Patients with neurologic diseases who require surgery may present the anesthetist with special challenges related to their pharmacotherapy. It is well established that such therapy may alter these patients’ otherwise normal response to anesthesia. There are many classes of drugs utilized and this AANA Journal course addresses the pharmacokinetic, pharmacodynamic, and anesthetic implications of anticholinesterase and antiepileptic drugs.

Objectives

1. List and discuss the classification of epilepsies.
2. Discuss the classification of epilepsies and differentiate between primary and secondary epilepsy.
3. Discuss the mechanism of action and the pharmacokinetics of phenytoin, carbamazepine, and the barbiturates in their use for partial and generalized tonic-clonic seizures.
4. Identify and discuss four groups of drugs of the benzodiazepines that play an important role in the treatment of the epilepsies.
5. Identify and discuss the drugs used in the treatment of the epilepsies that stimulate an increase in liver microsomal protein content.

Acetylcholinesterase

Acetylcholinesterase is the widespread and rapid acting enzyme responsible for terminating the action of acetylcholine. It is found at the ends of all cholinergic nerves in the human body, and exerts its effects within milliseconds at neuromuscular junctions. Cholinesterase also occurs in the blood.
stream, where it rapidly hydrolyzes circulating acetylcholine. Acetylcholine, the first chemical substance to have been recognized as a neurotransmitter, is synthesized in the terminals of cholinergic nerves. Most acetylcholine is stored in these terminals prior to release into nerve junctions during transmission activity.

Acetylcholine and acetylcholinesterase interact smoothly and efficiently because of their close proximity and because their molecular structures complement each other (Figure 1). Termination of acetylcholine's action, accomplished by hydrolysis of the acetylcholine molecule, occurs when their anionic and esteratic sites are joined.

**Anticholinesterase drugs**

Anticholinesterase drugs inactivate the enzymes acetylcholinesterase and plasma cholinesterase, thereby potentiating the action of acetylcholine by allowing it to accumulate at nerve terminals. They have several applications.

Clinically, anticholinesterase drugs are prescribed primarily to treat myasthenia gravis and glaucoma (neostigmine, pyridostigmine, ambenonium), and to reverse the actions of nondepolarizing muscle relaxants in conjunction with anesthesia (edrophonium, neostigmine, pyridostigmine). Physostigmine, because it is lipid soluble and crosses the blood brain barrier, is used to treat central anticholinergic syndrome, a deficiency of acetylcholine in the brain caused by other drugs. Agriculturally, anticholinesterases are used as insecticides. Finally, anticholinesterases have been used on humans in warfare. Some of these agents and their pharmacologic characteristics appear in Table I.

Anticholinesterase drugs exert their effects by forming an intermediate compound with acetylcholinesterase that is relatively or totally inactive. The enzyme's action is thereby halted. Edropho-

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**Figure 1**

Acetylcholine molecule and cholinesterase model, showing anionic and esteratic sites

```
O
(CH3)3NCH2CH2CCH3
                                  ACETYLCHOLINE
                                 \                                        /  \\
                                 \                                      /   \\
                                 +                                    +
                                 |                                    |
                                 CHOLINESTERASE

ANIONIC ESTERATIC SITES
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**Table I**

Anticholinesterase drugs and their customary doses for myasthenia gravis (MG), glaucoma (G), and reversal of nondepolarizing muscle relaxants (A)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Names</th>
<th>MG</th>
<th>Doses G</th>
<th>A</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>neostigmine</td>
<td>prostigmine</td>
<td>15-30 mg</td>
<td>NA</td>
<td>0.043 mg/kg (IV)</td>
<td>onset=intermediate duration=60 minutes</td>
</tr>
<tr>
<td></td>
<td>(PO TID)</td>
<td>.5-1 mg</td>
<td>(IM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pyridostigmine</td>
<td>mestinon</td>
<td>60 mg</td>
<td>NA</td>
<td>0.35 mg/kg (IV)</td>
<td>onset delayed duration 90 minutes (IV)</td>
</tr>
<tr>
<td></td>
<td>(PO)</td>
<td></td>
<td></td>
<td></td>
<td>3-6 hours (PO)</td>
</tr>
<tr>
<td>edrophonium</td>
<td>tensilon</td>
<td>10 mg</td>
<td>NA</td>
<td>.5 mg/kg (IM)</td>
<td>rapid onset duration 60 minutes</td>
</tr>
<tr>
<td></td>
<td>(IM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ambenonium</td>
<td>mytelase</td>
<td>6 mg</td>
<td>NA</td>
<td>NA</td>
<td>onset 20-30 minutes duration 3-8 hours</td>
</tr>
<tr>
<td></td>
<td>(PO TID)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>echothiophate</td>
<td>phospholine iodide</td>
<td>NA</td>
<td>1-2 gtt/day</td>
<td>0.03-0.25%</td>
<td>onset 10 minutes decreased IOP after 4-8 hours, miosis may last 1-4 weeks</td>
</tr>
<tr>
<td>physostigmine</td>
<td>isopto eserine eserine SO4</td>
<td>NA</td>
<td>1-2 gtt/day</td>
<td>0.25-0.5%</td>
<td>rapid acting lasts 12-36 hours</td>
</tr>
</tbody>
</table>

**Note:**

- IM—intramuscular
- IOP—intraocular pressure
- IV—intravenous
- NA—nonapplicable
- PO—oral administration
- TID—three times a day
nium, neostigmine, physostigmine and pyridostigmine are said to reversibly inactivate acetylcholinesterase since the intermediate compounds they form are unstable. By contrast, the organophosphates form very stable intermediates that do not hydrolyze for hours, if at all. Their effects may last until new acetylcholinesterase is synthesized by the body.

Anticholinesterase drugs interact with acetylcholinesterase at one or both of two active sites, (anionic or esteratic) on the enzyme's surface. Edrophonium bonds with cholinesterase, electrostatically at the anionic site and by hydrogen bonding at the ester site, to form a complex. The complex is incapable of bonding with acetylcholine substrate. Cholinesterase action therefore terminates until the bond dissolves, at which time the enzyme is once again capable of bonding with acetylcholine (Figure 2).

Neostigmine, physostigmine and pyridostigmine bond with cholinesterase at the ester site, forming a carbamyl ester complex (Figure 2). Carbamylated cholinesterase is capable of bonding with acetylcholine, but incapable of hydrolyzing it. Acetylcholine bound to carbamylated cholinesterase remains active. For this reason, carbamylated cholinesterase, neostigmine, physostigmine and pyridostigmine are considered competitive inhibitors of cholinesterase. They compete with free cholinesterase for the receptor site on the acetylcholine molecule.

The organophosphate, echothiophate (phospholine iodide), interacts with cholinesterase at the esteratic and anionic sites. The phosphorus atom forms a very stable bond that does not degenerate. Inhibition of cholinesterase by echothiophate is, therefore, irreversible.

In addition to their effect at the neuromuscular junction, anticholinesterase drugs affect the end organs of the cholinergic nervous system. Bradycardia and hypotension occur as conduction through the atrioventricular (AV) node and peripheral vascular tone falls. Mucosal glands of the bronchi and gastrointestinal tract increase their activity causing generalized bronchorrhea and gastric fluid secretion. Other glands also hypersecrete causing lacrimation, salivation, and perspiration. Urination occurs because the detrusor muscle contracts. Ciliary muscle contraction (miosis) follows application of anticholinesterase drops to the eye. These side effects are mediated mainly through the vagus nerve. Administration of an anticholinergic agent serves to suppress these side effects.

Overdose may take place, consisting mainly of the side reactions listed above occurring in an exaggerated manner. Overdose is the basis of pesticide and warfare use of cholinesterase inhibitors. Total bowel and bladder incontinence is not unusual. Muscarinic symptoms may be accompanied by neuromuscular symptoms ranging from weakness to apnea, and central nervous system derangements of seizures, ataxia, coma, and respiratory depression. Industrial or agricultural exposure to insecticides is usually the cause of overdose, since these substances readily cross all lipid barriers including skin. Overdose should be treated aggressively with intravenous anticholinergics.

Anticholinesterases interact adversely with certain classes of drugs. Anticholinesterases, because they deplete plasma cholinesterase levels, may prolong the effects of ester local anesthetics and depolarizing muscle relaxants. Patients receiving anticholinesterases are predisposed to phase two block. Aminoglycoside antibiotics (gentamicin, kanamycin, neomycin, streptomycin), local and general anesthetics, and antiarrhythmics (procaine, quinidine) interfere with neuromuscular transmission. They may increase the dose requirement of anticholinesterase drugs.

One therapeutic side effect of anticholinesterases involves the treatment of central nervous system effects of other drugs. Certain drugs inhibit the action of acetylcholine in the brain. Opioids, benzodiazepines, anesthetics and hystamine-2 receptor antagonists are all capable of causing what is termed the "central anticholinergic syndrome." Phystostigmine (1-2 mg, IV), because it crosses the blood brain barrier, may be used to combat central anticholinergic syndrome.

**Myasthenia gravis**

Myasthenia gravis is an autoimmune disease of the neuromuscular junction characterized by a diminished number of acetylcholine receptors. Weakness and fatigability are the chief symptoms. The
myoneural junctions of the face, lips, eyes, tongue, throat, and neck (bulbar nuclei) are especially af-
fected. However, the disease may affect any muscle
group in the body. Patients usually experience ex-
acerbations and remissions. Many live for years
with the disease. Treatment consists of anticholin-
esterases, corticosteroids, and surgical removal of
the thymus gland.

Patients with myasthenia gravis may be diag-
nosed and/or treated with anticholinesterase drugs.
Edrophonium or neostigmine is given in suspected
cases. If symptoms resolve, the diagnosis is con-
firmed.

Edrophonium is also used to distinguish anti-
cholinesterase overdose from myasthenic crisis. The
presentations may be similar in that patients may
have both nicotinic and muscarinic symptoms.
Their treatments, however, are opposite. Overdose,
which generally follows environmental exposure to
pesticides, should be treated with atropine (35-70
µg/kg every 3-10 minutes). This may be followed
by pralidoxime (15 mg/kg every 20 minutes). End
points for both drug treatments are the disappear-
ance of muscarinic symptoms.

A patient in myasthenic crisis, on the other
hand, will obviously have myasthenia gravis
(though this information may not be readily avail-
able in an emergency). Such patients require rapid
anticholinesterase therapy. If historical data is not
available on which to base a clinical decision, a
small dose of edrophonium may help. In response
to 5-15 mg, the myasthenic patient will improve.

Rapid intervention, including endotracheal in-
tubation, is called for in either the case of anti-
cholinesterase overdose or myasthenic crisis. Both
conditions can cause death.

Anticholinesterase therapy for myasthenia is
aimed at alleviating symptoms. Indeed, by increas-
ing diaphragmatic tone, anticholinesterase drugs
prevent respiratory arrest. Oral neostigmine (15 mg
three times a day), pyridostigmine (0.6 gm daily) or,
in critical cases, echothiophate restores skeletal mus-
cle strength by increasing the concentration of ace-
tylcholine at the neuromuscular junction. Large
oral doses are needed, because of poor absorption
from the gastrointestinal tract. Regulating the dose
and interval of anticholinesterase therapy is indi-
vidualized and reportedly difficult, as exacerbations
and remissions are often unpredictable.

Some myasthenia patients require treatment
only when engaging in fatiguing activities, in con-
trast to others who require treatment around the
clock. Anticholinesterase treatment for myasthenia
gravis is lifelong. Patients who become refractory
to one drug are given a larger dose or stronger
medication.

Anesthesia for patients with myasthenia gravis

Myasthenics require special attention in the
perioperative period, because they have special
needs and because they respond unpredictably to
anesthesia. Any stressful factor may exacerbate
the disease. It is well known that anesthesia interferes
with muscle tone, and it has been suggested that
anesthesia and surgery change the human response
to anticholinesterase therapy. A patient who was
well controlled preoperatively may emerge uncon-
trolled.

To avoid interactions between anesthetics and
anticholinesterases, it has been suggested that anti-
cholinesterase therapy be suspended the night be-
fore surgery and resumed carefully postoperatively.
For patients with mild myasthenia, this approach
may work well, but those with severe bulbar sym-
ptoms and weakness will require continuous therapy.
In some centers, plasmapheresis is performed to rid
the plasma of antipostsynaptic antibody.

The preoperative evaluation is extremely im-
portant. Examination of the airway and respiratory
status must include a review of pulmonary function
tests, chest film and arterial blood gases, plus physi-
ological assessment. Take note of the rate, rhythm, and
effort of respirations along with the symmetry and
adequacy of chest wall excursion. Auscultate for
adventitious breath sounds, and elicit from the pa-
tient a best effort to cough and swallow. Make note
of these findings.

Be aware of coexisting conditions, such as
asthma or a smoking history, that further complicate
matters. Myasthenics often have myocardial
degeneration, so a recent ECG should be read. Con-
current endocrine disease is not unusual. These
patients may be hypo- or hyper-thyroid. Since they
receive steroids frequently, they may be diabetic as
well. These patients' nutritional status should be
reviewed given the fact that steroids can cause seri-
ous metabolic effects.

Myasthenics are very sensitive to nondepolarizing
relaxants. Avoid use of these relaxants if at all
possible. If their use is unavoidable, such as in
upper abdominal surgery, it is important to titrate
carefully any muscle relaxants, expecting to use
much less than one-half the normal dose. Atrac-
urium is perhaps the nondepolarizing relaxant of
choice because its action is terminated by Hoffman
elimination rather than metabolism.

Depolarizing relaxants often fail to produce
fasciculations, and a baseline twitch may show the
myasthenic to be partially "curarized." Succinylcho-
line is not to be used, unless absolutely necessary,
because anticholinesterase drugs inhibit plasma
cholinesterase as well as true cholinesterase. Phase
two block is very likely.
Other drugs that predispose to respiratory depression, notably narcotics, should be minimized or avoided altogether. Vapors and gas may be the anesthetics of choice for the myasthenic patient. Regional blocks are also ideal, so long as amide anesthetics only are used.

The anesthetist should use caution when extubating the trachea of the myasthenic patient. Extubation should not begin until the patient has returned to full consciousness and there is a clear demonstration of adequate ventilation and control over airway reflexes. For this reason measurement of arterial blood gases and the placement of an arterial line seem warranted. Myasthenics deserve individualized counseling to alert them to the possibility of awakening with an endotracheal tube in place. Patients who have acclimated to the disease may accept this possibility more readily than a newly diagnosed myasthenic, who can be expected to be more anxious. Careful attention to the details of patient care can help ensure the safe anesthetization of myasthenics.

**Glucoma**

In glaucoma, a common cause of blindness, elevated intraocular pressure that is most often ideopathic leads to retinal and optic nerve ischemia. The pathophysiology of the disease involves obstructed outflow of aqueous humor through the trabeculae and canal of Schlemm. Most cases of glaucoma have no known cause, though it may result from infection or trauma in the eye. Two types of glaucoma have been designated based on the shape of the eye's anterior chamber.

*Narrow angle glaucoma.* Narrow angle (angle closure) glaucoma is the less frequent but acute variety. Narrow angle crisis, a painful exacerbation, may be precipitated by mydriasis or intraocular vascular engorgement. Contraction of the sphincter muscle of the iris, which accompanies mydriasis, narrows the entrance to the canal of Schlemm. Intraocular pressure, normally 12-20 mmHg, then soars as high as 70 mmHg. Engorgement of intraocular blood vessels has the same effect, because the canal is actually a venule.

Anything that blocks aqueous drainage raises intraocular pressure in glaucoma patients. Prompt efforts to reduce intraocular pressure are crucial to avoid loss of vision.

*Wide angle glaucoma.* With wide angle glaucoma (the more common variety), intraocular pressure rises as a result of lost patency within the trabeculae themselves. Onset of wide angle glaucoma is gradual, and may come to the attention of the patient only after the disease has progressed and vision is diminished.

Drug treatment of glaucoma involves anticholinesterases, cholinergics, carbonic anhydrase inhibitors, and beta blockers. Combining agents seems to enhance their effectiveness. All of these drugs relieve intraocular pressure either by decreasing the production of aqueous humor or by promoting its drainage. Among the cholinesterase inhibitors, topical physostigmine (0.02-1.0%) is the first line drug. The longer acting and more potent organic phosphate anticholinesterases, echothiophate (0.03-0.25%) and isofluorophate (0.005-0.2%), replace physostigmine after the disease worsens.

Side effects occur as a function of the particular drug type used and the length of therapy. Organophosphates produce more side effects than physostigmine. In addition to enhancing vagal tone and inhibiting plasma cholinesterase, anticholinesterase therapy of glaucoma for more than six months causes cataracts. Other adverse reactions include: headache, brow pain, blurred vision, periorbital injection, congestive iritis, allergy and retinal detachment.

**Anesthesia for patients with glaucoma**

There are a number of considerations for administering anesthesia to patients with glaucoma who receive anticholinesterase eye drops. First, it must be born in mind that glaucoma most often is a disease of the elderly. However, it may be a result of trauma, infection or the aging process. Consequently, many patients will have coexisting diseases and other evidence of advanced age that enhance the stress of anesthesia.

Second, in order to avoid an acute rise in intraocular pressure, intraoperative miosis must be maintained with eye drops either by the surgeon if the eye is within the surgical field or the anesthetist. If beta-adrenergic eye drops are in use, anticipate a systemic beta blockade.

Third, in glaucoma, as with myasthenia, succinylcholine must be avoided because of the propensity for phase two block. In the rare case where succinylcholine is needed, as for rapid sequence intubations, the dose should be minimized (0.1 mg/kg).

Last, consider that anticholinergics dilate the pupil. Since mydriasis raises intraocular pressure, it seems best to minimize the use of anticholinergic agents. In the dose range prescribed for achieving an antiallogogue effect, anticholinergics probably do not cause mydriasis. However, following their use with anticholinesterases for reversal of nondepolarizing relaxation, mydriasis may occur. As with myasthenia gravis, given proper attention to detail, patients with glaucoma may be anesthetized.
Epilepsies

A significantly different group of disorders of the central nervous system are the epilepsies. This group of disorders has been classified according to the type of seizure clinically demonstrated by the patient. Antiepileptic drugs are used for the treatment and management of seizure activity; effective pharmacology may be a single drug or a combination of the antiepileptic drugs.

John Hughlings Jackson, the father of modern concepts of epilepsy, proposed that seizures were caused by “occasional, sudden, excessive, rapid and local discharges of gray matter,” and that a generalized convolution resulted when normal brain tissue was invaded by the seizure activity initiated in the abnormal focus. Little has changed conceptually regarding Jackson’s work except for the development of the electroencephalogram (EEG) which proved his theory. Today, the EEG is routinely utilized in the diagnostic workup of patients with suspected epilepsy. However, the EEG diagnostics are not absolutely conclusive since readings may be normal for some patients who have infrequent seizures or abnormal in some disease states that do not cause epilepsy.

Epilepsy is the second most common neurologic disorder in occurrence (stroke is the first). The prevalence of epilepsy was reported by Hauser in 1978 as being between 3 to 6 per 1,000 population. Other investigators have reported approximately 1% of the population of the United States as having epilepsy and of these, 80% are controlled with therapy. This means that 500,000 Americans have uncontrolled epilepsy.

A variety of terminology classifying epilepsy can be found in the literature. Primary, known as idiopathic epilepsy, is the category used when no cause for the seizures can be identified. Secondary, also known as symptomatic epilepsy, categorizes the disorder when it is associated with trauma, neoplasm, infection, developmental abnormalities, cerebrovascular disease, or various metabolic conditions (Table II).

Further classification, based on the clinical manifestations of the attacks and the pattern of the EEG was done in 1981 by the Commission on Classification and Terminology of the International League Against Epilepsy (Table III). Classification of patients and their seizure histories assists in diagnosis and selective pharmacotherapy. Generally, pharmacotherapy incorporates two general ways in which drugs may abolish or attenuate seizures: (1) effect on pathologically altered neurons of seizure foci to prevent or reduce their excessive discharge, and (2) effects that would reduce the spread of excitation from seizure focus and prevent detonation and disruption of function of normal aggregates of neurons. Rall and Schleifer reported that antiepileptic agents currently available all modify, at least in part, the ability of the brain to respond to various seizure-evoking stimuli.

### Table II

<table>
<thead>
<tr>
<th>Causes of recurrent convolution in different age groups</th>
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<tbody>
<tr>
<td>Age of onset, years</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Infancy, 0-2</td>
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<tr>
<td>Childhood, 2-10</td>
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<tr>
<td>Adolescence, 10-18</td>
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<tr>
<td>Early adulthood, 18-35</td>
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<td>Middle age, 35-60</td>
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<td>Late life, over 60</td>
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### Table III

<table>
<thead>
<tr>
<th>Classification of seizure types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial seizures</td>
</tr>
<tr>
<td>Simple partial seizures</td>
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<tr>
<td>Complex partial seizures</td>
</tr>
<tr>
<td>Partial seizures secondarily generalized</td>
</tr>
<tr>
<td>Generalized seizures</td>
</tr>
<tr>
<td>Generalized tonic-clonic (grand mal) seizures</td>
</tr>
<tr>
<td>Absence (petit mal) seizures</td>
</tr>
<tr>
<td>Atonic seizures</td>
</tr>
<tr>
<td>Clonic and myoclonic seizures</td>
</tr>
<tr>
<td>Infantile spasms*</td>
</tr>
</tbody>
</table>

*Infantile spasms is an epileptic syndrome rather than a specific seizure type.

### Pharmacotherapy: Partial and generalized tonic-clonic seizures

Phenytoin and its congeners (mephenytoin, ethotoin, phenacemide), carbamazepine, and barbiturates are the three major drugs used for the control of partial and generalized tonic-clonic seizures.
Phenytoin. Phenytoin, (Dilantin®) is the oldest and most effective nonsedative antiepileptic drug available. It is a diphenyl-substituted hydantoin. While it has major effects on several physiologic systems, it is unclear which are related to its antiepileptic properties. Phenytoin affects ion conduction, membrane potentials, the concentrations of amino acids, and the neurotransmitters norepinephrine, acetylcholine, and gamma amino-butyric acid (GABA). Phenytoin blocks post-tetanic potentiation (thought to be the basis for its inhibition of the development and spread of epileptiform discharges) most probably by raising membrane potentials and suppressing burst activity and repetitive firing. The major actions of the drug are to decrease excitatory neurotransmission and potentiate GABA-mediated inhibition, resulting in a stabilizing effect on all neuronal membranes.

Phenytoin is best administered orally as its absorption is nearly complete in most patients, although the time to peak may range from 3 to 12 hours. The half-life for orally administered phenytoin varies from 12 to 36 hours, with an average of 24 hours for most patients. Intramuscular injection is not recommended as its absorption is unpredictable, and some drug precipitation in the muscle has been reported. Phenytoin can be given intravenously and is generally selected for the patient with status epilepticus. It is reportedly effective and can be given in a loading dose of 13-18 mg/kg in adults at a rate of 50 mg/min. It is safest to give directly by intravenous push. It can be diluted in saline, but precipitates rapidly in the presence of glucose.

The preparation of phenytoin for intravenous use contains a diluent, propylene glycol, which has been known to produce cardio-toxicity in some patients. It is, therefore, prudent to monitor carefully vital signs in these patients, especially the elderly patient who characteristically often has other coexisting diseases. The most notable toxic signs are cardiac arrhythmias, with or without hypotension, and/or central nervous system depression. To minimize the development of toxic signs, phenytoin should be given slowly when administered intravenously.

Phenytoin is highly bound to plasma proteins; about 90% is primarily bound to albumin. In patients with hypoalbuminemia or uremia and in the neonate, there is a larger fraction that remains unbound. The metabolism of phenytoin occurs primarily by the hepatic microsomal enzymes, with the major metabolite being a parahydroxyphenyl derivative which is inactive. The metabolites are excreted primarily in the urine, as glucuronide, with less than 5% of phenytoin excreted unchanged.

Carbamazepine. Carbamazepine (Tegretol®), an antiepileptic agent, was initially utilized for treatment of trigeminal neuralgia and has been available in the United States since 1974. It is chemically related to the tricyclic antidepressants and is used in the treatment of partial seizures. It is combined with phenytoin in patients who are difficult to control.

The mechanism of action of carbamazepine is reportedly unknown. It is similar in its activity to phenytoin. The similarities, based on research studies of membrane permeability, indicate that carbamazepine diminishes sodium and, to a lesser degree, potassium conductance. The dissimilarities are that carbamazepine has no significant effect on post-tetanic potentiation. It inhibits uptake and release of norepinephrine from brain synaptosomes but does not influence GABA uptake in the brain. Researchers suggest that its action is most likely independent of the GABA-ergic system.

The complex pharmacokinetics of carbamazepine have been well established, being influenced by its limited aqueous solubility and the ability to increase its conversion to an active metabolite by hepatic oxidative enzymes. Carbamazepine absorption varies and occurs slowly and erratically following oral administration. The distribution is generally limited to highly perfused tissues, with about 70% binding to plasma proteins.

Animal studies have indicated that the metabolism of carbamazepine occurs in its entirety by conversion to 10, 11-epoxide, an active metabolite that is as active as the parent compound. The active metabolite also has anticonvulsant activity; however, its contribution to carbamazepine activity is not known. Further metabolism of the active metabolite occurs resulting in inactive compounds that are excreted in the urine, principally as glucuronides. Further inactivation of carbamazepine also occurs through conjugation and hydroxylation, with less than 9% of the drug being recovered in the urine either as the parent compound or the epoxide.

Carbamazepine is available only in oral form. Steady state blood levels in therapeutic dosages appear to have frequent fluctuations based on the drug’s absorption and enzyme-inducing properties. Hyponatremia is a late complication occurring in the elderly patient with cardiac disease on long-term therapy.

Anticonvulsant barbiturates. The barbiturates utilized in the therapy of epilepsies are limited to two specific drugs: phenobarbital and primidone. The latter is deoxybarbiturate. Both of these drugs have effective anticonvulsant properties. Some authors report, from a chemistry perspective, four derivatives of barbituric acid that are clinically useful as
antiepileptic drugs: phenobarbital, mephobarbital, metharbital, and primidone. Of this group, the first three derivatives are very similar.

**Phenobarbital.** This drug has a relatively low toxicity, is inexpensive and exerts maximal anticonvulsant action at doses below those required for hypnosis, making it capable of limiting the spread of seizure activity while elevating the seizure threshold. It has been an effective agent for generalized tonic-clonic and partial seizures and considered a primary drug for use in children.

The exact mechanism of action of phenobarbital is unknown, however, from an electrophysiological perspective it prolongs post-tetanic potentiation and enhances presynaptic inhibition. Phenobarbital is similar to phenytoin in that it decreases sodium and potassium conductance at high concentrations. It is believed to enhance chloride conductance by binding to the dihydropicrotoxinin sites on the GABA receptor. In therapeutic dosages it antagonizes glutamate excitation while enhancing GABA inhibition.

Oral absorption of phenobarbital, although complete, is slow. Peak concentrations in plasma occur several hours following a single dose. It is bound to plasma proteins, 40% to 60%, including tissues and brain. Elimination of the drug, 25%, occurs through pH-dependent renal excretion of the unchanged drug; the remainder is inactivated by hepatic microsomal enzymes. A major metabolite is a parahydroxphenoxy derivative that is inactive and excreted in the urine partly as the glucuronide conjugate. The plasma half-life is about 100 hours in adults, longer in neonates and shorter and more variable in children.

**Deoxybarbiturate: Primidone.** The chemical aspect of primidone, Mysoline, or 2-deoxyphenoarbital, is that it is considered a congener of phenoarbital in which the carbonyl oxygen of the urea moiety is replaced by two hydrogen atoms. (Figure 3). In its anticonvulsant effect it resembles phenoarbital but is less potent than phenobarbital. Following the marketing of primidone in 1950, later studies reported that it is metabolized to phenobarbital and phenylethylmalonamide (PEMA), both of which are active metabolites and effective anticonvulsants.

The utilization of primidone in the treatment of complex partial seizures has reportedly increased, as its mechanism of action has been found to be more like phenytoin and its efficacy greater than phenobarbital. Research has continued to determine the relative potencies of the parent drug and its two metabolites. Thus far, animal studies have indicated that primidone possesses independent activity, however, its clinical use is similar to that of phenobarbital.

Primidone is slowly absorbed with the time required for peak concentrations following oral administration to be about three hours. It is not highly bound to plasma proteins, is generally confined to total body water, with a volume distribution of 0.6 L/kg and approximately 70% circulates as unbound drug. Metabolism occurs by oxidation to phenobarbital. Both primidone and phenobarbital are hydroxylated at the para position of the phenyl ring and undergo subsequent conjugation and excretion. Approximately 40% of the drug is excreted unchanged in the urine.

**Drugs used in epilepsies not classified by seizure type: Benzodiazepines**

This group of drugs plays an important role in the treatment of epilepsies but are not classified according to any specific seizure group. There are four drugs in this group that are marketed and utilized in the United States: diazepam (Valium®), lorazepam (Ativan®), clonazepam (Clonopin®) and clorazepate dipotassium (Tranxene®). They are all benzodiazepines, quite similar chemically, but it is their slight structural alterations that result in the differences in their activity.

In experimental models of epilepsy, the benzodiazepines suppress the spread of seizure activity produced by epileptogenic foci in the cortex, thalamus, and limbic structures but do not abolish the abnormal discharge of the focus. Based on extensive electrophysiological and biochemical observations, researchers have linked the actions of benzodiazepines to the functions of receptor-
Enzyme induction results from repeated and/or long-term drug therapy with agents that are dependent on the hepatic microsomal enzymes for metabolism. The ability of these drugs to stimulate an increase in liver microsomal protein content results in altered drug responses and interactions. This in effect results in accelerated metabolism of several agents used in anesthesia, such as the ultra-short-acting barbiturates and benzodiazepines. Carbamazepine is known to be a potent inducer of hepatic microsomal enzyme activity. Further, patients on long-term drug management may develop tolerance and physical dependence, particularly to the barbiturates.

The epileptic patient must be carefully assessed preoperatively and induction should be planned with the awareness that these patients may have altered responses to induction agents. Further, induction agents such as etomidate should probably be avoided because they produce myoclonic movement upon induction in 10% to 60% of patients. Second injections of etomidate may precipitate new and severe myoclonic movements.

The use of enflurane should probably be avoided in the epileptic patient because it is known to produce fast frequency and high voltage activity on the EEG that often progress to spike-wave activity indistinguishable from changes that accompany a seizure. Such EEG activity may be accompanied by tonic-clonic twitching of the skeletal muscles of the face and extremities. The likelihood of enflurane-evoked seizure activity is increased when the concentration of enflurane exceeds 2 MAC or when hyperventilation of the lungs lowers the PaCO₂ below 30 mmHg.

Isoflurane, in contrast to enflurane, does not evoke seizure activity on the EEG, even when administered in the presence of deep levels of anesthesia, hypocapnia or repetitive auditory stimulation. Clinical trials and research have demonstrated that isoflurane appears of have anticonvulsant properties by suppressing seizure activity.

**ADDITIONAL READING**


Test Yourself

1. What is the goal of pharmacotherapy for the patient with epilepsy?
2. What antiepileptic drugs are known to result in enzyme induction with long-term use?
3. What are the clinical manifestations of phenytoin when administered rapidly intravenously?
4. What is the clinical importance of lipid solubility among the anticholinesterases?
5. What are the major points to recall when planning to anesthetize a myasthenic patient?

(Answers appear on page 56.)