The rational use of antiepileptic drugs in children

BLAISE F.D. BOURGEOIS, MD

A RATIONAL approach to the drug management of epilepsy in newborns, infants and children requires an understanding not only of the basic general rules of antiepileptic drug therapy, but also of the major differences between children and adults. Children with epilepsy differ from adults mainly because, first, they can present certain types of seizures or forms of epilepsy which are not seen in adults; second, because their epilepsy is a dynamic process whose response to therapy can change as maturation occurs; and third, because the pharmacokinetics of antiepileptic drugs are markedly affected by age. The questions that need to be answered when dealing with a child with seizures are when and for how long to treat, what drugs to use, and how to use them.

WHEN AND HOW LONG SHOULD A CHILD BE TREATED?

When considering the use of antiepileptic drugs in a child, every effort should be made to document the diagnosis of epilepsy, i.e., of recurrent spontaneous unprovoked epileptic seizures. Failure to do so may result in unnecessary chronic side effects and costs that can be associated with a daily medication over several years. Since normal electroencephalographic (EEG) recordings by no means rule out the epileptic nature of a paroxysmal clinical event, possible clues from the history or the physical examination indicating a lesion or a disease more likely to be associated with epilepsy should be sought carefully. If such evidence is found,

Department of Neurology, Sections of Epilepsy, Clinical Neurophysiology and Pediatric Neurology, The Cleveland Clinic Foundation.

neuroimaging studies may help to confirm the presence of a progressive or residual brain pathology. One of the most useful pieces of information remains the best available description of the suspected seizure, if it was witnessed. Even in children, the spectrum of possible clinical manifestations of true epilepsy is limited and fairly well defined. Experience has also shown that in patients with clinical episodes suspected of being epileptic seizures, normal variants or nonspecific alterations of the EEG tracing are all too often interpreted as probable evidence of epilepsy. Since the spontaneous recurrence of seizures is often included in the definition of epilepsy, the question as to whether drug treatment should be initiated after a first seizure or only after a recurrence is the subject of an ongoing debate.[1] The decision should be based on an evaluation of the risk of recurrence in any given patient.

The treatment of febrile seizures, which in most cases do not meet the criteria for epilepsy since they are not spontaneous, has also been the subject of changing views. Factors that have contributed to the marked trend against chronic prophylactic drug therapy of febrile seizures have been the publication of large series on the prognosis of febrile seizures, the increased awareness of the deleterious effects of chronic therapy and the successes achieved with intermittent administration of benzodiazepines.[2]

Information regarding the required duration of prophylactic antiepileptic therapy in children has been provided by recent prospective studies. There is good agreement that, among children with epilepsy who have remained free from seizures for 2 to 4 years on antiepileptic therapy, approximately 75% will remain seizure-free if their medication is discontinued, and the great majority of recurrences will take place within the

first year.[3-6] Certain parameters were shown to have a predictive value with regard to recurrence. The risk of seizure recurrence after withdrawal of medication appears to increase with increasing age of the child at the time of the first seizure. According to one study, this risk is also higher if the EEG obtained before discontinuation shows slowing, spikes or focal abnormalities, and if this EEG shows worsening or no improvement when compared with the previous EEG.[6] A history of atypical febrile seizures at some time during the course of the epilepsy also seems to be associated with an increased risk of recurrence. One study addressed the effect of the seizure-free interval before discontinuation of therapy on the risk of recurrence.[7] This risk was 56% among children in whom drugs were discontinued after 1 year without seizures, 50% for 2 years, 25% for 3 years, and 22% if 4 seizure-free years had elapsed before drugs were discontinued. These results would suggest an optimal cut-off time of 3 years without seizures.

WHAT DRUGS SHOULD BE USED?

The choice of the appropriate antiepileptic drug in any given patient is dictated almost exclusively by the type of seizure. Therefore, the first step in the proper management of a child with seizures should be a precise seizure diagnosis. If this is not possible on the basis of the history and of a conventional EEG, intensive monitoring techniques with video and long-term EEG must be used whenever possible. Each one of the antiepileptic drugs has a certain spectrum of activity, and for each seizure type there is one or more drugs of choice (see Table 1).

Ethosuximide and valproate have been shown to be equally effective against absence seizures.[8,9] Compared with ethosuximide, valproate has the disadvantage of rare but severe side effects, and the advantage of being effective also against primarily generalized tonic-clonic seizures, which can occur in patients with absences.[10-12] Benzodiazepines such as clonazepam are also effective against absences, but are not recommended as drugs of first choice because of frequent sedative side effects and the common development of tolerance to the antiepileptic effect.

The response of generalized convulsive seizures (tonic, clonic, tonic-clonic) to therapy will depend on whether they are primarily or secondarily generalized. In a patient with an idiopathic epilepsy, tonic-clonic seizures that are primarily generalized have been shown to respond very well to valproate alone.[10-12] Convul-

TABLE 1
ANTIEPILEPTIC SPECTRUM OF COMMONLY USED ANTIEPILEPTIC DRUGS

Drug	Seizure Type
Carbamazepine Phenytoin Phenobarbital Primidone	Partial seizures Primary and secondary generalized convulsive seizures
Valproate	All seizure types, particularly primary generalized convulsive, absence and myoclonic seizures
Ethosuximide Methsuximide Trimethadione	Absences Certain myoclonic seizures
Clonazepam Clobazam	All seizure types
Nitrazepam	Myoclonic epilepsies of infancy Infantile spasms
Acetazolamide	All seizure types (as adjunct), particularly absences

sive seizures which are secondarily generalized are best treated with drugs effective against partial seizures. For the treatment of partial seizures, the same drugs are used, whether the seizures are simple partial or complex partial. The four major drugs effective against partial seizures are carbamazepine, phenytoin, phenobarbital and primidone. No study comparing these four drugs in children with partial seizures has been reported; but in a recent prospective multicenter trial in adults, the four drugs were found to be equally effective.[13] However, there were more treatment failures with phenobarbital and primidone because of side effects. Thus, in patients with partial seizures, carbamazepine and phenytoin would be the drugs of first choice, a trial with barbiturates being indicated only if the two have failed.

One form of epilepsy which is seen exclusively during infancy is the West syndrome, characterized by infantile spasms and an EEG pattern of hypsarrhythmia. There is increasing evidence that intramuscular (IM) ACTH is the treatment of choice and that it should be given as soon as the diagnosis has been established, since better results have been obtained when ACTH was begun within one month of the onset of spasms.[14,15] It appears that ACTH is particularly effective in patients with infantile spasms of idiopathic origin. Despite divergent published results, evidence suggests that ACTH is superior to prednisone and that the therapeutic effect of ACTH on infantile spasms is independent of steroid secretion.[16-18] Recently, intravenous (IV) or IM thyrotropin-releasing hormone has been shown to be also effective against infantile spasms and to have fewer undesirable side effects than

ACTH.[19] In patients whose infantile spasms are not controlled by ACTH, or if spasms recur, the antiepileptic drugs used are valproate and the benzodiazepines. Valproate was found to be equally effective[20] with or somewhat less effective[21] than ACTH, and to have fewer side effects. Among the benzodiazepines, clonazepam is most commonly used, although it was found to be of little help in a group of infants who had failed to respond to ACTH or prednisone.[16] Nitrazepam, which has been used against infantile spasms since the 1960s, has been the focus of renewed interest.[22] A less conventional but apparently successful approach to the management of infantile spasms has been the administration of high doses of vitamin B6 (pyridoxine).[23,24] Pyridoxine-dependent seizures do not necessarily have their onset during the neonatal period, but should actually be considered in any patient with seizure onset before the age of 18 months.[25,26]

In addition to the management of infantile spasms, one of the major challenges in the care of children with seizures remains the treatment of what has been variably referred to as "petit mal variant," "minor motor seizures," "myoclonic epilepsies of infancy," the "Lennox-Gastaut syndrome," and "symptomatic (or secondary) generalized epilepsy." These patients, who typically have a so-called "mixed-seizure disorder," should also be treated according to their seizure type. The atypical absences which commonly occur in these patients should be treated with valproate, ethosuximide or methsuximide. The convulsive seizures are either myoclonic, or brief tonic or in most cases nocturnal tonic episodes. They are particularly resistant to therapy and may require the addition of one of the major anticonvulsant drugs such as phenobarbital, phenytoin or carbamazepine. The association of valproate with a low dose of phenobarbital was found to be more effective than phenobarbital alone.[27] Carbamazepine, which is also often administered with valproate, has recently been suspected of causing an increase in seizures in these patients.[28,29] Benzodiazepines such as clonazepam can be effective in the early stages of this syndrome, but they have also been shown to precipitate a status of predominantly tonic seizures.[30] Other therapeutic options in this type of epilepsy include ACTH and steroids, and the ketogenic diet. A less conventional approach, which is gaining interest, has been the administration of high doses of gammaglobulins.[31] Neonatal seizures and the treatment of status epilepticus are discussed elsewhere (see contributions of Painter in Part 1 of this supplement, pages S-124–S-131, and of Cruse in Part 2, pages S-254–S-259).

HOW SHOULD ANTIEPILEPTIC DRUGS BE USED?

The goal of antiepileptic therapy is to achieve seizure control while keeping undesirable side effects at a minimum. The basic rule of giving "as much as needed, as little as possible" is evident but not always applied. More and more studies suggest that multiplying the number of antiepileptic drugs administered simultaneously is more likely to multiply the number of side effects than to markedly increase the seizure protection. These reports have led to current recommendations for monotherapy or single-drug therapy of epilepsy.[32–35] Once a drug has been chosen on the basis of seizure type and considerations related to possible side effects, this drug should be given alone. The dosage should be increased at intervals of two to seven days, depending on the drug, until either the seizures are controlled or the patient has persistent significant side effects. A drug should not be considered ineffective unless seizures persist at a dosage associated with evidence of toxicity. Also, the response may not be immediate, and an observation period of a few weeks may be necessary. This seems to be the case in particular for valproate.[12,36] If the first drug is ineffective, it should be replaced by a second drug selected according to the same criteria as the first, and administered alone. If the second drug is ineffective, either a third single drug or a combination of two drugs would be the next option, depending on the number of drugs available for a given type of seizure. Specific cases in which a combination of drugs is more likely to be justified are those with so-called myoclonic epilepsies of infancy and early childhood (e.g., Lennox-Gastaut syndrome), because they are likely to have two or more seizure types not responding to the same drug. The same is true of patients with absence seizures not controlled by valproate alone or ethosuximide alone, since there is some evidence that the combination of valproate and ethosuximide may then be superior.[37] Thus, it is conceivable for a patient with a myoclonic epilepsy of infancy to be taking three drugs simultaneously: valproate and ethosuximide against the usually more resistant atypical absences occurring in this syndrome, and a third anticonvulsant against the convulsive seizures occurring in this mixed seizure disorder.

Determining the appropriate drug dosage is usually more difficult in children than in adults, because the pharmacokinetics of many drugs in children exhibit marked interindividual variability as well as age-dependency. Because of their relatively high metabolic rate, children are more likely to be underdosed than over-

TABLE 2
UNEXPECTED ANTIEPILEPTIC DRUG LEVELS

I. The level does not seem to correlate with the dosage
Poor compliance
Altered bioavailability
Steady-state not reached
Drug interactions
Nonlinear kinetics
Different metabolic rate (genetic)
Age-dependent kinetics
Liver or kidney disease
II. The level does not seem to correlate with the clinical effect
Toxic side effects on multiple drugs
Idiosyncratic intoxication
Drug-induced seizures
Change in free drug fraction
Active metabolites

TABLE 3
MAJOR ANTIEPILEPTIC DRUG INTERACTIONS

First drug	Second drug	Effect of first drug on level of second drug
Phenytoin Carbamazepine Phenobarbital Primidone	Valproate	Decrease
Phenytoin Phenobarbital Primidone	Carbamazepine	Decrease
Valproate	Phenobarbital (also derived from primidone)	Increase
Valproate	Carbamazepine epoxide	Increase
Valproate	Ethosuximide	Increase

dosed. Because of these pharmacokinetic aspects, blood levels of antiepileptic drugs are particularly useful in children, if they are used and interpreted appropriately.[38] Therefore, the values and limitations of these levels should be briefly reviewed. It must be remembered that drug levels at times will be unexpected. The main causes for unexpected drug levels are summarized in *Table 2*.

When levels do not seem to correspond to the prescribed dosage, poor compliance is often suspected, especially when the levels are low. Although this does occur, various pharmacokinetic factors can also be responsible. The absorbed fraction or bioavailability of a drug can vary if the patient is given a different preparation of the same drug by the pharmacist. A concentration can also be low if it is determined before a steady state has been reached on a recently introduced drug. Pharmacokinetic interactions between antiepileptic drugs are particularly pronounced in children. (The most significant interactions are summarized in *Table 3*.)

As has been demonstrated for phenytoin, a nonlinear relationship between dose and steady-state concentration can also be the cause of unexpected levels after a change in dosage. Genetically determined slow metabolism has also been documented for various drugs. The age-dependency of pharmacokinetics is such that the daily dosage in mg/kg can be several times higher in children, if levels similar to those in adults are to be achieved. Since liver and kidneys are almost entirely responsible for the elimination of antiepileptic drugs, disease of these organs will of course affect the concentration.

Sometimes the blood level of an antiepileptic drug does not seem to correlate with clinical observations,

either with regard to evidence of toxicity or to a change in seizure frequency. For instance, toxic side effects can be idiosyncratic rather than dose-related. A particular form of idiosyncratic reaction can present itself as a stuporous state when valproate is prescribed with other antiepileptic drugs.[39] A series of recent reports, particularly in children, suggests that certain antiepileptic drugs can actually increase seizure frequency.[28,29,40] A change in the free fraction of a drug in the blood can alter the relationship between total drug concentration and pharmacologic effect, since it is the free concentration that is in equilibrium with the concentration in the brain. Finally, an active drug metabolite can add to the effect of a drug. This is possibly the case with carbamazepine, and it has been suspected that an increase in the concentration of the active carbamazepine epoxide can cause unexpected side effects in children.[41,42]

For every laboratory result there has to be a reference value. In the case of antiepileptic drug levels, it is the so-called optimal range or therapeutic window. One should always keep in mind that the therapeutic range is a relative concept and should never be applied blindly.[39,43] It is a statistical compromise, and there can be marked individual variations. However, the therapeutic range can be a very useful guide, as long as one adheres to the principle of treating always the patient, never the level.

SUMMARY

The general rules of antiepileptic drug therapy in children with epilepsy have been reviewed. The first

step should always consist of making every effort to document the diagnosis of epilepsy and to determine the exact type of seizure. The choice of the appropriate antiepileptic drug is dictated entirely by the seizure type. Once the drug of choice has been selected, it should be given alone. If the first drug remains ineffective against the seizures at the highest tolerated dose, a second drug should be tried alone. Drug combinations may be justified in patients with resistant disease or in patients with multiple seizure types. Because of their relatively high metabolic rate, children require high

dosages of antiepileptic drugs in relation to their body weight. Determining blood levels of antiepileptic drugs is particularly important in children, but it should be kept in mind that the therapeutic range is a relative concept and that it should not be applied blindly.

BLAISE F.D. BOURGEOIS, MD
Department of Neurology
The Cleveland Clinic Foundation
One Clinic Center
9500 Euclid Avenue
Cleveland, Ohio 44195

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