroids is not one to be taken lightly in these chronic maladies.

Prophylaxis of Recurrent Seizures

The recommendation to parents that their child should be treated with long-term anticonvulsants should be prefaced by an explanation of their purpose. It is also wise to indicate that success may not be immediate, in that both the choice of drug or drug combination and dosage is a matter of individual variation, and changes may be necessary without predicating a poor prognosis. Otherwise all-important family morale may be quickly depressed by a succession of changes.

Choice of Drugs

Bewildered by an array of expansive claims for the efficacy of nearly a score of anticonvulsants, the choice of drug or drugs is largely governed by considerations of potency, toxicity, and economics.

The sheet-anchors of treatment of major fits and most minor seizures are phenobarbitone, phenytoin, or primidone, singly or in combination, either with each other or with other less potent and often more toxic and expensive agents. Though there is theoretically no limit to the numbers of drugs given, most patients are well controlled on one or two drugs. If more than three drugs are used because of the difficulty of achieving control of fits, it is doubtful if further additions contribute anything of benefit.

Drug changes should preferably be gradual, and not more frequent than fortnightly. Withdrawal of drugs, especially phenobarbitone, should be slow, otherwise withdrawal fits may occur. Certain combinations of drugs are best avoided, such as phenobarbitone and primidone (because of its torpid tendency) and primidone and sulthiame (which may provoke psychotic excitement).

With the current concern over drugs, parents need a lot of reassurance that, as used in these conditions, anticonvulsants are not drugs of addiction, nor do they lead to moral turpitude.

Haematological Changes

There have been occasional reports of serious blood dyscrasias occurring in patients treated with several anticonvulsants, and these have prompted the advocacy of routine blood counts. It is not my policy to undertake these, because they are unlikely to be of much prophylactic value unless carried out more frequently than the majority of children would tolerate.

The risk, however, must be recognized, along with the risk of developing other complications, such as rashes, hepatorenal damage, and psychoses.

With the prolonged use of barbiturates and related drugs (phenytoin and primidone) anaemia due to folate deficiency may occur in children as well as in adults.³ Though it has been suggested that giving folate to patients on anticonvulsants who are thought to be deficient in it may lead to relapse in fit control, the evidence is equivocal, and it is reasonable to remedy folate depletion as necessary.

Duration of Treatment

In general, continuation of anticonvulsants for two to three years after the last fit is recommended. If after that time an E.E.G. still shows numerous discharges, I recommend continuation of treatment, with annual review.

If the end of a three-year period of freedom coincides with, for example, adolescence, I usually urge patients to continue taking their tablets into late teens because of the tendency for control of fits to relapse during adolescence.

Proprietary Combinations

While it may be more convenient to give a drug combination as one tablet or capsule, such an arrangement does not allow the flexibility of varying individual dosages to suit the particular needs of the patient, and I do not recommend its use for this reason.

The drugs available will now be systematically described: dosages are included in an appended Table.

Phenobarbitone enjoys an undeservedly high reputation as an anticonvulsant in childhood. Though its anticonvulsant action is recognized, its use often results in such marked personality changes—irritability, aggression, depression, excitement—that parents often conclude that the cure is worse than the disease and stop the drug themselves. For adults, combinations with D-amphetamine are much favoured abroad, but there is little evidence that its use is thereby favoured in childhood.

In a new patient it is worth trying the effect of phenobarbitone, but it should be discontinued if adverse effects persist after two weeks' use.

Methylphenobarbitone is claimed to be less depressing than phenobarbitone, but it has to be given in considerably higher dosage. It is worth a trial, but, like phenobarbitone, may have to be withdrawn on account of its effect on temperament.

Phenytoin Sodium is also a potent anticonvulsant, similar to phenobarbitone, but only rarely complicated by effects on temperament. In a daily divided dosage of 5 mg./kg./day it is usually well tolerated, but because of its intensely alkaline character it should be introduced over a few days to avoid nausea, and should not be taken on an empty stomach. Hypertrophy of the gums is a frequent complication, but this can be controlled by the rigorous maintenance of good dental hygiene and resection if necessary. Hirsutism in girls can sometimes be troublesome. In overdosage, anorexia, drowsiness, ataxia, nystagmus, and dysarthria may appear, and may even be seen after a previously well-tolerated dosage. The condition is usually reversible, but permanent neurological deficit has been described following the prolonged use of daily dosages of 8–10 mg./kg. Certain patients are abnormally sensitive to phenytoin, being unable to metabolize it normally, and toxic effects are seen in them with much smaller dosage.

Primidone is not only structurally similar to phenobarbitone, but its metabolic fate also has common intermediaries. It is usually well-tolerated in a divided dosage of 20 mg./kg./day, but may cause drowsiness and depression, as well as more dramatic effects on personality.

Sulthiame is one of the newer anticonvulsants and is claimed to be particularly effective in the treatment of temporal lobe seizures. It may cause gastrointestinal upset if its introduction is too rapid, and psychological disturbance is not uncommon. Hyperventilation is frequent in the larger dosages.

Phenacemide is too toxic to have widespread use, causing damage to both liver and bone marrow.

Pheneturide, though structurally related to phenacemide, is not so toxic. When given with phenytoin, the therapeutic effect may be enhanced. It must be introduced gradually.

Beclamide is structurally dissimilar from the older anticonvulsants, and its anticonvulsant effect is much less impressive. It is relatively expensive.

Ethotoin is a hydantoin, like phenytoin. Though it may be given in combination with phenytoin, it is less toxic but also less effective.

Methoin is another hydantoin, and tends to be more toxic than phenytoin.

Carbamazepine has less effect than other anticonvulsants on temperament and behaviour in children, and this newer agent is a helpful adjuvant to existing regimens. It should be introduced gradually to avoid gastrointestinal upsets and drowsiness. Jaundice, rashes, and blood dyscrasias have occurred, but the only serious contraindication to its use, apart from previous sensitivity, is the use of monoamine oxidase inhibitors at the same time.

Acetazolamide. Well-known as a carbonic anhydrase inhibitor, with diuretic properties, this drug can also be used as an anticonvulsant. Though not a powerful anticonvulsant, it is devoid of the depressant effect of conventional anticonvulsants, and its different structure, associated with a different mode of action, can be utilized as an adjuvant to other drugs.

Diazepam. As mentioned earlier in the discussion of the management of status epilepticus, this drug is under certain conditions an effective anticonvulsant. Apart from status, its use has been particularly advocated in the treatment of myoclonic epilepsy. Unfortunately, however, its value in both situations is seriously limited by the rapidity with which tolerance develops, and if it is to be used at all in the treatment of fits it is perhaps best reserved for the treatment of status.

Petit Mal

The brief "absences" associated with the so-called 3–5 c.p.s. spike and wave E.E.G. activity, which normally respond readily to treatment with the succinimides or diones, are easily confused clinically with "temporal lobe" seizures, which are more responsive to treatment with major anticonvulsants. It is important therefore to be clear about the nature of the condition being treated.

Many workers advocate the addition of a major anticonvulsant to the more specific agents used in the treatment of petit mal, since major fits often complicate the management.

Ethosuximide.—If introduced gradually, toxic effects are usually avoided. These may include nausea and vomiting, headache, ataxia and depression, even psychosis. Transient rashes and photophobia may disappear when the dosage is temporarily reduced. In high dosage, hiccup is, in my experience, the commonest side-effect.

Methsuximide may cause minor side-effects similar to those produced by ethosuximide in up to one-third of patients. Rarely there is hepatorenal damage.

Troxidone has been largely superseded in the treatment of petit mal by the less toxic and more effective ethosuximide. It is, however, a useful reserve for those patients who do not respond to ethosuximide. Gastrointestinal upsets and mood disturbances are inconvenient, but not as worrying as the possibility of blood dyscrasias, exfoliative dermatitis, and nephrosis, which seriously limit its use.

Phensuximide is less effective than either ethosuximide or troxidone, and of intermediate toxicity.

Paramethadione is similar to troxidone in its toxic effects, but less potent in the control of petit mal.

Drug Dosage in Recurrent Seizures

This is meant to be no more than a guide. Some patients will not tolerate even the minimum doses recommended. Where a range of dosage is given, it is desirable to commence at the lower dosage.

Drug	Presentation	Total Daily Dosage (mg./kg.)
*Phenobarbitone ..	Tabs. 15 mg., 30 mg., 60 mg., 100 mg. Elixir 15 mg. in 5 ml.	5–10
Methylphenobarbitone ..	Tabs. 30 mg., 60 mg., 180 mg.	10
*Phenytoin ..	Caps. Tabs. 30 mg., 50 mg., 100 mg.	5–7
*Primidone ..	Suspension: 30 mg. in 5 ml.	20–30
*Sulthiame ..	Tabs. 50 mg.	10–15
Phenacemide ..	Tabs. 500 mg.	40–80
*Pheneturide ..	Tabs. 200 mg.	15
Beclamide ..	Tabs. 500 mg.	20–40
Ethotoin ..	Tabs. 500 mg.	15–50
Methoin ..	Tabs. 100 mg.	2–10
Acetazolamide ..	Tabs. 250 mg.	20–25
*Ethosuximide ..	Caps. 250 mg.	15–50
*Methsuximide ..	Caps. 300 mg.	4–15
Troxidone ..	Tabs. 150 mg.	30
Phensuximide ..	Caps. 250 mg.	40–50
Paramethadione ..	Tabs. 300 mg.	15–25
*Carbamazepine ..	Tabs. 200 mg.	20

* Indicates those drugs most commonly used.

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