Problems in Family Practice

Seizure Disorders

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The current seizure classification recognizes two major categories, partial (focal) and generalized. Subclasses of this system are determined by clinical and electroencephalographic manifestations of the seizures.

Neonatal seizures are difficult to recognize and classify but require prompt and appropriate treatment for best results. Infantile spasms are important to recognize because of their grave prognosis and because they respond to steroid medications but not standard anticonvulsants. Febrile convulsions represent a continuing treatment controversy but have a good prognosis.

The diagnosis of epilepsy is based on clinical history. Laboratory studies help classify the type of seizure and identify the etiology. The computerized tomography (CT) scan has simplified diagnostic evaluation. The extent of the evaluation must be adjusted to meet individual requirements.

The choice of anticonvulsant is dependent on seizure type as well as the side effects and cost of the drug. Anticonvulsants have potential side effects which can be minimized by judicious dosage adjustments utilizing serum anticonvulsant levels when appropriate.

Epilepsy is the condition of recurrent seizures due to paroxysmal neuronal discharges associated with changes in behavior, mentation, and motor or sensory activity. Single seizures due to external stimuli such as fevers, toxins, or metabolic disturbances do not necessarily imply epilepsy.

Recent estimates indicate that there are more than two million persons with epilepsy in the United States, of whom only two thirds have been identified. The prevalence of epilepsy is approximately 10 cases per 1,000 population. The highest incidence of epilepsy is in the first few months of life and the lowest is in the third decade of life.[1]

Effective treatment of epileptic persons requires an accurate diagnosis as well as a precise classification of the type of seizure under investigation. Since the physician rarely witnesses a seizure, he/she must rely on a detailed history for diagnosis. More often than not, family members or other witnesses will have to be questioned.

Simple syncope, migraine, hysteria, temper tantrums (and other behavioral changes), hypoglycemia, narcolepsy, and cardiac arrhythmias are frequently misdiagnosed as epilepsy. The authors believe that underdiagnosis of epilepsy is preferable to overdiagnosis in view of the medical and social consequences of the diagnosis.

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Table 1. International Classification of Epileptic Seizures

Partial Seizures (seizures begin focally)
Elementary partial seizures
(focal motor or focal sensory seizures)
Complex partial seizures
(frequently called psychomotor seizures)
Partial seizures secondarily generalized
(eg, a focal motor seizure which becomes a generalized tonic-clonic seizure)

Generalized Seizures (symmetrical, no focal onset)
Absence spells (petit mal)
Epileptic myoclonus
Infantile spasms
Tonic or clonic seizures
Tonic-clonic seizures (grand mal)
Akinetic seizures

Unilateral Seizures

Unclassified Seizures (incomplete data)

Classification

The current International Classification of Epileptic Seizures is based on combined clinical and electroencephalographic data; it groups seizures into four major categories, two of which will be discussed in this paper: partial (focal) and generalized (Table 1). These designations refer to the origin and onset of the seizure.[2] Although partial seizures result from abnormal activity of a portion of a cerebral hemisphere, they may become generalized as they progress. Their focal classification refers *only* to their mode of onset.

Partial Seizures

Elementary Partial Seizures

Symptoms associated with these seizures may be motor or sensory. Seizures with simple motor symptoms ordinarily consist of focal clonic contractions of voluntary muscle groups. These seizures originate from the corresponding area of the motor cortex of the opposite cerebral hemisphere. Seizures involving sensory symptoms are usually characterized by tingling, numbness, or paresthesias of a portion of the body, determined by the area of the contralateral sensory cortex involved.

Complex Partial Seizures

Partial seizures manifested by complex symptoms are frequently called psychomotor seizures and often originate from the temporal lobe. Complex partial seizures may consist of brief episodes of impaired consciousness; the patient may perform repetitive automatic movements such as chewing, swallowing, lip smacking, fumbling with the fingers, and pacing. Hallucinations of smell, taste, vision, and hearing may also occur.[3]

Partial Seizures Secondarily Generalized

Some seizures remain focal, while others spread to nearby cortical areas and become generalized. The aura which is experienced prior to generalized convulsion may be a clue to the focal origin of the discharge. When a focal discharge becomes generalized rapidly, the patient may not experience or recall the focal aspects of the seizure. In such instances, the electroencephalogram (EEG) may be the only evidence of the localized origin of the spell.

Generalized Seizures

Generalized seizures are not focal in origin. Their clinical symptoms indicate bilateral symmetrical involvement of the entire cerebral cortex.

Absence Spells

Absence spells are defined as seizures during which there is a sudden alteration of consciousness which may or may not be associated with other manifestations. Clinical absence spells may be manifestations of several types of seizures. The three most common varieties of absence spells

are: (1) typical petit mal (associated with generalized three-per-second spike and wave activity); (2) atypical absence spells or petit mal variant (associated with generalized slow spike and wave activity); and (3) psychomotor seizures (associated with temporal lobe epileptiform activity). An electroencephalogram reading is often necessary for the differentiation of these types of absence spells.

Typical Petit Mal

This seizure consists of brief arrests in voluntary activity associated with momentary alteration of consciousness. The patient stares off into space; he may or may not drop objects from his hands; he rarely loses muscle tone and will remain standing if he was standing at the onset. The entire spell usually lasts less than ten seconds. Typical petit mal occurs without warning and resolution of the spells is as abrupt as onset.

Before treatment, a three-minute period of hyperventilation will result in an absence episode in the majority of patients with typical petit mal. Typical petit mal usually begins in children between four and ten years of age. Persons with typical petit mal have normal intelligence and a normal neurological examination. As many as 50 percent of patients with true petit mal may have additional kinds of seizures (most often grand mal).

Atypical Absence Spells (Petit Mal Variant)

These absence spells tend to occur between two and six years of age. They are frequently associated with a variety of seizures. The term Lennox-Gastaut syndrome refers to the triad of atypical absence seizures, generalized slow spike and wave activity on EEG examination, and mental retardation. Patients with atypical absence spells and the other associated seizures usually respond poorly to medications.

Tonic-Clonic Seizures

These generalized seizures are known as grand mal convulsions. They classically begin with a short cry and loss of consciousness. The tonic phase begins shortly thereafter and is accompanied by generalized rigidity. The upper extremities are usually semiflexed and the lower extremities extended. At the beginning of the tonic phase, the heart rate and blood pressure rise, the pupils dilate, the eyes deviate upwards, and the urinary sphincter relaxes. It is during this phase that cyanosis and/or congestion of the face is frequently observed. Following the tonic phase by 15 to 20 seconds is the clonic phase which consists of about a minute of rhythmic contractions of the skeletal muscles. A short period of apnea may precede the recovery of consciousness. After resolution of the spell, the patient may be confused, lethargic, or drowsy, and may complain of extreme fatigue, headache, or even nausea.

Generalized seizures may be manifested by tonic or clonic phenomena exclusively. These variations in seizure pattern do not alter the approach to evaluation or management of the seizures.

Psychomotor Absence Spells

Psychomotor absence spells may be confused with *generalized absence spells*. They tend to occur in an older age group, usually beginning in early adolescence or in the adult. These absence spells often last 20 to 30 seconds. The patient may have other symptoms suggesting complex partial seizures.

Age-Specific Seizures

It is useful in children to deal with seizures in relation to the specific age groups in which they occur. In this discussion, the International Classification of Epileptic Seizures will be used for the general description, and the classification of seizures by age group will follow.

Seizures affecting infants less than one month of age are designated as *neonatal seizures*. These affect approximately 0.8 percent of all newborn infants. The clinical manifestations of seizure disorders in newborns differ from those of older children: they are usually fragmentary in nature and only rarely are generalized, symmetrical, tonic-clonic seizures. Less common clinical varieties include generalized or focal tonic seizures, focal clonic seizures, and myoclonic seizures.

A seizure with fragmentary manifestations may

Table 2. Most Common Causes of Neonatal Seizures (In order of decreasing frequency)
Perinatal asphyxia
Intracranial hemorrhage
Hypoglycemia
Hypocalcemia
Intracranial infection
Developmental defects
Drug withdrawal

consist of apnea, bradycardia, hypotonia, deviation of the eyes, or slight movements of the mouth and/or limbs. When partial or focal seizures do occur, the origin changes with each episode. In neonates, a partial seizure cannot be assumed to be the result of focal pathology unless the focal nature is consistent over time by both clinical and EEG criteria.

The unusual manifestations of seizures in the newborn period are the result of an immature central nervous system. A small number of the possible causes of neonatal seizures account for the majority of these convulsive episodes (Table 2). Perinatal hypoxic-ischemic encephalopathy accounts for almost two thirds of all noenatal seizures and contributes to the likelihood of seizures associated with hypoglycemia and hypocalcemia.

For a discussion of the causes and treatment of neonatal seizures the reader is referred to a recent review by Bodensteiner.[4] In general, rapid correction of the underlying metabolic or infectious etiology should be undertaken. When no specific etiology has been identified, phenobarbital 10 mg/kg is given intravenously and may be repeated in one hour if necessary. The maintenance dose is 5 to 10 mg/kg/day. Intravenous phenytoin (10 to 15 mg/kg) may be used; oral phenytoin is not absorbed in the neonate and is ineffective.

The prognosis for infants suffering from neonatal convulsions is related to the underlying etiology of the seizure disorder and the interval between the onset of seizures and the initiation of appropriate therapy.

The term *infantile spasms* refers to a particular type of seizure which occurs in early childhood, usually between four months and two years of age with a peak incidence between six and nine months. These seizures are usually associated with a very abnormal electroencephalogram reading consisting of high voltage, disorganized spike and slow wave activity called hypsarrhythmia. Clinically, these spasms are characterized by sudden flexion of the extremities and the trunk. The spasms last longer than a myoclonic jerk and occur in clusters of several spasms. Frequently, an infant will experience an arrest in development at the time these seizures begin. The EEG pattern of hypsarrhythmia, the developmental arrest, and the generally poor prognosis of these infants indicate a severe generalized encephalopathy. Etiologies include a number of inherited metabolic diseases such as phenylketonuria, maple syrup urine disease, and Tay-Sachs disease. Other diseases which may be associated are tuberous sclerosis and Down syndrome. Acquired encephalopathies associated with these spasms include those of hypoxia-ischemia, trauma, hypoglycemia, and post-infection. The high incidence of structural abnormalities of the brain in patients with infantile spasms makes computerized tomography almost mandatory.

When an etiology can be identified, treatment should be directed toward the elimination of that problem. When no specific treatment is available, symptomatic treatment is employed. Currently, the treatment of choice is corticosteroids or ACTH. Prednisone in an initial dose of 2 mg/kg/day is continued for approximately six weeks to three months beyond the onset of clinical response. The steroid medication is then tapered.

Alternately, 10 units of ACTH may be given intramuscularly on a daily basis over a similar period of time. Serial EEG studies are helpful in determining the degree of response to the medication. If no response occurs within six weeks, the steroid medication may be considered ineffective and secondary drugs such as clonazepam or sodium valproate may be tried. The major importance of identifying infantile spasms is that they do not respond to the ordinary medications and that they have a grave prognosis. Combined data from a number of series indicate that no more than 10 to 20 percent of patients with infantile spasms survive without serious sequelae.[5]

Febrile Convulsions

Between two and five percent of all children from six months to four years of age will convulse if their body temperature rises significantly in the course of an acute illness. Only a few of these individuals will have spontaneous convulsions later in life. It is possible to identify those persons who are at the highest risk to develop epilepsy by subclassifying them into two groups: (1) those with simple febrile convulsions (no significant risk of developing epilepsy); and (2) those who have convulsions with fever (ten times the risk of the general population of developing epilepsy).

Simple febrile convulsions are: (1) associated with fever which is (a) significant, ie, 38.5 C, and (b) not due to central nervous system infection; (2) brief, usually less than 10 minutes, absolutely less than 15 minutes; (3) generalized tonic-clonic seizures, with absolutely no focal components; (4) found to occur in a child of the appropriate age (one to four years) who is otherwise normal, ie, *no previous seizures,* completely normal neurological history and examination, and family history negative for epilepsy (but frequently positive for simple febrile seizures); and (5) associated with a normal interictal electroencephalogram reading (done at least ten days after the convulsion). A single simple febrile convulsion thus defined does not warrant a complete laboratory work-up or anticonvulsant medication. The chief responsibility of the physician, in this instance, is to investigate the possibility of meningitis or other serious infection.

Convulsions which occur with fever, but do not satisfy all the criteria for simple febrile convulsions, must be considered abnormal and such patients must be regarded as having a seizure disorder which requires a more extensive evaluation and anticonvulsant medication.[6]

Etiology

With respect to etiology, epilepsy can be divided into two major categories: primary epilepsy and secondary epilepsy. Primary or idiopathic epilepsy refers to seizures which are generalized from the start when the cause is not known or suspected. A strong genetic influence is present in this type of epilepsy. Primary generalized epilepsy includes simple absence seizures (classic petit mal) and tonic-clonic seizures (grand mal). Secondary or symptomatic epilepsy is that in which the etiology is known or suspected, as with perinatal hypoxia, tumor, or trauma. Secondary epilepsy may be generalized from the onset or may be partial epilepsy with or without secondary generalization. There are genetic influences in secondary epilepsy as well; seizures associated with trauma or tumor are more common in individuals with a positive family history of epilepsy than in individuals with no family history. In general, epilepsy which begins in the age range of 4 to 25 years is most often primary. Seizures beginning under the age of six months and in older adults are more often secondary to identifiable causes (Table 3).[7]

Laboratory Evaluation

No laboratory tests are required to make a diagnosis of epilepsy. The diagnosis is best established by a carefully taken history. Laboratory studies are performed: (1) to classify the epilepsy; (2) to attempt to establish an etiology for the seizures; and (3) to confirm the diagnosis. The appropriate examinations depend on the age of the patient, the type of seizure, and the clues provided by the history and physical examination.

In the evaluation of a patient with epilepsy, the electroencephalogram reading should include a sufficient period of wakefulness to properly evaluate the background activity; sleep, as many epileptiform discharges are seen only in sleep; hyperventilation, which is an excellent provocative test for certain types of seizures and which may uncover other abnormalities as well; and photic stimulation. In certain clinical situations, sleep deprivation studies, nasopharyngeal leads,

Table 3. Etiologies of Convulsions

Strong Genetic Influence
Without associated neurologic or medical illness
(eg, petit mal, grand mal, benign febrile convulsions)
With associated neurologic or medical illness
(eg, tuberous sclerosis, degenerative diseases)

Trauma
Closed head injury (low percentage of patients develop epilepsy)
Penetrating head injuries (high percentage of patients develop epilepsy)

Tumor
(More common after 25 years of age, rare in children)

Circulatory
Stroke, including hemorrhagic, thrombotic, embolic
Arteriovenous malformation
Subarachnoid hemorrhage
Sickle cell anemia
Eclampsia

Metabolic
Anoxia
Hyponatremia
Hypoglycemia
Hypocalcemia and hypomagnesemia
Hyperosmolar syndrome
Renal failure
Hepatic failure
Porphyria

Toxic
Penicillin (high intravenous doses, especially with renal disease)
Aminophylline
Alcohol withdrawal (usually within 48 hours of withdrawal)
Withdrawal from sedative and hypnotic drugs
Strychnine and other exogenous poisons

Infectious
Encephalitis
Meningitis
Abscess (up to 50 percent of patients eventually develop epilepsy)

and prolonged EEG monitoring may be helpful. In most cases anticonvulsants should *not* be stopped to obtain an EEG reading and, with the exception of emergency circumstances, it is preferable to postpone administration of anticonvulsants until the initial EEG reading is obtained. Pentylenetetrazol (Metrazol) activation tests should not be done except in a well-equipped laboratory when surgery for focal epilepsy is contemplated. A routine EEG reading is abnormal in only one third to one half of cases of idiopathic tonic-clonic seizures. An electroencephalogram reading is, however, a good screening procedure for focal pathology or a significant metabolic encephalopathy.

A normal EEG reading does not exclude the diagnosis of epilepsy; conversely, an abnormal

reading does not necessarily confirm the diagnosis of epilepsy. Generalized epileptiform discharges may be seen in asymptomatic patients, and epileptic spike foci may exist in patients who have no clinical seizures. For example, only about 50 percent of children with occipital spike foci have clinical seizures. Most electroencephalographers no longer believe that 14 and 6 positive spikes, the psychomotor variant pattern, phantom spikes, and paroxysmal theta activity are evidence of epilepsy. Caution is indicated here. Since a test is only as good as the laboratory providing it, it is essential that the physician be certain of the quality of the EEG laboratory to which he/she refers the patient.

Investigation into the structural causes of epilepsy has been simplified by the introduction of computerized tomography (CT). Angiography and pneumoencephalography are not routine tests in the evaluation of epileptic persons. These tests should only be done to better evaluate a lesion *already discovered* on CT, or under rare clinical circumstances. The authors believe a CT scan should be obtained in all adults with epilepsy, children with neurologic abnormalities or focal epilepsy, and in infants with infantile spasms. CT scanning is not worthwhile in benign febrile convulsions, in simple absence seizures (petit mal), and in generalized tonic-clonic seizures occurring in a neurologically normal individual aged 4 to 20 years. Approximately 60 percent of patients with secondary generalized epilepsy or partial epilepsy have abnormal CT scans.[8] Arteriovenous malformations, tumors, infarcts, abscesses, subdural hematomas, atrophic lesions, and diffuse structural abnormalities are best diagnosed by CT scanning.

A routine skull x-ray is of little value in the diagnosis of epilepsy. An exception is the investigation of the source of brain abscess or meningitis.

Spinal fluid examination is not a routine procedure in the evaluation of epileptic patients. Lumbar punctures should be performed only when encephalitis or meningitis is suspected. The procedure is *contraindicated* in the presence of tumor, cerebral abscess, or other intracranial mass lesions.

A complete blood and platelet count, urinalysis, and SGOT, creatinine, calcium, and blood glucose tests are suggested as baseline screening in metabolic studies.

Depending upon clinical circumstances other tests may be desired. These may include sickle cell preparation, serum electrolytes, urine screen for amino acids and reducing substances, glucose tolerance test (to exclude reactive hypoglycemia), and cardiac monitor (to exclude cardiac arrhythmias).

Anticonvulsant Therapy

The mechanism of action of the various anticonvulsants is poorly understood and will not be discussed in this review.[9] There is no standard treatment for most seizure types. The choice of anticonvulsant depends upon the individual circumstances.[10] The following may be used as general guidelines:

1. Try to use the safest and least expensive drug first. For example, phenobarbital may be preferable to phenytoin in the young woman with tonic-clonic seizures who is planning to have children or in whom the gingival hyperplasia and hypertrichosis seen with phenytoin use would be disfiguring. Carbamazepine may be preferable in some patients who are bothered by the sedating effects of phenobarbital or phenytoin.
2. It is better to utilize a single drug in adequate doses than multiple drugs in low doses.
3. Alterations in drugs or dosages should be made one at a time so that one can determine the effect of a given change.
4. Medication should be given at convenient times of day to encourage compliance. Frequency of administration is determined in part by the half-life of the medication and in part by the absorption from the gastrointestinal tract. For example, phenobarbital seldom needs to be given more than once per day, whereas phenytoin, ethosuximide, and carbamazepine seldom require more than two daily doses.

Serum anticonvulsant levels are now available for most of the major drugs and are helpful in the following situations:

1. To determine whether the initial dose results in the desired blood level; determination must be done after the patient has reached a steady state, which requires two to three weeks for phenobarbital and five to seven days for phenytoin.
2. To determine the effect of a change in dosage on serum levels.
3. To ascertain whether or not a patient is actually taking the medications as directed.
4. To document anticonvulsants as the cause of

Table 4. Commonly Used Anticonvulsant Drugs

Drug	Adult	Daily Dose Children	Frequency of Administration	Therapeutic Serum Level	Serum Half-Life
Phenobarbital	100- 240 mg	4- 8 mg/kg	QD	10- 40 μg/ml	72-96 hr
Phenytoin	200- 400 mg	4- 8 mg/kg	QD or BID	10- 20 μg/ml	18-24 hr
Primidone	500-1,500 mg	10-20 mg/kg	TID or QID	6- 10 μg/ml*	6-12 hr
Carbamazepine	600-1,200 mg	10-20 mg/kg	BID or TID	6- 10 μg/ml	8-12 hr
Ethosuximide	750-2,000 mg	15-20 mg/kg	QD or BID	40-100 μg/ml	24-72 hr
Sodium valproate	1,000-5,000 mg	30-60 mg/kg	TID or QID	50-100 μg/ml	6- 8 hr
Clonazepam	1.5-20 mg	.01-.3 mg/kg	BID or TID	.01-.07 μg/ml	18-48 hr
Diazepam IV	5 -10 mg	0.3 mg/kg	Over 2-5 minutes, may repeat in 15-30 minutes		
Phenytoin IV	15 mg/kg	15 mg/kg	30-50 mg/minute, begin maintenance dose in 12 hours (proportionately slower for children)		
Phenobarbital IV	120-480 mg	5-8 mg/kg	Over 5-10 min, may repeat one half dose in 30-60 min		
		10 mg/kg†			

*Significant amounts of phenobarbital will accumulate
†For treatment of neonatal seizures

toxic symptoms or to determine which of multiple drugs is responsible for toxic symptoms.

5. Whenever difficulty with seizure control arises.[11]

The following discussion will focus on the major anticonvulsant drugs currently in use in the United States (Table 4). Phenobarbital was introduced in 1912 and is still the most widely prescribed anticonvulsant. The drug is effective for neonatal seizures, generalized tonic-clonic seizures including febrile seizures, and withdrawal seizures. While not as effective for partial seizures, it does have anticonvulsant activity against these as well. Phenobarbital is the drug most often recommended for children with partial or generalized tonic-clonic seizures. The drug is well absorbed by oral and intramuscular administration. Approximately 70 percent of ingested phenobarbital is metabolized by the liver and the remainder is excreted by the kidney. The biological half-life of the drug is 72 to 96 hours, and the drug can be effectively administered in a single daily dose without decreasing its anticonvulsant activity or increasing its sedative effect. Because of the half-life of phenobarbital, approximately 15 to 20 days are required to achieve a steady state. This period of time may be shortened by doubling the dose for the first two or three days the drug is taken; however, sedation often limits the usefulness of this technique.

The average dose of phenobarbital is 10 mg/kg/day for neonates, 4 to 8 mg/kg/day for older children, and 2 to 3 mg/kg/day for adults. The effective serum level is 10 to 40 μg/ml. Because of drug interaction, the dose of phenobarbital frequently needs to be lowered by 25 to 50 percent in patients receiving sodium valproate (Depakene). Phenobarbital should not be given to patients receiving primidone (Mysoline) because approximately 20 percent of primidone is metabolized to phenobarbital. Other barbiturates, mephobarbital (Mebaral) and metharbital (Gemonil), also have anticonvulsant activity. However, these drugs are more expensive than phenobarbital and are not less sedating when given in equal therapeutic dosage.

Common side effects of phenobarbital administration include sleepiness, ataxia, and hyper-

activity in children. There are reports that even at therapeutic levels, phenobarbital may lower school performance in children.[12]

Phenytoin (Dilantin) was introduced as an anticonvulsant in 1938. The drug is effective for partial seizures as well as generalized tonic-clonic seizures. Phenytoin has not been proven to be effective in the prophylaxis of febrile seizures, absence seizures, or withdrawal seizures. Phenytoin is usually well absorbed orally except in neonates, but it is poorly and erratically absorbed when given intramuscularly and should not be given by this route. Phenytoin has a biological half-life of 18 to 24 hours and should be given once or twice daily. Five to seven days are required to achieve a steady blood level after oral therapy is begun. If it is desired to obtain a therapeutic blood level more rapidly, 15 mg/kg of oral phenytoin in divided doses can be administered over a 24-hour period, followed by the usual maintenance daily dose. In an emergency, phenytoin may be given very slowly intravenously provided careful monitoring of blood pressure and cardiac rhythm is done during the infusion because of cardiotoxicity. A dose of 15 mg/kg is given at a rate of no greater than 50 mg/min (the rate should be proportionately slower for children).

The average maintenance dose of phenytoin is 4 to 8 mg/kg/day, but young children may require up to 8 to 10 mg/kg/day. This dose will result in a therapeutic blood level in only 70 percent of patients. Accordingly, a serum level should be obtained one to two weeks after therapy is begun, and appropriate adjustments made and checked by repeating the anticonvulsant levels. The therapeutic serum level is 10 to 20 μg/ml. Small changes in dosage can conveniently be made by utilizing a 30 mg capsule or the 50 mg scored tablet preparations. Use of phenytoin suspension is strongly discouraged because of the difficulty of achieving proper mixing. Since the generic phenytoin made by different companies may have different absorption characteristics, it is recommended that the physician use a single brand.

Relatively common side effects of phenytoin include gastrointestinal upset, gingival hypertrophy, hirsutism, and mild sedation. Gastrointestinal upset can usually be avoided by administration of the drug with meals. Scrupulous oral hygiene can help to minimize the gingival hypertrophy. Phenytoin affects folic acid and vitamin D metabolism adversely, but only rarely does this result in macrocytic anemia or osteomalacia. Supplemental vitamins are rarely needed and are not routinely recommended.

Less common effects include a morbilliform rash, abnormal liver function tests, adenopathy, hepatosplenomegaly, pseudolymphoma, and pseudodegenerative disease. All are indications for discontinuation of the drug.

Primidone (Mysoline) was introduced as an anticonvulsant in 1952. Primidone is available for oral use only and is effective for partial seizures as well as tonic-clonic seizures. Primidone has a biological half-life of 6 to 12 hours and is metabolized by the liver to phenylethyl mevalonic acid (PEMA) and phenobarbital. Both of these latter compounds also possess anticonvulsant activity. Phenobarbital should not be administered concurrently with primidone because the combination frequently leads to phenobarbital intoxication. Severe transient side effects of vertigo, diplogia, and sedation may occur on initiation of therapy with primidone. Because of this, the drug should be started in a low bedtime dose with small increments made every two to four days. The usual effective dose is 10 to 20 mg/kg/day given in three to four spaced dosages. The therapeutic primidone blood level is 6 to 10 μg/ml. When primidone levels are measured, phenobarbital levels should also be measured since phenobarbital will be found in significant amounts if the patient is taking adequate doses of primidone. Primidone is available in 50 and 250 mg tablets and as a suspension, but the use of the latter preparation is discouraged because of the difficulties in obtaining uniform dosages.

Carbamazepine (Tegretol) was approved as an anticonvulsant in the United States in 1974. The drug has a chemical structure similar to that of the tricyclic antidepressants. Carbamazepine is effective for tonic-clonic and partial seizures. The drug is well absorbed orally and has a biological half-life of approximately 8 to 12 hours. The usual dose is 10 to 20 mg/kg/day given in two or three spaced doses. The therapeutic serum level is 6 to 10 μg/ml. In chronic usage, carbamazepine has little or no sedative effect and is well tolerated by patients. Because on initiation of therapy, vertigo, diplopia, and sedation may occur, the drug should be started at a low bedtime dose with gradual increases every three days until full dosage is

achieved. Transient leukopenia is relatively common with carbamazepine; the drug need not be stopped unless the white cell count falls below 3,500/mm.[3] Severe leukopenia, thrombocytopenia, and even aplastic anemia have occurred with carbamazepine therapy; however, significant hematologic effects are rare and usually occur in elderly individuals within three months of beginning therapy. Complete blood counts and platelet counts should be made weekly during the first three months of therapy and monthly for the first year or two thereafter. The authors have not encountered serious hematologic toxicity with carbamazepine in clinical practice. For the patient who complains of sedation with other anticonvulsants, carbamazepine is an excellent alternative.

Ethosuximide (Zarontin) is currently considered the drug of choice in the treatment of simple absence seizures (classic petit mal) in a patient who does not have tonic-clonic seizures as well. Ethosuximide is well absorbed orally. Because of the long serum half-life of 24 to 72 hours, depending upon the age of the patient, the drug may be administered in a once or twice daily regimen. Gastrointestinal side effects are relatively common, but may be lessened by giving the medication with food or by giving smaller doses more frequently. Rare hematologic toxicity has been reported and periodic blood counts should therefore be obtained. The dose of ethosuximide is 15 to 20 mg/kg/day. The therapeutic blood level is approximately 40 to 100 μg/ml.

Trimethadione (Tridione) is effective for treatment of simple absence seizures (petit mal), but since more effective and safer drugs are available, the authors do not recommend its use.

Sodium valproate (Depakene) is the newest anticonvulsant marketed in the United States. It has a simple chemical structure totally unrelated to that of other anticonvulsants. Sodium valproate is effective for absence seizures; it may also be effective for tonic-clonic seizures as well, but is not yet approved by the Food and Drug Administration for this use. Sodium valproate is readily absorbed orally. It has a short biological half-life of six to eight hours, necessitating administration three to four times daily. Treatment is begun with a total daily dosage of 15 mg/kg/day, which is slowly increased to 30 mg/kg over one to two weeks; difficult-to-manage seizures may require even higher doses. The therapeutic blood level is 50 to 100 μg/ml. Gastrointestinal side effects are common, but may be minimized by giving the drug with food and by increasing the dose very slowly. Sedation occurs rarely and usually with concurrent administration of phenobarbital or primidone. Frequently, significant reduction of phenobarbital or primidone dosages must be made after sodium valproate is begun. Anticonvulsant serum levels are helpful in this instance. Serious liver and hematologic toxicity are rare, but periodic liver function tests and blood counts should be made during therapy with sodium valproate. Abnormal liver function tests may return to normal with a reduction in sodium valproate dosage. In many patients sodium valproate has an alerting effect which is independent of its effect on seizure control.

Diazepam (Valium) is well absorbed orally, but blood levels are too low to exert significant anticonvulsant effect. Diazepam is poorly and erratically absorbed when given intramuscularly and should not be administered by this route. In general, diazepam is the drug of choice in the treatment of tonic-clonic status epilepticus. For this purpose 5 to 10 mg should be given slowly intravenously to adults; the pediatric dosage is 0.3 mg/kg. Respiratory depression and hypotension may occur and should be watched for closely. Children who have previously received barbiturates are particularly prone to develop respiratory depression with intravenous diazepam and caution is advised. Because of a rapid redistribution phase, the anticonvulsant effect of intravenous diazepam lasts only 15 to 20 minutes, necessitating repeated intravenous administration or administration of another anticonvulsant as soon as the seizure has stopped.

Clonazepam (Clonopin) is another benzodiazepine and has the same side effects as diazepam. Clonazepam is effective by the oral route in myoclonic, akinetic, and absence seizures. Clonazepam may be helpful in treating infantile spasms or minor motor seizures. Treatment should begin with a low dose of 0.01 to 0.03 mg/kg/day with slow increments to 0.1 to 0.2 mg/kg/day in divided dosage. Sedation is common with this drug.

Prednisone or ACTH is used in the treatment of infantile spasms, although the efficacy of such treatment is still unproved. Prednisone should be used in a dose of 2 mg/kg/day.

Acetazolamide (Diamox) is occasionally of benefit as a secondary drug in treating absence, akinetic, or myoclonic and atonic seizures. Occasionally, the ketogenic diet or medium-chain triglyceride diet is helpful in treating minor motor seizures.[13]

Several other anticonvulsants are available: mephenytoin (Mesantoin), methsuximide (Celontin), phensuximide (Milontin), and phenacemide (Phenurone). As a general rule, these drugs are less effective and more toxic than the previously described anticonvulsants. If these drugs are used, they should be used by neurologists experienced in the treatment of difficult epileptic disorders.

Anticonvulsants and Pregnancy

There is a four to five percent risk of congenital anomalies in the offspring of women with epilepsy. In addition to this general risk figure, there are recognizable patterns of malformation associated with phenytoin, trimethadione, and perhaps phenobarbital. The magnitude of the risk of occurrence of one of these patterns of malformation has not been clearly established. Furthermore, there are insufficient data to establish the safe use of other anticonvulsant drugs during pregnancy.

It is recommended that if the prospective mother has been seizure free for many years it might be possible to withdraw anticonvulsants *prior to* pregnancy. In the prospective mother who requires anticonvulsants, there is at present no indication to switch from one drug to another. She can be advised of a risk of malformation of less than ten percent, which is still three times that of the normal population. Women who seek advice after the first trimester should *not* have their medication stopped because the period of risk for teratogenic effects has already passed. Of course, no woman should receive anticonvulsant medication unnecessarily.[14] If the epileptic mother breast feeds her child, the physician can assure her that although the drugs are present in the milk in essentially the same concentration as in the serum, this usually is not enough to cause any demonstrable effect on the baby.

Further Considerations in Management

Parents and teachers of epileptic children frequently ask the physician questions about limiting school activities. The authors do *not* believe that children whose epilepsy is controlled by medication should be restricted in classroom activity, physical education, or competitive sports (including football). However, swimming alone and hobbies or jobs involving serious risks should not be permitted.

Most states permit epileptic persons to drive if they are under the care of a physican and if they have been seizure free for at least one year. Only a few states require the physician to report epileptic drivers to the licensing authorities.

After an individual has been seizure free for two to four years, it may be possible to slowly withdraw medications with the patient remaining seizure free. Only 30 to 50 percent of patients will continue to be seizure free when not taking anticonvulsants, however. Many individuals prefer to take anticonvulsants indefinitely rather than run the risk of future seizures. The authors generally discuss the pros and cons of anticonvulsant withdrawal with the patient and a mutual decision is reached. Of course, anticonvulsants should never be stopped abruptly. The authors generally taper the dosage over a three to six month period, and it is best to taper one anticonvulsant at a time.

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