32 Antiepileptic Drugs

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DRUG LIST

Epilepsy (or epilepsies, since markedly different clinical entities exist) is a common neurological abnormality affecting about 1% of the human population. Epilepsy is a chronic, usually life-long disorder characterized by recurrent seizures or convulsions and usually, episodes of unconsciousness and/or amnesia. Table 32.1 illustrates the major types of epileptic seizures. Patients often exhibit more than one type. In most instances, the cause of the seizure disorder is not known (idiopathic epilepsy), although trauma during birth is suspected of being one cause.

Head trauma, meningitis, childhood fevers, brain tumors, and degenerative diseases of the cerebral circulation are conditions often associated with the appearance of recurrent seizures that may require treatment with anticonvulsant drugs. Seizures also may be a toxic manifestation of the action of central nervous system (CNS) stimulants and certain other drugs. Seizures often occur in hyperthermia (febrile seizures are very common in infants); sometimes in eclampsia, uremia, hypoglycemia, or pyridoxine deficiency; and frequently as a part of the abstinence syn-

TABLE 32.1 Major Seizure Types

Clinical Seizure Type	Key Ictal EEG Manifestations	Major Clinical Manifestations
I. Partial (focal, local) seizures A. Simple partial seizures	Local contralateral discharge	Seizures may be limited to a single limb or muscle group; may show sequential involvement of body parts (epileptic march); consciousness usually preserved; may be somatosensory (hallucinations, tingling, gustatory sensations); may have autonomic symptoms or signs such as epigastric sensations, sweating, papillary dilation
B. Complex partial seizures (psychomotor epilepsy, temporal lobe epilepsy)	Unilateral or bilateral asynchronous focus, most often in temporal region	Impairment of consciousness, may have automatisms, flashback (déjà vu, terror); autonomic activity such as pupil dilation, flushing, piloerection
C. Partial seizures evolving to secondary generalized seizures		May generalize to tonic, clonic, or tonic-clonic
II. Generalized seizures A. Absence seizures (petit mal epilepsy)	3-Hz polyspike and wave	Brief loss of consciousness with or without motor involvement; occurs in childhood with a tendency to disappear following adolescence
B. Myoclonic seizures		Sudden, brief, shocklike contractions of musculature (myoclonic jerks)
C. Clonic seizures	Fast activity (10 Hz or more; slow waves)	Repetitive muscle jerks
D. Tonic seizures	Low-voltage, fast activity	Rigid, violent muscular contraction with limbs fixed
E. Tonic-clonic seizures (grand mal epilepsy)	Fast activity (10 Hz or more) increasing in amplitude during tonic phase; interrupted by slow waves during clonic phase	Loss of consciousness; sudden sharp tonic contractions of muscles, falling to ground, followed by clonic convulsive movements; often postictal depression and incontinence
F. Atonic seizures (astatic)	Polyspikes and wave	Sudden diminution in muscle tone affecting isolated muscle groups or loss of all muscle tone; may have extremely brief loss of consciousness

Modified from the International Classification of Epileptic Seizures. Various methods of seizure classification are used by different authors.

drome of individuals physically dependent on CNS depressants.

The therapeutic goal in epilepsy treatment is complete seizure control without excessive side effects. The prognosis depends in part upon the type of seizure disorder, but overall, only about 40 to 60% of patients become totally seizure free with available drugs. These agents are chemically and pharmacologically diverse, having in common only their ability to inhibit seizure activity without impairing consciousness. The choice of drug or drugs used depends on seizure classification, since a particular drug may be more or less specific for a particular type of seizure; patients having a mixture of seizure types present particular therapeutic difficulties. It is not always clear when to treat with one drug (monotherapy) or more than one drug (polytherapy) in a particular patient. Approximately 25% of patients given a single anticonvulsive agent do not achieve successful seizure control because of an unacceptable level of side effects. Therefore, two or more drugs may be combined in an attempt to provide better seizure control.

Convulsive disorders often begin in childhood, and drug therapy must be continued for decades; therefore, any adverse reaction is especially significant. A knowledge of interactions between anticonvulsants and other drugs is necessary, since the patient usually must continue anticonvulsant medication regardless of the need for other drugs. Since it may be dangerous to withdraw anticonvulsant medication from a pregnant woman with epilepsy, the teratogenic potential of anticonvulsant drugs also is a consideration in the treatment of women of childbearing age.

The Development of Effective Drug Treatment for Convulsive Disorders

The first effective treatment of seizure disorders was the serendipitous finding in 1857 that potassium bromide could control seizures in some patients. Even though side effects were troublesome, the bromides were widely used for many years. Phenobarbital was introduced as a treatment for epilepsy in 1912 and was immediately shown to be markedly superior to bromides. While other barbiturates were synthesized and used, none were shown to be superior to phenobarbital, and the latter compound is still used. A chemically related

nonbarbiturate, phenytoin, was discovered about 20 years later and also remains a valuable drug today. Approaches being used for the identification of new anticonvulsant drugs include the search for agents that block specific cationic channels in neuronal membranes, agents that enhance the activity of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), and agents that are capable of inhibiting the activity of the excitatory neurotransmitters glutamic and aspartic acids.

Mechanism of Action

In epilepsy certain neurons and/or groups of neurons become hyperexcitable and begin firing bursts of action potentials that propagate in a synchronous manner to other brain structures (and in the case of generalized seizures, to practically all areas of the brain). These may be the result of abnormalities in neuronal membrane stability or in the connections among neurons. It is known that the epileptic bursts consist of sodium-dependent action potentials and a calcium-dependent depolarizing potential.

Recent drug development studies have centered on the capacity of known antiepileptic drugs (AEDs) to interact with ion channels, and it is now established that several agents appear to be exerting their effects primarily by inhibiting ion channels. Modulation of neuronal sodium channels decreases cellular excitability and the propagation of nerve impulses. Inhibition of sodium channels appears to be a major component of the mechanism of action of several anticonvulsant drugs.

Much interest is also centered on the role of calcium channels in neuronal activity, since the depolarization associated with burst firing is mediated by the activation of calcium channels. At therapeutically relevant concentrations, the antiabsence drug ethosuximide appears to exert its effect by inhibiting the T-type calcium channels. A portion of valproic acid's activity may also be attributable to this effect.

Disinhibition may play an important role in the generation of epileptic seizures, since a reduction of GABAergic inhibition is necessary to produce the synchronous burst discharges in groups of cells. Compounds that antagonize the activity of GABA (picrotoxinin, penicillin C, bicuculline) are CNS convulsants, while agents that facilitate GABA's inhibition have anticonvulsant activity. Several anticonvulsant drugs act to facilitate the actions of GABA.

Excitatory neurotransmitters also may be involved in the appearance of epilepsy, since the bursting activity typically seen during epileptic discharges may be due in part to the action of glutamate acting on *N*-methyl-D-aspartate (NMDA) receptor channels to produce depolarization. It is likely that a major part of the anticonvulsant activity of felbamate involves blockade of the NMDA receptor. Table 32.2 summarizes the most likely mechanism of action associated with available anticonvulsant drugs.

CLINICALLY USEFUL DRUGS

Anticonvulsant drugs may be divided into four classes, based on their most likely mechanism of action. Although it may be premature to assign a mechanism of action to some of these compounds, the proposed classes are a convenient way to group the drugs. Furthermore, the classes themselves may have rele-

TABLE 32.2 Categorization of Anticonvulsants by Their Proposed Mechanism

Class	Description	Drugs
Type I	Block SRF by enhancing sodium channel inactivation	Phenytoin Carbamazepine Oxcarbazepine Lamotrigine Felbamate[a]
Type II	Multiple actions: enhance GABAergic inhibition, reduce T-calcium currents, and possibly block SRF	Valproic acid Benzodiazepines Phenobarbital Primidone
Type III	Block T-calcium currents only	Ethosuximide Trimethadione
Type IV	Only enhances GABAergic inhibition	Vigabatrin
Noncategorized	Has no known effect on SRF, GABAergic inhibition, or T-calcium currents	Gabapentin[b]

Adapted with permission from designation of classes described by Macdonald RL and Meldrum BS. In Levy RH et al. (eds.). *Antiepileptic Drugs* (4th ed.). New York: Raven, 1995:61-77.
[a]Felbamate probably possesses other actions.
[b]The mechanisms of action of gabapentin are unknown.
SRF, sustained high-frequency repetitive firing.

vance, since compounds in a particular category are often used for the same clinical indication. For a proposed mechanism of action to be considered relevant for a given drug, the effect must occur at concentrations similar to those that are likely to be achieved therapeutically.

Sodium Channel Blocking Agents

Drugs sharing this mechanism include phenytoin (*Dilantin*), carbamazepine (*Tegretol*), oxcarbazepine (*Trileptal*), topiramate (*Topamax*), valproic acid (*Depakene*), zonisamide (*Zonegran*), and lamotrigine (*Lamictal*). All of these agents have the capacity to block sustained high-frequency repetitive firing (SRF) of action potentials. This is accomplished by reducing the amplitude of sodium-dependent action potentials through an enhancement of steady-state inactivation. The sodium channel exists in three main conformations: a resting (R) or activatable state, an open (0) or conducting state, and an inactive (I) or nonactivatable state. The anticonvulsant drugs bind preferentially to the inactive form of the channel. Because it takes time for the bound drug to dissociate from the inactive channel, there is time dependence to the block. Since the fraction of inactive channels is increased by membrane depolarization as well as by repetitive firing, the binding to the I state by antiepileptic drugs can produce voltage-, use-, and time-dependent block of sodium-dependent action potentials. This effect is similar to that of local anesthetic drugs (see Chapter 27) and is shown in Figure 32.1.

These agents are discussed together because their pharmacological properties, clinical indications for the treatment of epilepsy, and presumed mechanisms of action are similar. They differ from each other in several ways, however, and one drug cannot routinely be substituted for another. They differ primarily in their pharmacokinetic properties, their adverse reactions, and their interactions with other drugs. In addition to blocking sodium channels, some possess other therapeutically relevant mechanisms of action as well.

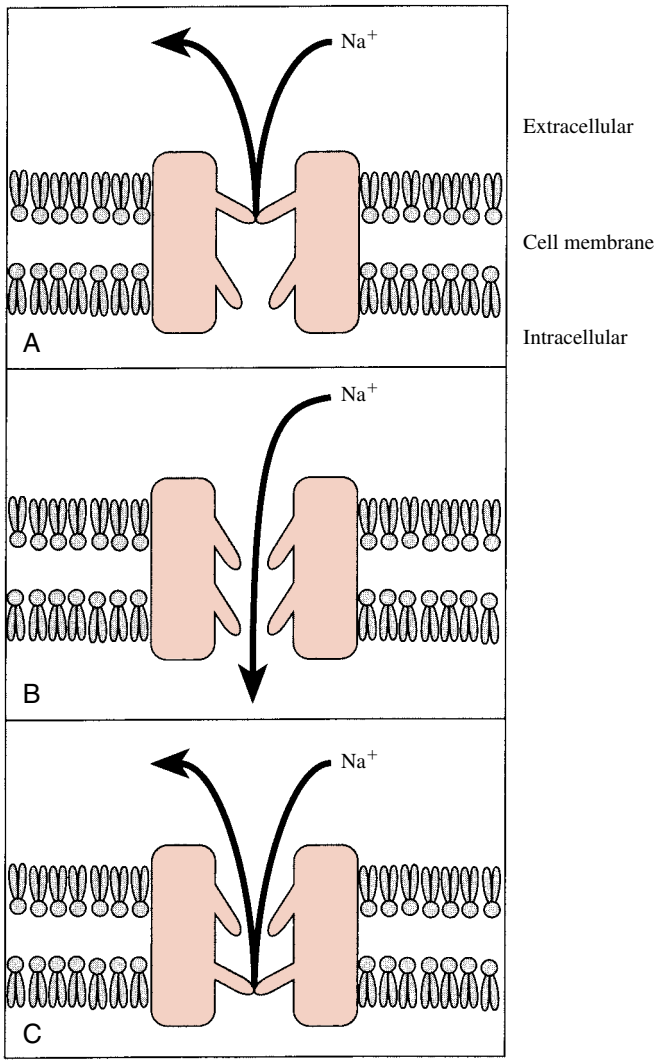

FIGURE 32.1
Mechanism of action of anticonvulsant drugs that act on sodium channels. The sodium channel can normally exist in a closed (**A**), open (**B**), or inactivated (**C**) state. **A.** An activation gate is closed and sodium ions cannot pass through the channel. **B.** The channel activation gate opens rapidly following depolarization and sodium enters freely. Soon after opening, an inactivation gate (**C**) closes, preventing further entry of sodium ions into the cell. Phenytoin and drugs with a similar mechanism of action stabilize and prolong the existence of the inactivated state, and therefore, sodium entry is impeded longer than occurs in the absence of the drug.

Phenytoin

Phenytoin is a valuable agent for the treatment of generalized tonic–clonic seizures and for the treatment of partial seizures with complex symptoms. The establishment of phenytoin (at that time known as diphenylhydantoin) in 1938 as an effective treatment for epilepsy was more than simply the introduction of another drug for treatment of seizure disorders. Until that time the only drugs that had any beneficial effects in epilepsy were the bromides and barbiturates, both classes of compounds having marked CNS depressant properties. The prevailing view among neurologists of that era was that epilepsy was the result of excessive electrical activity in the brain and it therefore seemed perfectly reasonable that CNS depressants would be effective in antagonizing the seizures. Consequently, many patients received high doses of barbiturates and spent much of their time sedated. Also, since CNS depression was considered to be the mechanism of action of AEDs, the pharmaceutical firms were evaluating only compounds with profound CNS depressant properties as potential

antiepileptic agents. It was, therefore, revolutionary when phenytoin was shown to be as effective as phenobarbital in the treatment of epilepsy without any significant CNS depressant activity. This revolutionized the search for new anticonvulsant drugs as well as immediately improving the day-to-day functioning of epileptic patients.

An understanding of absorption, binding, metabolism, and excretion is more important for phenytoin than it is for most drugs. Following oral administration, phenytoin absorption is slow but usually complete, and it occurs primarily in the duodenum. Phenytoin is highly bound (about 90%) to plasma proteins, primarily plasma albumin. Since several other substances can also bind to albumin, phenytoin administration can displace (and be displaced by) such agents as thyroxine, triiodothyronine, valproic acid, sulfafurazole, and salicylic acid.

Phenytoin is one of very few drugs that displays zero-order (or saturation) kinetics in its metabolism. At low blood levels the rate of phenytoin metabolism is proportional to the drug's blood 1evels (i.e., first-order kinetics). However, at the higher blood levels usually required to control seizures, the maximum capacity of drug-metabolizing enzymes is often exceeded (i.e., the enzyme is saturated), and further increases in the dose of phenytoin may lead to a disproportionate increase in the drug's blood concentration. Since the plasma levels continue to increase in such a situation, steady-state levels are not attained, and toxicity may ensue. Calculation of half-life ($t_{1/2}$) values for phenytoin often is meaningless, since the apparent half-life varies with the drug blood level.

Acute adverse effects seen after phenytoin administration usually result from overdosage. They are generally characterized by nystagmus, ataxia, vertigo, and diplopia (cerebellovestibular dysfunction). Higher doses lead to altered levels of consciousness and cognitive changes.

A variety of idiosyncratic reactions may be seen shortly after therapy has begun. Skin rashes, usually morbilliform in character, are most common. Exfoliative dermatitis or toxic epidermal necrolysis (Lyellís syndrome) has been observed but is infrequent. Other rashes occasionally have been reported, as have a variety of blood dyscrasias and hepatic necrosis.

The most common side effect in children receiving long-term therapy is gingival hyperplasia, or overgrowth of the gums (occurs in up to 50% of patients). Although the condition is not serious, it is a cosmetic problem and can be very embarrassing to the patient. Hirsutism also is an annoying side effect of phenytoin, particularly in young females. Thickening of subcutaneous tissue, coarsening of facial features, and enlargement of lips and nose (hydantoin facies) are often seen in patients receiving long-term phenytoin therapy. Peripheral neuropathy and chronic cerebellar degeneration have been reported, but they are rare.

There is evidence that phenytoin is teratogenic in humans, but the mechanism is not clear. However, it is known that phenytoin can produce a folate deficiency, and folate deficiency is associated with teratogenesis.

Only a few well-documented drug combinations with phenytoin may necessitate dosage adjustment. Coadministration of the following drugs can result in elevations of plasma phenytoin levels in most patients: cimetidine, chloramphenicol, disulfiram, sulthiame, and isoniazid (in slow acetylators). Phenytoin often causes a decline in plasma carbamazepine levels if these two drugs are given concomitantly.

Ethotoin and mephenytoin are congeners of phenytoin that are marketed as AEDs in the United States. They are not widely used.

Carbamazepine

Carbamazepine has become a major drug in the treatment of seizure disorders. It has high efficacy, is well tolerated by most patients, and exhibits fewer long-term side effects than other drugs.

Oral absorption of carbamazepine is quite slow and often erratic. Its half-life is reported to vary from 12 to 60 hours in humans. The development of blood level assays has markedly improved the success of therapy with this drug, since serum concentration is only partially dose related. Carbamazepine is metabolized in the liver, and there is evidence that its continued administration leads to hepatic enzyme induction. Carbamazepine-10,11-epoxide is a pharmacologically active metabolite with significant anticonvulsant effects of its own.

Carbamazepine is an effective agent for the treatment of partial seizures and generalized tonic–clonic seizures; its use is contraindicated in absence epilepsy. Carbamazepine is also useful in the treatment of trigeminal neuralgia and is an effective agent for the treatment of bipolar disorders (see Chapter 33).

Like most of the agents that block sodium channels, side effects associated with carbamazepine administration involve the central nervous system (CNS). Drowsiness is the most common side effect, followed by nausea, headache, dizziness, incoordination, vertigo, and diplopia. These effects occur particularly when the drug is first taken, but tolerance often develops over a few weeks. There appears to be little risk of cognitive impairment with carbamazepine.

Carbamazepine causes a variety of rashes and other allergic reactions including fever, hepatosplenomegaly, and lymphadenopathy, but the incidence of serious hypersensitivity reactions is rare. Systemic lupus erythematosus can occur, but discontinuation of the drug leads to eventual disappearance of the symptoms. Idiosyncratic hematological reactions to carbamazepine

may occur, but serious blood dyscrasias are rare. Carbamazepine has been shown to exacerbate or precipitate seizures in some patients, particularly those exhibiting generalized atypical absences.

While the number of side effects may be fairly large, most are not serious and can be managed. Severe adverse reactions occur less commonly than with phenytoin and similar drugs. The overall incidence of toxicity seems to be fairly low at usual therapeutic doses.

Most of the drug interactions with carbamazepine are related to its effects on microsomal drug metabolism. Carbamazepine can induce its own metabolism (autoinduction) after prolonged administration, decreasing its clearance rate, half-life, and serum concentrations. The possibility of autoinduction requires the clinician to reevaluate the patient's blood levels after a month of carbamazepine therapy. The autoinduction phenomenon is over in about a month.

Carbamazepine also can induce the enzymes that metabolize other anticonvulsant drugs, including phenytoin, primidone, phenobarbital, valproic acid, clonazepam, and ethosuximide, and metabolism of other drugs the patient may be taking. Similarly, other drugs may induce metabolism of carbamazepine; the end result is the same as for autoinduction, and the dose of carbamazepine must be readjusted. A common drug–drug interaction is between carbamazepine and the macrolide antibiotics erythromycin and troleandomycin. After a few days of antibiotic therapy, symptoms of carbamazepine toxicity develop; this is readily reversible if either the antibiotic or carbamazepine is discontinued.

Cimetidine, propoxyphene, and isoniazid also have been reported to inhibit metabolism of carbamazepine. It is essential to monitor blood levels and adjust the dose if necessary whenever additional drugs are given to patients taking carbamazepine.

Oxcarbazepine

Oxcarbazepine is chemically and pharmacologically closely related to carbamazepine, but it has much less capacity to induce drug-metabolizing enzymes. This property decreases the problems associated with drug interactions when oxcarbazepine is used in combination with other drugs. The clinical uses and adverse effect profile of oxcarbazepine appear to be similar to those of carbamazepine.

Lamotrigine

Lamotrigine has a broad spectrum of action and is effective in generalized and partial epilepsies. Its primary mechanism of action appears to be blockage of voltage-dependent sodium channels, although its effectiveness against absence seizures indicates that additional mechanisms may be active. Lamotrigine is almost completely absorbed from the gastrointestinal tract, and peak plasma levels are achieved in about 2 to 5 hours. The plasma half-life after a single dose is about 24 hours. Unlike most drugs, lamotrigine is metabolized primarily by glucuronidation. Therefore, it appears likely that lamotrigine will not induce or inhibit cytochrome P450 isozymes, in contrast to most AEDs.

Severe skin rashes appear to be the major concern with lamotrigine use. The incidence of rash is greater in children than in adults. Other adverse effects are similar to those of drugs with the same mechanism of action, such as cerebellovestibular changes leading to dizziness, diplopia, ataxia, and blurred vision. Disseminated intravascular coagulation has been reported.

Topiramate

Topiramate is most useful in patients with generalized tonic–clonic seizures and those with partial complex seizures. Topiramate causes a higher incidence of CNS-related side effects (primarily cognitive slowing and confusion) than other AEDs. It does not appear to cause a significant incidence of rashes or other hypersensitivity reactions; however, a significantly higher incidence of kidney stones has been observed in persons receiving topiramate than in a similar untreated population.

Zonisamide

Zonisamide has only recently been approved for use in the United States, although it has been available in Japan for several years. It is effective in partial complex and generalized tonic–clonic seizures and also appears to be beneficial in certain myoclonic seizures. It has a long half-life (about 60 hours) and requires about 2 weeks to achieve steady-state levels. It causes cerebellovestibular side effects similar to those of most other AEDs sharing its mechanism of action. In addition, it appears to cause an increased incidence of kidney stones.

Valproic Acid (Sodium Valproate)

Although it is marketed as both valproic acid (*Depakene*) and as sodium valproate (*Depakote*), it is the valproate ion that is absorbed from the gastrointestinal tract and is the active form.

As with several other AEDs, it is difficult to ascribe a single mechanism of action to valproic acid. This compound has broad anticonvulsant activity, both in experimental studies and in the therapeutic management of human epilepsy. Valproic acid has been shown to block voltage-dependent sodium channels at therapeutically relevant concentrations. In several experimental studies, valproate caused an increase in brain GABA; the mechanism was unclear. There is evidence that valproate

may also inhibit T-calcium channels and that this may be important in its mechanism of action in patients with absence epilepsy.

Valproic acid is well absorbed from the gastrointestinal tract and is highly bound (~90%) to plasma protein, and most of the compound is therefore retained within the vascular compartment. Valproate rapidly enters the brain from the circulation; the subsequent decline in brain concentration parallels that in plasma, indicating equilibration between brain and capillary blood. A large number of metabolites have been identified, but it is not known whether they play a role in the anticonvulsant effect of the parent drug. Valproic acid inhibits the metabolism of several drugs, including phenobarbital, primidone, carbamazepine, and phenytoin, leading to an increased blood level of these compounds. At high doses, valproic acid can inhibit its own metabolism. It can also displace phenytoin from binding sites on plasma proteins, with a resultant increase in unbound phenytoin and increased phenytoin toxicity. In this instance, the dosage of phenytoin should be adjusted as required. These examples reinforce the need to determine serum anticonvulsant levels in epileptic patients when polytherapy is employed.

Valproic acid has become a major AED against several seizure types. It is highly effective against absence seizures and myoclonic seizures. In addition, valproic acid can be used either alone or in combination with other drugs for the treatment of generalized tonic–clonic epilepsy and for partial seizures with complex symptoms.

The most serious adverse effect associated with valproic acid is fatal hepatic failure. Fatal hepatotoxicity is most likely to occur in children under age 2 years, especially in those with severe seizures who are given multiple anticonvulsant drug therapy. The hepatotoxicity is not dose related and is considered an idiosyncratic reaction; it can occur in individuals in other age groups, and therefore, valproic acid should not be administered to patients with hepatic disease or significant hepatic dysfunction or to those who are hypersensitive to it. Valproic acid administration has been linked to an increased incidence of neural tube defects in the fetus of mothers who received valproate during the first trimester of pregnancy. Patients taking valproate may develop clotting abnormalities.

Valproic acid causes hair loss in about 5% of patients, but this effect is reversible. Transient gastrointestinal effects are common, and some mild behavioral effects have been reported. Metabolic effects, including hyperglycemia, hyperglycinuria, and hyperammonemia, have been reported. An increase in body weight also has been noted. Valproic acid is not a CNS depressant, but its administration may lead to increased depression if it is used in combination with phenobarbital, primidone, benzodiazepines, or other CNS depressant agents.

Drugs That Primarily Enhance the Action of GABA

A major effort has been directed to the search for agents that can mimic, facilitate, prolong, or enhance the actions of GABA, with the expectation that such compounds will likely be beneficial in the treatment of convulsive disorders. Although there have been some disappointments, in general this appears to be a fruitful approach in the search for better and safer antiepileptic compounds.

Benzodiazepines

Several benzodiazepines are used in the management of epileptic seizures, although only a few are approved for the treatment of seizure disorders in the United States. Since the benzodiazepines share many properties, they will be discussed as a class; individual members will be mentioned for specific indications.

The primary action of the benzodiazepines as anticonvulsants is to enhance inhibition through their interaction with the $GABA_A$ receptor at the benzodiazepine binding site. However, there appears to be an additional action of benzodiazepines: blocking voltage-dependent sodium channels. This effect is not seen at usual doses but is likely a factor in their use in the treatment of status epilepticus (discussed later).

Benzodiazepines are well absorbed, and the oral route is preferred in most situations. In the treatment of status epilepticus, the preferred route is usually intravenous. Benzodiazepines are extensively metabolized by the microsomal drug-metabolizing system; frequently an active compound is broken down to another agent that is also active pharmacologically. This is the reason for the long duration of action of several benzodiazepines.

The benzodiazepines have many clinical indications and are discussed in Chapters 25, 30, 35, and 40. As AEDs, they have their major usefulness in the treatment of absence, myoclonic, and atonic seizures and in the emergency treatment of status epilepticus.

Drowsiness occurs readily and unfortunately is usually a problem at therapeutic doses. The other limiting side effect of the benzodiazepines is the rapid development of tolerance to their anticonvulsant effects.

Although all of the benzodiazepines are similar, certain ones are employed more for the treatment of seizure disorders. Clonazepam was the first benzodiazepine approved in the United States specifically for the treatment of convulsive disorders. Clonazepam is a very long acting compound with potent anticonvulsant activity. Unfortunately, sedation and tolerance tend to limit its usefulness. Drooling and hypersalivation may be troublesome in children and in infants.

Lorazepam is the benzodiazepine of choice for emergency treatment of status epilepticus, serial seizures,

and prolonged seizures and for prophylaxis of febrile seizures. The intravenous route is preferable for emergency treatment.

Clorazepate dipotassium is approved in the United States as an adjunct in the treatment of partial complex seizures. It appears to be useful, especially in patients with high seizure frequencies and psychic disturbances.

Other benzodiazepines have been used as AEDs but are not approved for this use in the United States. They include lorazepam (*Ativan*), nitrazepam (*Mogadon*), and clobazam (*Urbanil*). It is unlikely that these drugs offer any advantages over similar agents.

Tiagabine

Tiagabine (*Gabitril*) blocks the reuptake of GABA into neurons and glia, thereby resulting in higher levels of GABA in the synaptic cleft. The ability to increase GABA concentrations is presumed to be involved in the effectiveness of tiagabine in the treatment of seizure disorders. It is primarily used in the treatment of partial complex seizures. Adverse effects of tiagabine administration include dizziness, somnolence, nervousness, nausea, and confusion.

Vigabatrin

Vigabatrin (*Sabril*) is a relatively specific irreversible inhibitor of GABA-transaminase (GABA-T), the major enzyme responsible for the metabolism of GABA in the mammalian CNS. As a result of inhibition of GABA-T, there is an increase in the concentration of GABA in the brain and consequently an increase in inhibitory neurotransmission. Vigabatrin is well absorbed orally and is distributed to all body systems. The major route of elimination for vigabatrin is renal excretion of the parent compound; no metabolites have been identified in humans.

At present, the primary indication for vigabatrin is in the treatment of patients with partial seizures, but it appears to be an effective and generally well tolerated antiepileptic medication for other seizure types as well. It should not be used in patients with absence epilepsy or with myoclonic seizures. Vigabatrin is not approved as an AED in the United States, although it is approved in many other countries.

Phenobarbital and Primidone (Mysoline)

Phenobarbital and primidone are quite similar both chemically and pharmacologically, and much of the anticonvulsant activity of primidone may be ascribed to its metabolic conversion to phenobarbital. As would be expected in such a case, the clinical indications for the two compounds are very similar. There is some indication that primidone may be more effective in the treatment of partial seizures with complex symptoms, but the evidence is not compelling.

The primary mechanism of action of phenobarbital is related to its effect of facilitating GABA inhibition. By binding to an allosteric site on the GABA-benzodiazepine receptor, hence by prolonging the opening of the chloride channels, phenobarbital enhances GABA's inhibitory activity. At somewhat higher concentrations, phenobarbital can block sodium channels, similar to drugs previously discussed, and may block excitatory glutamate responses.

Phenobarbital is effective orally and is distributed widely throughout the body. It is metabolized by microsomal drug-metabolizing enzymes, but up to 50% of the parent drug is excreted unchanged by the kidneys. Primidone is metabolized to phenobarbital and phenylethylmalonamide. The latter metabolite has anticonvulsant activity, but most of the anticonvulsant efficacy of primidone is due to the phenobarbital that is produced.

The major untoward effect of phenobarbital and primidone, when used as anticonvulsants, is sedation. Another side effect of considerable importance, particularly in children, is a possible disturbance in cognitive function. Even when the serum concentration is within the therapeutic range, apparently the ability to concentrate and perform simple tasks is decreased.

At present, phenobarbital and primidone are considered as alternative drugs for the treatment of partial seizures and for generalized tonic–clonic epilepsy. They are judged to be less effective than carbamazepine and phenytoin.

Phenobarbital and primidone are classic agents capable of inducing microsomal drug-metabolizing enzymes (See Chapter 4), and this fact must be considered when using either drug singly or in combination with other agents. Consequently, many interactions can occur between phenobarbital and primidone and a variety of other drugs, and it is necessary, therefore, to monitor drug blood concentrations to ensure that therapeutic levels of all administered agents are being maintained. Phenobarbital and primidone are known to alter blood phenytoin levels. If valproic acid is administered with either phenobarbital or primidone, striking increases in phenobarbital blood levels are frequently observed.

Two other barbiturates, mephobarbital (*Mebaral*) and metharbital (*Gemonil*) continue to be marketed as anticonvulsant drugs, but they are infrequently used.

Agents That Block T-Calcium Channels

Ethosuximide

It is now generally accepted that the specific antiepileptic action of ethosuximide (and the older agent trimethadione, no longer employed) against absence epilepsy is its ability to reduce the low-threshold calcium current (LTCC) or T (transient) current. These currents underlie the 3-Hz spike wave discharges that are characteristic of absence epilepsy. A blockade of

T-calcium current is likely also to be a mechanism used by valproic acid.

The only clinical use for ethosuximide (*Zarontin*) is in the treatment of absence epilepsy. If absence attacks are the only seizure disorder present, ethosuximide alone is effective. If other types of epilepsy are present, ethosuximide can be readily combined with other agents.

For the most part, ethosuximide is a safe drug. Most of the side effects are dose related and consist of nausea, gastrointestinal irritation, drowsiness, and anorexia. A variety of blood dyscrasias have been reported, but serious blood disorders are quite rare.

Agents Whose Mechanism of Action Is Not Known

Felbamate

Felbamate (*Felbatol*) was introduced with the expectation that it would become a major drug in the treatment of epilepsy. Felbamate exhibited few manifestations of serious toxicity in early clinical trials. Soon after its introduction, however, it became apparent that its use was associated with a high incidence of aplastic anemia. Consequently, felbamate is indicated only for patients whose epilepsy is so severe that the risk of aplastic anemia is considered acceptable.

While its mechanism of action has not been clearly established, felbamate shows some activity as an inhibitor of voltage-dependent sodium channels in a manner similar to that of phenytoin and carbamazepine. Felbamate also interacts at the strychnine-insensitive glycine recognition site on the NMDA receptor–ionophore complex. Whether this effect is important to its anticonvulsant activity is not clear.

Gabapentin

Gabapentin (*Neurotonin*) was initially designed to be a rigid analogue of GABA. When it was discovered to have antiepileptic properties, it was assumed that this activity was related to a GABAergic mechanism. However, subsequent studies have failed to show any GABAergic activity of gabapentin. Although it has not yet been possible to ascribe any definite mechanism to its antiepileptic activity, there is recent evidence that it may function as an agonist at $GABA_B$ receptors in the brain.

Gabapentin is recommended as adjunctive therapy in the treatment of partial seizures in adults. When used with other drugs, it appears to be an effective AED; it is usually not effective when employed alone for patients with severe seizures.

Gabapentin is generally well tolerated, with somnolence, dizziness, and ataxia the most commonly reported adverse effects. A low incidence of potentially serious side effects and no significant allergic reactions have been reported.

Levetiracetam

Levetiracetam (*Keppra*) has recently been approved for the treatment of partial-onset seizures. It appears to be safe and effective; its exact therapeutic profile has yet to be determined. It does not appear to share any of the mechanisms of action of agents that have been discussed to this point. It does have a highly specific brain binding site, but the significance of this observation to its mechanism of action has not been elucidated.

ANTICONVULSANT DRUGS AND PREGNANCY

The treatment of epileptic pregnant women poses particularly difficult questions. There is good evidence of an increased risk of congenital malformations in infants born of women taking antiseizure medication during pregnancy, although most such women give birth to normal infants. Because most patients are taking multiple medications and congenital malformations can occur even without medication, it is difficult or impossible to demonstrate a cause and effect relationship for most agents. In some cases the evidence is clearer. Valproic acid has been known to cause spina bifida in a small percentage of cases. Phenytoin has also long been implicated in causing birth defects, and a specific fetal hydantoin syndrome has been suggested. The most common abnormality seen in children of mothers receiving antiepileptic therapy is cleft palate.

Withdrawal of medication from an epileptic pregnant woman is not without its hazards, to the patient and possibly to the fetus. It is not clear whether maternal seizures can directly affect the fetus. If it is feasible, the physician should prescribe only one drug at the lowest effective dosage to minimize teratogenic risks.

The U. S. Food and Drug Administration has developed a use-in-pregnancy rating system that attempts to provide physicians with information that they can use to evaluate the risk to the fetus compared to the benefit to the patient. This classification uses five categories: (A) controlled studies show no risk; (B) no evidence of risk to humans; (C) risk cannot be ruled out; (D) positive evidence of risk; and (X) contraindicated in pregnancy. Using this classification, all approved AEDs are in pregnancy category C except carbamazepine, which is in pregnancy category D. Neither phenytoin nor valproic acid is classified, but both have black box warnings regarding teratogenicity.

A deficiency of folate during gestation has been associated with abnormal fetal growth and development. Since most AEDs cause some degree of folate deficiency, it is considered worthwhile to administer folate

daily as a supplement during the period of organogenesis in the first trimester.

Another concern in infants of mothers with epilepsy is a serious hemorrhagic disorder that is associated with a high (25–35%) mortality. This probably results from the finding that many AEDs can act as competitive inhibitors of vitamin K–dependent clotting factors. The competitive inhibition can be overcome by the administration of oral vitamin K supplements to the mother during the last week or 10 days of pregnancy.

TREATMENT OF FEBRILE SEIZURES

Convulsions associated with fever often occur in children 3 months to 5 years of age. Epilepsy later develops in approximately 2 to 3% of children who exhibit one or more such febrile seizures. Most authorities now recommend prophylactic treatment with anticonvulsant drugs only to patients at highest risk for development of epilepsy and for those who have multiple recurrent febrile seizures. Phenobarbital is the usual drug, although diazepam is also effective. Phenytoin and carbamazepine are ineffective, and valproic acid may cause hepatotoxicity in very young patients.

TREATMENT OF STATUS EPILEPTICUS

Status epilepticus is a continuous seizure state that can prove fatal unless the convulsions are terminated. It is a leading cause of death in epileptic patients and must be considered a medical emergency. The choice of drug may not be as important as establishing and correcting the cause of the seizures, maintaining vital functions, and beginning drug treatment as soon as possible. Virtually any general CNS depressant, including general anesthetics, can be used to terminate the seizure state. The pharmacological treatment of choice at present consists of intravenous infusion of either diazepam or lorazepam (the only benzodiazepines available in the United States for parenteral administration) or fosphenytoin.

Fosphenytoin (*Cerebyx*) is a prodrug that is highly soluble in intravenous solutions without solubilizing agents and is supplied in vials for intravenous use. Fosphenytoin is converted to phenytoin following parenteral administration. It is very effective in terminating seizures and will stop most status epilepticus episodes and provide long-term control without any decreased level of consciousness. All of these drugs should be administered slowly to avoid respiratory depression and apnea.

Study Questions

1. A 10-year-old boy with generalized tonic seizures is seen by his dentist at a routine checkup. The dentist observes that the patient has an overgrowth of gum tissue. The patient was most likely receiving which of the following agents?
(A) ethosuximide
(B) clonazepam
(C) primidone
(D) phenytoin
(E) zonisamide

2. The metabolism of which AED frequently displays zero-order kinetics following moderate to high therapeutic doses?
(A) Carbamazepine
(B) Phenytoin
(C) Valproic acid
(D) Ethosuximide
(E) Zonisamide

3. Many anticonvulsant drugs, as a major part of their mechanism of action, block the sodium channel, but other effective agents do not use this mechanism. Which of the following anticonvulsants has the ability to block T-calcium currents as its primary mechanism of action?
(A) Ethosuximide
(B) Phenytoin
(C) Topiramate
(D) Carbamazepine
(E) Lamotrigine

4. A 14-year-old patient is diagnosed with absence epilepsy. Any of the following drugs could be considered a reasonable choice to prescribe EXCEPT
(A) Ethosuximide
(B) Phenobarbital
(C) Carbamazepine
(D) Valproic acid

5. Which of the following agents has the capacity to inhibit the reuptake of GABA into neurons and glia?
(A) Zonisamide
(B) Vigabatrin
(C) Tiagabine
(D) Ethosuximide
(E) Gabapentin

ANSWERS

1. D. This is a rather specific effect of phenytoin. Although the gum tissue can be cut back and in some cases overgrowth prevented with good oral

hygiene, this is a source of embarrassment to the patient and constitutes a deterrent to the use of this agent.

2. **B.** Phenytoin is one of a handful of drugs that demonstrates zero-order (or saturation) kinetics. If a patient is showing signs of toxicity to phenytoin, it is important to measure blood levels, since the likelihood that phenytoin is demonstrating zero-order kinetics is very high.
3. **A.** Ethosuximide has no effect on blocking the sodium channel at therapeutics doses; however, it is very effective in blocking the T-calcium current in the therapeutic dose range. All other choices block the sodium channel at therapeutic doses, and it is acknowledged that this is their sole (or major) mechanism of action.
4. **C.** The only drug listed that would be expected to offer no benefit to a patient with absence seizures is carbamazepine. In fact, there is clinical evidence that it may actually increase the incidence of absence seizure episodes.
5. **C.** Tiagabine is the first agent that has been shown to elevate GABA levels by inhibiting the reuptake of this neurotransmitter at neuronal and glial sites in the brain. Vigabatrin can also elevate GABA levels, but it does so by inhibiting the metabolism of GABA.

SUPPLEMENTAL READING

Adkins JC and Noble S. Tiagabine: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. Drugs 1998;55:437–460.

Bertrand S et al. The anticonvulsant, antihyperalgesic agent gabapentin is an agonist at brain gamma-aminobutyric acid type B receptors negatively coupled to voltage-dependent calcium channels. J Pharmacol Exper Therap 2001;298:15–24.

Ferrendelli JA. Concerns with antiepileptic drug initiation: Safety, tolerability, and efficacy. Epilepsia 2001;42:28–30.

Leppik IE. Issues in the treatment of epilepsy. Epilepsia 2001;42:1–6.

Treiman DM. GABAergic mechanisms in epilepsy. Epilepsia 42:8–12.

CASE Study Epilepsy and Pregnancy

A 28-year-old woman you have been treating for a seizure disorder tells you that she is 2 months pregnant and thought you should know about it. She has exhibited absence seizures in the past, but currently her episodes are generalized tonic–clonic. She usually has two or three generalized seizures per month. She indicates that she has had only one episode during the past 2 months and wonders if she should stop her medication. She is taking oxcarbazepine, valproic acid, and ethosuximide. Are any of the agents that the patient is taking clearly more teratogenic than others? Is there any significance to the apparent decreased incidence of seizures during pregnancy? How would you propose treating this patient?

ANSWER: Valproic acid has been shown to be implicated in causing birth defects. Ethosuximide has not, but there is little evidence that ethosuximide is effective, since her absence seizures terminated months ago. Oxcarbazepine has not been clearly shown to be teratogenic, but teratogenicity cannot be ruled out, since its close chemical and pharmacological relative carbamazepine has been implicated in causing teratogenicity.

A decrease in seizure frequency is frequently seen during pregnancy. This is not always the case, and the explanations are not established.

Ethosuximide should be discontinued immediately. It is probably appropriate to discontinue the valproic acid over the next week or so. At that time, the dose of oxcarbazepine should be decreased by 50% if there is no increased incidence of seizures following termination of valproic acid. Since the woman has had a relatively long duration of seizure episodes, it is probably not reasonable to discontinue all medication. She should keep a log of her seizure incidence and contact you immediately if the incidence appears to be increasing.