Chapter 197: Anticonvulsants

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INTRODUCTION

Anticonvulsants, or antiepileptics, are used to treat acute seizures and prevent convulsions in patients with epilepsy. The first generation of antiepileptics was developed between 1939 and 1980 (Table 197-1). Since 1993, 15 additional agents have been introduced into clinical use, termed the "second and third generation" of antiepileptic drugs. In general, these new anticonvulsants have fewer serious adverse side effects and fewer drug interactions than the first-generation agents. The first-generation drugs have an established therapeutic range for serum levels that can guide therapy during long-term management and that correlate with acute toxicity from an overdose. Consistent therapeutic levels have not been established for the second and third-generation anticonvulsants, and serum levels are not a useful guide to therapy.
TABLE 197-1

**Anticonvulsant Drugs**

<table>
<thead>
<tr>
<th>First Generation</th>
<th>Second and Third Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Eslicarbazepe acetate</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Ezogabine or retigabine</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Felbamate</td>
</tr>
<tr>
<td>Phenytoin and fosphenytoin</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Primidone</td>
<td>Lacosamide</td>
</tr>
<tr>
<td>Valproate</td>
<td>Lamotrigine</td>
</tr>
</tbody>
</table>

**PHENYTOIN AND FOSPHENYTOIN**

Phenytoin is a primary anticonvulsant for partial and generalized tonic-clonic seizures. It is useful in the treatment of non–drug-induced status epilepticus in conjunction with rapidly acting anticonvulsants.\(^1\) Phenytoin has been used to prevent seizures due to head trauma (in the immediate post-traumatic period) and in the management of some chronic pain syndromes. Serious complications are extremely rare after intentional phenytoin overdose if supportive care is provided. Most phenytoin-related deaths have been caused by rapid IV administration or hypersensitivity reactions.

**Phenytoin** is available in oral and injectable forms. Phenytoin has poor solubility in water, so the vehicle for the parenteral formulation is 40% propylene glycol and 10% ethanol, adjusted to a pH of 12 with sodium hydroxide. The acute cardiovascular toxicity seen with IV phenytoin infusion has frequently been ascribed to the propylene glycol diluent. Other limitations with parenteral phenytoin are the irritating nature of the vehicle and a tendency to precipitate in IV solutions. **Fosphenytoin** (a disodium phosphate ester of phenytoin) is a prodrug that is converted to phenytoin by phosphatases in the body with a conversion half-
The advantage with parenteral fosphenytoin is that it is soluble in aqueous solutions, is buffered to a pH of 8.8, is nonirritating to the tissues, and can be given by IM injection.  

**PATHOPHYSIOLOGY**

### Mechanism of Action

Phenytoin exerts its anticonvulsant effect by blocking voltage-sensitive and frequency-dependent sodium channels in the neurons, suppressing repetitive neuronal activity, and preventing the spread of a seizure focus. At higher concentrations, phenytoin delays activation of outward potassium currents in nerves and prolongs the neuronal refractory period. It also may exert an anticonvulsant effect by influencing calcium channels and γ-aminobutyric acid receptors or by inhibiting adenosine reuptake.

### Pharmacokinetics

Phenytoin is a weak acid with a \( pK_a \) of 8.3. In the acid milieu of the stomach and even at physiologic pH, more of the drug is nonionized, and its aqueous solubility is limited. Absorption after oral ingestion is slow, variable, and often incomplete, especially after an overdose. Different phenytoin preparations can possess major differences in bioavailability. Consequently, it may be necessary to obtain serial measurements of serum level in suspected overdose to determine peak levels. Peak levels typically occur between 3 and 12 hours after a single therapeutic oral dose.

After absorption, phenytoin is distributed throughout the body, with a volume of distribution of 0.6 to 0.8 L/kg. Brain tissue concentrations equal those in plasma within about 10 minutes of IV infusion and are correlated with therapeutic effects, whereas cerebrospinal fluid and myocardium equilibrate within 30 to 60 minutes.

### Protein Binding

Phenytoin is extensively (about 90%) bound to plasma proteins, especially albumin. The free, unbound form is the biologically active moiety responsible for the drug’s clinical effect and toxicity. The unbound fraction of the drug is greater in neonates, the elderly, pregnant women, renal failure, hypoalbuminemia (cirrhosis, nephrosis, malnutrition, burns, trauma, or cystic fibrosis), and hyperbilirubinemia. Drugs that displace phenytoin from binding sites (salicylate, valproate, phenylbutazone, tolbutamide, and sulfisoxazole) also result in an increased unbound fraction.

Patients with decreased protein binding have higher levels of free phenytoin and experience a greater biologic effect despite lower levels of total phenytoin. Free phenytoin concentrations are more useful in predicting toxicity. **Corrected serum phenytoin levels** (the concentration that would be present if a patient’s serum albumin level were normal) can be calculated as follows: corrected phenytoin concentration = (measured phenytoin concentration × 4.4)/(albumin concentration), with phenytoin concentration measured in micrograms/mL and the albumin concentration measured in grams/dL.
Metabolism

After absorption and distribution, only 4% to 5% of phenytoin is excreted unchanged in the urine. The remainder is metabolized by hepatic microsomal enzymes, primarily hydroxylated through a series of inactive compounds. The metabolism of phenytoin is capacity limited (dose dependent). At plasma concentrations of <10 micrograms/mL, elimination is first-order kinetics (a fixed percentage of drug metabolized per unit of time). At higher concentrations, including those in the therapeutic range of 10 to 20 micrograms/mL, the metabolic pathways may become saturated, and the elimination may change to zero-order kinetics (a fixed amount metabolized per unit of time). With zero-order kinetics, small increases in maintenance doses may saturate the enzyme systems, markedly prolonging the half-life of phenytoin, and result in a disproportionate increase in the plasma level. Thus incremental dose increases should be limited to 30 to 50 milligrams at a time, and levels should be carefully monitored when it is necessary to raise phenytoin doses above 300 milligrams (or above 5 milligrams/kg) per day.

Concomitant use of drugs that inhibit or enhance hepatic microsomal activity may result in an increase or decrease of phenytoin level, respectively. Phenytoin also affects the metabolism of various other agents (Table 197-2).
TABLE 197-2

Phenytoin Drug Interactions (Partial List)

<table>
<thead>
<tr>
<th>Increases Serum Levels Of</th>
<th>Increases Toxicity Of</th>
<th>Decreases Serum Levels Of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Carbamazepine</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>Oral Anticoagulants</td>
<td>Disopyramide</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td>Doxycycline</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
<td>Ethanol (chronic use)</td>
</tr>
<tr>
<td>Primidone</td>
<td></td>
<td>Furosemide</td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Phenytoin increases</td>
<td></td>
<td>Levodopa</td>
</tr>
<tr>
<td>toxicity of</td>
<td></td>
<td>Methadone</td>
</tr>
<tr>
<td></td>
<td>Phenytoin levels</td>
<td>Mexiletine</td>
</tr>
<tr>
<td></td>
<td>are increased by</td>
<td>Quinidine</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Theophylline</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>Valproate</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disulfiram</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral anticoagulants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenylbutazone*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salicylate (high dose)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trimethoprim</td>
<td></td>
</tr>
</tbody>
</table>

Phenytoin levels are decreased by:
- Antineoplastic drugs
- Calcium
- Ethanol
- Diazepam
- Diazoxide
- Folic acid
- Phenobarbital
- Rifampin
- Sucralfate
- Sulfonamides*
- Theophylline
- Tolbutamide*
- Valproate*

*These drugs displace phenytoin from its protein-binding sites, thus increasing the free phenytoin fraction, although the total phenytoin level may decrease.

**Propylene Glycol and Ethanol Diluents**

Propylene glycol is a potent myocardial depressant and vasodilator and also enhances vagal tone. This chemical can cause coma, seizures, circulatory collapse, ventricular dysrhythmias, atrioventricular node
depression, and hypotension in experimental animals. Other toxic effects from propylene glycol include hyperosmolality, hemolysis, and lactic acidosis. The ethanol diluent fraction of parenteral phenytoin may precipitate a reaction in patients taking disulfiram.

CLINICAL FEATURES

Central Nervous System Toxicity

As toxic phenytoin levels are reached, inhibitory cortical and excitatory cerebellar and vestibular effects begin to occur. The initial sign of toxicity is usually nystagmus, which is seen first on forced lateral gaze and later becomes spontaneous (Table 197-3). Vertical, bidirectional, or alternating nystagmus may occur with severe intoxication. A decreased level of consciousness is common, with initial sedation, lethargy, ataxic gait, and dysarthria. This may progress to confusion, coma, and even apnea in a large overdose. Nystagmus may disappear as the level of consciousness decreases, and complete ophthalmoplegia and loss of corneal reflexes may occur. Therefore, absence of nystagmus does not exclude severe phenytoin toxicity. Nystagmus returns as serum drug levels decrease and coma lightens.
TABLE 197-3

Clinical Features of Phenytoin Toxicity

<table>
<thead>
<tr>
<th>System</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Dizziness, tremor (intention), visual disturbance, horizontal and vertical nystagmus, diplopia, miosis or mydriasis, ophthalmoplegia, abnormal gait (bradykinesia, truncal ataxia), choreoathetoid movements, irritability, agitation, confusion, hallucinations, fatigue, coma, encephalopathy, dysarthria, meningeal irritation with pleocytosis, seizures (rare)</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>Peripheral neuropathy, urinary incontinence</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Eosinophilia, rash, pseudolymphoma (diffuse lymphadenopathy), systemic lup erythematosus, pancytopenia, hepatitis, pneumonitis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, hepatotoxicity</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Hirsutism, acne, rashes (including Stevens-Johnson syndrome)</td>
</tr>
<tr>
<td>Other organs</td>
<td>Fetal hydantoin syndrome, gingival hyperplasia, coarsening of facial features, hemorrhagic disease of the newborn, hyperglycemia, hypocalcemia</td>
</tr>
<tr>
<td>Parenteral toxicity</td>
<td>May cause hypotension, bradycardia, conduction disturbances, myocardial depression, ventricular fibrillation, asystole, and tissue necrosis from infiltration</td>
</tr>
</tbody>
</table>

Paradoxically, very high levels of phenytoin may be associated with seizures, although this is a rare occurrence, and such phenytoin-induced seizures are usually brief and generalized and almost always are preceded by other signs of toxicity, especially in acute overdose. 7

Cerebellar stimulation and alterations in dopaminergic and serotonergic activities may cause acute dystonias and movement disorders, such as opisthotonos and choreoathetosis. Hyperactive deep tendon reflexes, clonus, and extensor toe responses also may be elicited. Chronic neurologic toxicity includes peripheral neuropathy and cerebellar degeneration with ataxia.

**Cardiovascular Toxicity**

Cardiovascular complications have been almost entirely limited to cases of IV administration, in large part due to the constituents of the parenteral vehicle, or in rare cases of chronic oral toxicity. 8 Cardiac toxicity
after oral phenytoin overdose in an otherwise healthy patient has not been reported and, if observed, is due to other causes (e.g., hypoxia and other drugs).  

Reported cardiovascular complications include hypotension with decreased peripheral vascular resistance, bradycardia, conduction delays progressing to complete AV nodal block, ventricular tachycardia, primary ventricular fibrillation, and asystole. ECG changes include increased PR interval, widened QRS interval, and altered ST segments and T waves. Cardiovascular toxicity is more common in the elderly, those with underlying cardiac disease, and the critically ill. Guidelines for parenteral phenytoin administration stress a slow rate of infusion and constant monitoring (Table 197-4).

**TABLE 197-4**

**Guidelines for Phenytoin or Fosphenytoin Loading**

|IV| Loading dose is 18 milligrams/kg as phenytoin or fosphenytoin PE. †  
Mix total dose in 150–200 mL of normal saline.  
Keep phenytoin concentration <6 milligrams/mL or fosphenytoin PE concentration <25 milligrams/mL.  
Administer phenytoin through Millipore filter using an infusion pump.  
Rate of administration should not exceed 25–50 milligrams/min of phenytoin or 150 milligrams/min of fosphenytoin PE.  
Use a slower rate of infusion in patients with cardiovascular disease.  
Monitor the blood pressure and cardiac rhythm continually during the infusion.  
In the event of complications, immediately stop the infusion and administer isotonic crystalloid and other treatment as indicated. |

|IM| Administer 15 milligrams/kg fosphenytoin PE preparation in one or multiple IM sites. |

|PO†| Loading dose is 20 milligrams/kg.  
Phenytoin tablets or suspension may be used.  
Patient must be conscious with an intact gag reflex and not actively seizing or vomiting.  
Administer the total amount in one dose. |

**Abbreviation:** PE = phenytoin equivalents.

†For simplicity, the pharmaceutical concentration and dose of fosphenytoin is expressed in PE, with 150 milligrams fosphenytoin = 100 milligrams PE.

†Unlike with IV loading, not all patients will reach a therapeutic level with oral loading.
Even though fosphenytoin does not contain the propylene glycol diluent, cardiovascular toxicity can occur with IV administration. Hypotension is seen in about 8%, and rare cases of bradycardia, AV nodal block, and asystole have been observed.\(^2,10,11\)

**Vascular and Soft Tissue Toxicity**

IM injection of *phenytoin* may result in localized crystallization of the drug with hematoma, sterile abscess, and myonecrosis at the injection site. IV extravasation may produce skin and soft tissue necrosis, compartment syndrome, and limb gangrene. Delayed bluish discoloration of the affected extremity ("purple glove syndrome") followed by erythema, edema, vesicles, bullae, and local tissue ischemia has been described.\(^12\)

**Hypersensitivity Reactions**

Hypersensitivity reactions usually occur within 1 to 6 weeks of beginning phenytoin therapy and can present as a febrile illness with skin changes (erythema multiforme, toxic epidermal necrolysis or Stevens-Johnson syndrome) and internal organ involvement (hepatitis, rhabdomyolysis, acute interstitial pneumonitis, renal failure, lymphadenopathy, leukopenia and/or disseminated intravascular coagulation). **Patients with a history of previous hypersensitivity reactions should not receive phenytoin, and because of similar reactions to phenobarbital, lamotrigine, felbamate, and carbamazepine, these anticonvulsants should also be avoided.**

**Miscellaneous Effects**

Gingival hyperplasia is relatively common and is associated with poor dental hygiene (gingivitis and dental plaques). Because of the risk of fetal hydantoin syndrome, oral phenytoin therapy should never be initiated in a pregnant patient without consultation with and close follow-up by a neurologist and obstetrician.

**DIAGNOSIS**

The therapeutic phenytoin serum level is 10 to 20 micrograms/mL (40 to 80 micromoles/L), which generally corresponds to a free phenytoin level of 1 to 2 micrograms/mL.\(^13\) Although 50% of patients achieve reduction in seizure frequency below these levels, some patients require levels as high as 20 micrograms/mL for adequate control. The ratio of toxic dose to therapeutic dose for phenytoin is rather low, and there is wide individual variability in the levels required to cause adverse effects. In general, toxicity is correlated with increasing plasma levels (Table 197-5).
### Table 197-5

**Correlation of Plasma Phenytoin Level and Toxic Effects**

<table>
<thead>
<tr>
<th>Total Plasma Level (micrograms/mL)</th>
<th>Toxic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>Usually none</td>
</tr>
<tr>
<td>10–20</td>
<td>Occasional mild nystagmus</td>
</tr>
<tr>
<td>20–30</td>
<td>Nystagmus</td>
</tr>
<tr>
<td>30–40</td>
<td>Ataxia, slurred speech, nausea and vomiting</td>
</tr>
<tr>
<td>40–50</td>
<td>Lethargy, confusion</td>
</tr>
<tr>
<td>&gt;50</td>
<td>Coma, seizures</td>
</tr>
</tbody>
</table>

### TREATMENT

The initial treatment of severe oral phenytoin overdose is similar to that for ingestion of other drugs. Correct acidosis (respiratory or metabolic) to decrease the active free phenytoin fraction. Multidose activated charcoal may decrease drug half-life but does not decrease time to recovery and does not change outcome in overdose patients. Seizures may be treated with IV benzodiazepines or phenobarbital, with the caution that seizures are uncommon in phenytoin overdose. **For patients with severe and persistent toxicity, hemodialysis and hemoperfusion can produce substantial improvement in neurologic toxicity.**

Cardiac monitoring after isolated oral ingestion is unnecessary. Atropine and temporary cardiac pacing may be used for symptomatic bradyarrhythmias associated with IV phenytoin. Hypotension that occurs during IV administration of phenytoin or fosphenytoin usually responds to discontinuation of the infusion and administration of isotonic crystalloid.

### DISPOSITION AND FOLLOW-UP

Phenytoin has a long and erratic absorption phase after oral overdose, so the decision to discharge or medically clear a patient for psychiatric evaluation cannot be based on one serum level. After acute ingestions, serum level should be measured every few hours. Patients with serious complications after an oral ingestion (seizures, coma, altered mental status, or significant ataxia) should be admitted for further evaluation and treatment. Those with mild symptoms should be observed in the ED and discharged once
their levels of phenytoin are declining and they are clinically well. Mental health or psychiatric evaluation should be obtained, as indicated, in cases of intentional overdose.

Patients with symptomatic chronic intoxication should be admitted for observation unless signs are minimal, adequate care can be obtained at home, drug levels are decreasing, and 6 to 8 hours have elapsed since the patient's last therapeutic dose. Phenytoin therapy should be stopped in all cases, and if toxicity continues to resolve, serum level may be reassessed in 2 to 3 days to guide resumption of therapy. Surgical consultation should be obtained for patients with significant extravasation of IV phenytoin or with other signs of local vascular or tissue toxicity after infusion.

CARBAMAZEPINE

Carbamazepine is a primary anticonvulsant used in the treatment of partial and tonic-clonic seizures. Other uses include trigeminal neuralgia, chronic pain disorders, manic disorder, and bipolar disorder.

PATHOPHYSIOLOGY

Carbamazepine inhibits sodium channels and interferes with muscarinic acetylcholine receptors, nicotinic acetylcholine receptors, \textit{N}-methyl-\textit{d}-aspartate receptors, and central nervous system adenosine receptors. Carbamazepine may relieve neuropathic pain through blockade of synaptic transmission in the trigeminal nucleus. Carbamazepine also possesses anticholinergic, antiarrhythmic, antidepressant, sedative, and neuromuscular-blocking properties. It has central antidiuretic effects, which may lead to the syndrome of inappropriate antidiuretic hormone secretion. Carbamazepine is a potent cytochrome P-450 enzyme inducer and enhances its own metabolism over time.

Carbamazepine is an iminostilbene derivative that is chemically and structurally similar to imipramine. Gastrointestinal absorption is slow, and peak serum concentrations usually occur within 8 hours but may be as late as 12 hours after ingestion. A therapeutic carbamazepine concentration is 4 to 12 micrograms/mL.

Carbamazepine has a protein binding of about 80\% and a volume of distribution of 0.8 to 1.2 L/kg. It is metabolized by liver cytochrome P-450 isoenzymes to an active metabolite (10,11-epoxide). The epoxide concentration comprises 15\% of the parent compound in adults and slightly higher in children. The epoxide metabolite is responsible for much of the neurotoxicity seen in overdose. Autoinduction of the enzymes that metabolize carbamazepine occurs with about 1 month of continuous use. Because of this, the drug's half-life shortens over time: the half-life after an isolated carbamazepine dose is about 35 hours, much longer than the 10 to 20 hour half-life at steady state after 3 to 5 weeks of continuous therapy.

CLINICAL FEATURES

After an overdose, the delayed and erratic absorption due to anticholinergic properties (which delay gastrointestinal motility) and low water solubility can cause delayed clinical deterioration or a crescendo-
decrescendo clinical course.\textsuperscript{19} Manifestations of acute toxicity include mental status depression, ataxia, nystagmus, ileus, hypertonicity with increased deep tendon reflexes, dystonic reactions, and an anticholinergic toxidrome.\textsuperscript{19,20,21} Paradoxical seizures can occur in patients with high carbamazepine concentrations and an underlying seizure disorder. There are sporadic reports of left ventricular dysfunction with heart failure and transient heart block (without hemodynamic compromise). Cardiac arrhythmias are rarely seen, but carbamazepine is one of the few drugs that can potentially cause both a wide QRS interval and seizures. Laboratory abnormalities seen with acute overdose include hyponatremia, hyperglycemia, and transient elevation of serum liver enzyme levels.

Adverse effects occur in 25\% of patients receiving long-term carbamazepine therapy. Mild transient leukopenia may occur during the first month of treatment. This is unrelated to the more serious side effect of aplastic anemia, which has a reported incidence of 1 to 5 per million patient-years, approximately 11 times higher than in the normal population. Mild liver enzyme elevation occurs in up to 10\% of patients on long-term therapy. Stevens-Johnson syndrome and toxic epidermal necrolysis are reported with about the same frequency as aplastic anemia.

**DIAGNOSIS**

Serum carbamazepine concentrations are not linearly correlated with poisoning severity. However, serum concentrations of >40 micrograms/mL are associated with an increased risk of serious complications such as seizures, respiratory failure, coma, and cardiac conduction defects.\textsuperscript{22} Serum concentrations higher than 60 to 80 micrograms/mL may be fatal. The seriousness of toxicity should be judged by the clinical status of the patient, not by the serum concentration.\textsuperscript{20,21,22}

Because the chemical structure of carbamazepine is related to imipramine, carbamazepine can cause a false-positive tricyclic antidepressant result on a urine drug screen.\textsuperscript{23} Both carbamazepine and epoxide metabolite are measured by the standard enzyme-multiplied immunoassay to determine serum levels.

**TREATMENT**

Activated charcoal may be considered if the patient is not obtunded and presents within 1 hour of ingestion, because delayed absorption is possible.\textsuperscript{14} Multidose activated charcoal may decrease drug half-life but does not decrease time to recovery or change outcome in overdose patients.\textsuperscript{24} In patients with severe toxicity and multiorgan dysfunction, hemodialysis, hemoperfusion, or hemodiafiltration is effective.\textsuperscript{25–31} Although cardiac conduction delays are rare, if conduction delay is noted on the electrocardiogram, sodium bicarbonate treatment seems reasonable.

**DISPOSITION AND FOLLOW-UP**

Patients can be medically cleared from the ED if at least two carbamazepine measurements obtained a few hours apart show decreasing levels (preferably below 15 micrograms/mL) and the patient is awake,
Valproate (or valproic acid) is used to treat tonic-clonic seizures, absence seizures, partial complex seizures, and post-traumatic epilepsy. Valproate is also used in migraine headache prophylaxis, to control manic episodes in bipolar disorder, and to treat neuropathic pain.

**PATHOPHYSIOLOGY**

Valproate affects neurotransmitters and the function of electrically excitable cells. Valproate increases γ-aminobutyric acid concentrations, reduces release of γ-hydroxybutyrate, and blocks N-methyl-d-aspartate receptors. Valproate prolongs recovery of inactivated sodium channels, enhances potassium conductance, and reduces T-type calcium current firing.

With standard preparations at therapeutic doses, peak serum concentrations occur within 4 hours after ingestion. If the enteric-coated or controlled-release formulation has been ingested, peak serum concentration may be delayed for 12 to 17 hours.

Valproate is metabolized by the liver by glucuronic acid conjugation and mitochondrial beta oxidation. Valproate enters mitochondria by using L-carnitine as a cofactor. Protein binding is extensive and influenced by serum concentration, with 90% of the drug protein bound at concentrations of 40 micrograms/mL. Valproate is an eight-carbon fatty acid and has a small volume of distribution of 0.13 to 0.23 L/kg. The half-life of valproate is 8 to 21 hours but may be two or three times longer after overdose.

**CLINICAL FEATURES**

After an overdose with acute toxicity, the most frequent sign is CNS depression, ranging from drowsiness to coma. Other findings include respiratory depression, hypotension, hypoglycemia, hypocalcemia, hypernatremia, hypophosphatemia, and anion gap metabolic acidosis that may persist for days. Toxicity to the liver produces elevated serum levels of aminotransferases, ammonia, and lactate. Pancreatitis may occur, and thrombocytopenia may be clinically significant and severe.

Valproate increases renal ammonia production and blocks hepatic ammonia metabolism. Hyperammonemia in the absence of liver failure has been reported following valproate overdose and during long-term therapy. Cerebral edema has been seen in acute overdose. During long-term therapeutic use, increased serum liver enzyme levels occur in >50% of patients with therapeutic valproate serum concentrations. Liver enzyme levels typically normalize with dosage reduction or discontinuation of the drug. Hepatic failure, histologically evident as microvesicular steatosis, occurs in about 1 in 20,000 patients receiving long-term therapy. Valproate-induced hepatotoxicity may be either intrinsic and benign (reversible, reproducible, and dose dependent) or idiosyncratic and fatal (unpredictable, not dose...
dependent, with a long latent period). Children <3 years of age who are receiving multiple antiepileptic agents and have additional medical problems are at highest risk for fatal hepatotoxicity, with an incidence of about 1 in 500. Serum levels of transaminases and ammonia should be checked in children on valproate therapy who demonstrate somnolence or lethargy.

**DIAGNOSIS**

Therapeutic valproate concentrations are 50 to 100 micrograms/mL. Although serum concentration does not correlate well with either seizure control or toxicity, adverse side effects increase as concentrations rise above 150 micrograms/mL, and coma may occur with levels above 800 micrograms/mL. When serum valproate concentrations are measured, the enzyme-multiplied immunoassay technique yields higher values than gas-liquid chromatography, so a consistent analytic methodology should be used when monitoring treatment. Serum ammonia and glucose concentrations should be measured with suspected valproate toxicity. Valproate is eliminated partly as ketone bodies and may cause a positive test result for ketones in the urine or blood.

**TREATMENT**

Single-dose activated charcoal alone is sufficient for the vast majority of patients with a valproate overdose. Consider multidose activated charcoal and/or whole-bowel irrigation after ingestion of enteric-coated, delayed-release preparations to prevent the ongoing absorption that may occur from delayed capsule or tablet dissolution. Because of delayed peak serum levels after an overdose, serial concentrations should be measured.

Administration of high-dose naloxone has been reported to reverse valproate-induced neurologic depression, possibly by reversal of valproate-induced release of endogenous opioids or reversal of valproate-induced blockade of γ-aminobutyric acid uptake. Because the serious toxic effects of valproate involve more than just these two mechanisms, naloxone is unlikely to be helpful in the management of a comatose patient after valproate overdose.

Overdose patients have been given L-carnitine in an attempt to increase valproate metabolism by beta oxidation, and this therapy appears to hasten the resolution of coma, prevent hepatic dysfunction, and reverse mitochondrial metabolic abnormalities in patients with acute valproate intoxication. Administration of L-carnitine 100 milligrams/kg IV initially followed by infusions of 50 milligrams/kg every 8 hours is recommended in cases of valproate toxicity with lethargy, coma, hyperammonemia, and hepatic dysfunction. For patients receiving long-term valproate therapy, oral carnitine administration reverses carnitine deficiency, decreases elevated ammonia levels, and reduces lethargy.

**Hemoperfusion and hemodiafiltration** have been used to treat severe valproate overdose. Although valproate should not be amenable to dialysis due to significant protein binding, unbound (free) drug is markedly increased in overdose, and removal of valproate from this pool appears beneficial. During
hemoperfusion and hemodiafiltration treatment, elimination half-life ranges from 1.7 to 3 hours compared with 4.8 to 21 hours in patients before and after extracorporeal therapy. Clinical comparison of extracorporeal detoxification with supportive care reports a benefit to extracorporeal removal.\textsuperscript{53}

**DISPOSITION AND FOLLOW-UP**

Assess valproate levels every few hours until a decline in the level is noted and the patient is asymptomatic.

**SECOND- AND THIRD-GENERATION ANTICONVULSANTS**

As a group, the second- and third-generation anticonvulsants are less toxic in acute overdose than the first-generation agents, and most of the serious complications reported occur in cases of mixed ingestion.\textsuperscript{54} Some specific acute toxic effects are notable (Table 197-6).
### TABLE 197-6

**Unique Aspects of Overdose With Second- and Third-Generation Anticonvulsants**

<table>
<thead>
<tr>
<th>Drug (Generation)</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eslicarbazepine acetate (3&lt;sup&gt;rd&lt;/sup&gt;)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Vertigo, ataxia, hemiparesis</td>
</tr>
<tr>
<td>Ezogabine or retigabine (3&lt;sup&gt;rd&lt;/sup&gt;)</td>
<td>Agitation, irritability, aggressive behavior</td>
</tr>
<tr>
<td>Felbamate (2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>Crystalluria, hematuria, aplastic anemia, liver failure</td>
</tr>
<tr>
<td>Gabapentin (2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>Drowsiness, ataxia, nausea, vomiting</td>
</tr>
<tr>
<td>Lacosamide (3&lt;sup&gt;rd&lt;/sup&gt;)</td>
<td>Limited experience; serious toxicity unlikely</td>
</tr>
<tr>
<td>Lamotrigine (2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>Drowsiness, vomiting, ataxia, and dizziness; serious neurologic and cardiovascular toxicity with co-ingestants; &quot;Stevens-Johnson syndrome&quot;</td>
</tr>
<tr>
<td>Levetiracetam (2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>Lethargy, coma, respiratory depression</td>
</tr>
<tr>
<td>Oxcarbazepine (2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>Little toxicity from isolated oxcarbazepine overdose</td>
</tr>
<tr>
<td>Pregabalin (2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>Drowsiness and depressed level of consciousness</td>
</tr>
<tr>
<td>Rufinamide (2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>Limited experience; serious toxicity unlikely</td>
</tr>
<tr>
<td>Stiripentol (2&lt;sup&gt;nd&lt;/sup&gt;)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>No information</td>
</tr>
<tr>
<td>Tiagabine (2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>Rapid onset of lethargy, coma, seizures, and status epilepticus; myoclonus, muscular rigidity, and delirium</td>
</tr>
<tr>
<td>Topiramate (2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>Somnolence, vertigo, agitation, and mydriasis; seizures and status epilepticus; metabolic acidosis</td>
</tr>
<tr>
<td>Drug (Generation)</td>
<td>Effects</td>
</tr>
<tr>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Vigabatrin (2\textsuperscript{nd})</td>
<td>Drowsiness, unconsciousness, coma</td>
</tr>
<tr>
<td>Zonisamide (2\textsuperscript{nd})</td>
<td>Little toxicity from isolated zonisamide overdose</td>
</tr>
</tbody>
</table>

*Not available in the United States as of March 2012.

**ESLICARB AZEPINE ACETATE**

*Eslicarbazepine acetate* is a prodrug drug for eslicarbazepine, an anticonvulsant that stabilizes sodium-dependent channels in their inactivated state.\textsuperscript{55,56} Eslicarbazepine acetate has a half-life of 10 to 20 hours and possesses modest and possible clinically relevant drug interactions with phenytoin, carbamazepine, and oral contraceptives.\textsuperscript{55,56,57} Symptoms of vertigo, ataxia, and hemiparesis have been observed after accidental overdose. Eslicarbazepine acetate is available in Europe but not in the United States as of March 2012.

**EZOGABINE**

*Ezogabine* (generic name in the United States) or *retigabine* (generic name in Europe) activates voltage-gated potassium channels in the brain, a unique mechanism among the anticonvulsants.\textsuperscript{55,56,58} Ezogabine has a half-life of 6 to 10 hours and possesses drug interactions with phenytoin, carbamazepine, and lamotrigine.\textsuperscript{55,56,57} Side effects seen with ezogabine therapy include dizziness, fatigue, confusion, tremor, and ataxia.\textsuperscript{58} Increased rate of urinary retention and slight increase in QT interval have been reported. There is limited experience with overdose, but agitation, irritability, and aggressive behavior have been noted.

**FELBAMATE**

*Felbamate* was the first of the second-generation antiepileptics.\textsuperscript{54} However, shortly after its introduction in 1993 it received a "black box warning" because of the association with aplastic anemia (with an incidence 100 times higher than in the general population) and hepatic failure. Hence it is only recommended when other treatment regimens have failed. The proposed mechanism of action of felbamate is inhibition at γ-aminobutyric acid receptors and excitation at \textit{N}-methyl-d-aspartic acid receptors. Felbamate has a half-life of 20 to 23 hours and possesses drug interactions with the first-generation anticonvulsants and oral contraceptives. In overdose, the symptoms are usually mild, but in large ingestions, felbamate can crystallize in the kidney, producing crystalluria, hematuria, and possibly acute renal failure.\textsuperscript{59,60,61} Treatment is supportive.
**GABAPENTIN**

Gabapentin, as its name suggests, increases γ-aminobutyric acid levels in the brain. It also has indirect effects on calcium channels located on the postsynaptic terminal. Gabapentin has a half-life of 5 to 9 hours and possesses drug interactions with cimetidine and antacids. With an overdose, gabapentin produces little toxicity, usually drowsiness, ataxia, nausea, and vomiting that resolve in about 10 hours. Depressed level of consciousness has been described in a patient with end-stage renal disease who ingested multiple doses of gabapentin over 2 days without intervening hemodialysis; hemodialysis was associated with rapid recovery. The only reported suicide from gabapentin overdose is controversial.

**LACOSAMIDE**

Lacosamide affects voltage-gated sodium channels in the central nervous system. Lacosamide has a half-life of 12 to 16 hours and has no significant drug interactions. During therapeutic use, adverse reactions are usually mild to moderate and typically include dizziness, headache, nausea, and diplopia. There is limited clinical experience with lacosamide overdose, but serious toxicity after an isolated overdose would not be expected to occur.

**LAMOTRIGINE**

Lamotrigine inhibits sodium channels in CNS neurons and likely has the same effect in the heart. Lamotrigine has a half-life of 15 to 35 hours and interacts with the first-generation antiepileptics. Autoimmune reactions, such as Stevens-Johnson syndrome, have occurred during therapeutic use. With an overdose, the clinical course is usually benign, and the most common effects are drowsiness, vomiting, ataxia, and dizziness. Serious neurologic and cardiovascular toxicity is rare, but has been reported after lamotrigine overdose, sometimes with coingestants. Neurologic toxicity includes oculogyric crisis, provoking of seizures, status epilepticus, and coma. Cardiac toxicity includes QRS complex widening, AV nodal block, and cardiovascular collapse. Acute pancreatitis has been reported in association with a lamotrigine overdose. Treatments used in lamotrigine overdose include activated charcoal to reduce absorption, sodium bicarbonate for QRS complex widening, magnesium sulfate for QT interval prolongation, and IV lipid emulsion to remove active drug from binding sites and sequester it in a lipid sink.

**LEVETIRACETAM**

The mechanism of action of levetiracetam is not known. Levetiracetam has a half-life of 6 to 8 hours and possesses drug interaction only with phenytoin. During therapeutic use, the major side effect is somnolence, usually seen during the initial 4 weeks of therapy. There are few reports of levetiracetam overdose, and the
most common symptom is lethargy that can progress to coma and respiratory depression.\textsuperscript{85,86,87,88} Recovery is usually rapid with supportive care alone.

**OXCARBAZEPINE**

Oxcarbazepine inhibits voltage-sensitive sodium channels in the nervous system.\textsuperscript{89} Oxcarbazepine has a half-life of 8 to 15 hours and interacts with phenytoin, lamotrigine, and oral contraceptives.\textsuperscript{56,57} During therapeutic use, hyponatremia and drug rash can be seen. There appears to be little toxicity from isolated oxcarbazepine overdose; most of the serious neurologic depression has been seen with mixed ingestions.\textsuperscript{90,91,92,93}

**PREGABALIN**

Pregabalin has a mechanism of action similar to that of gabapentin, increasing \(\gamma\)-aminobutyric acid levels in the brain in addition to having indirect effects on calcium channels located on the postsynaptic terminal. Pregabalin has a half-life of 5 to 7 hours and possesses drug interactions with ethanol, lorazepam, and oxycodone.\textsuperscript{56,57} During long-term therapeutic use, the most commonly reported side effects are somnolence and dizziness; serious adverse effects are rare. There is little reported experience with pregabalin overdose; depressed level of consciousness appears to be the major symptom.\textsuperscript{94,95} Similar to the experience with gabapentin, toxicity from pregabalin has been reported in patients with end-stage renal failure but resolves with dialysis.\textsuperscript{96}

**RUFINAMIDE**

Rufinamide inhibits the activity of sodium channels, prolonging their inactive state.\textsuperscript{97} Rufinamide has a half-life of 6 to 10 hours and has drug interactions with other anticonvulsants—phenytoin, carbamazepine, valproate, phenobarbital, and lamotrigine—as well as with oral contraceptives.\textsuperscript{56,57} During long-term therapy, commonly reported adverse reactions include headache, dizziness, fatigue, and somnolence. There is limited clinical experience with rufinamide overdose, but given the lack of symptoms seen with doses of more than six times the recommended amount, toxicity would not be expected after an isolated overdose.

**STIRIPENTOL**

Stiripentol inhibits the reuptake of \(\gamma\)-aminobutyric acid into the presynaptic neuron, thereby increasing \(\gamma\)-aminobutyric acid concentrations in the synaptic cleft and promoting \(\gamma\)-aminobutyric acid activity. Stiripentol has a half-life of 5 to 13 hours and possesses modest drug interactions with valproate and clobazam.\textsuperscript{56,57} Side effects during therapeutic use include drowsiness, ataxia, tremor, anorexia, nausea, and vomiting. Transient aplastic anemia and leukopenia have occurred. There is no information on clinical overdose with this medication. Stiripentol is available in Europe and Canada, but not in the United States as of March 2012.
TIAGABINE

Tiagabine inhibits the reuptake of γ-aminobutyric acid into the presynaptic neuron, thereby increasing γ-aminobutyric acid concentrations in the synaptic cleft and promoting γ-aminobutyric acid activity. Tiagabine has a half-life of 5 to 8 hours and interacts with most of the first-generation antiepileptics, including phenytoin, valproate, carbamazepine, phenobarbital, and primidone.56,57 In overdose, tiagabine can cause the rapid onset of neurologic toxicity, including lethargy, coma, and seizures.98,99,100,101 Tiagabine overdose can provoke status epilepticus, even in patients without an underlying seizure disorder.102,103,104,105 Other signs seen in tiagabine overdose include myoclonus, muscular rigidity, and delirium.98 Recovery usually occurs in about 24 hours.

TOPIRAMATE

Topiramate inhibits γ-aminobutyric acid receptors in addition to affecting sodium channels in the brain. Topiramate has a half-life of 20 to 30 hours and possesses drug interactions with other anticonvulsants—phenytoin, valproate, carbamazepine, phenobarbital, and primidone—as well as with oral contraceptives.56,57 Adverse effects observed during therapeutic use include promotion of renal stone formation and glaucoma. In overdose, topiramate can produce somnolence, vertigo, agitation, and mydriasis.106,107,108 Seizures and status epilepticus have been reported.109,110 A unique aspect of topiramate overdose is the production of a non-anion gap metabolic acidosis.111,112,113 The cause is inhibition of renal carbonic anhydrase, and because of the long half-life of topiramate, metabolic acidosis can last up to 7 days. However, this effect is completely reversible, and no permanent sequelae have been seen.

VIGABATRIN

Vigabatrin is a structural analog of γ-aminobutyric acid that increases brain concentrations of this neurotransmitter. Vigabatrin has a half-life of 5 to 7 hours and has a modest drug interaction with phenytoin.56,57,114 During chronic therapy, vigabatrin may worsen mood and exacerbate psychosis. Sedation, headache, and weight gain are common side effects. After acute overdose, drowsiness, unconsciousness, and coma are described in the majority of cases.115

ZONISAMIDE

Zonisamide inhibits voltage-sensitive sodium channels in CNS - neurons.116 Zonisamide has a long half-life, 50 to 70 hours, and possesses drug interactions with most of the first-generation antiepileptics, including phenytoin, valproate, carbamazepine, phenobarbital, and primidone.56,57 Serious adverse effects during therapeutic use include the promotion of renal stone formation and a drug-induced rash. Isolated zonisamide overdose is associated with lethargy.117,118 A death ascribed to zonisamide overdose was actually a mixed ingestion that included mirtazapine, diphenhydramine, and caffeine.119
REFERENCES


**USEFUL WEB RESOURCES**

American Association of Poison Control Centers—http://www.aapcc.org/DNN/

American Academy of Clinical Toxicology—http://www.clintox.org/index.cfm

European Association of Poisons Centres and Clinical Toxicologists—http://www.eapcct.org/

Asia Pacific Association of Medical Toxicology—http://www.asiatox.org/

South Asian Clinical Toxicology Research Collaboration—http://www.sactrc.org/
TOXBASE: The primary clinical toxicology database of the National Poisons Information Service (free access for UK National Health Service hospital departments and general practices, and National Health Service departments of public health and health protection agency units; available to hospital EDs in Ireland by contract; available to European poison centers whose staff are members of the European Association of Poisons Centres and Clinical Toxicologists; overseas users may be allowed access on payment of a yearly subscription, subject to the approval of the Health Protection Agency)—http://www.toxbase.org/