controlled trial of pigs poisoned by propranolol showed a dose response over time, with improvements of cardiac output with increasing HDI doses up to 10 units/kg per hour. No ceiling dose has yet been established.[52] Page et al[50] showed no significant increase in complications between use of lower- and higher-dose insulin in a retrospective study. The hemodynamic response to HDI is usually seen in 15 to 45 minutes, so begin the infusion at 1 unit/kg per hour, and increase the infusion rate if there is no clinical improvement within 30 minutes. Monitor the serum glucose concentrations and adjust the dextrose infusion to maintain an acceptable glucose range. Maintain the HDI infusion until toxicity has resolved; durations of 9 to 49 hours may be necessary. The insulin infusion may be reinstituted if toxicity recurs. Due to persistent elevated insulin concentrations, dextrose supplementation may be required for up to 24 hours after the infusion is discontinued.

GLUCAGON

Glucagon, a hormone synthesized by the pancreas, is the therapy of choice for β-adrenergic blocker poisoning because of its ability to bypass the β-adrenergic receptor and stimulate cardiac activity via activation of adenylate cyclase (see Chapter 194, "Beta-Blockers"). In CCB poisoning, the inhibition is downstream from glucagon's binding site; therefore, glucagon theoretically offers no advantage over other agents. Nevertheless, glucagon administration improves blood pressure in animal models, and several case reports have also noted improvement in hemodynamics after glucagon therapy.[53-56] However, failure to respond has also been reported.[43]

The recommended glucagon dose is an initial IV bolus of 5 milligrams in adults and 0.03 milligram/kg in children given over 1 to 2 minutes (Figure 195-1). A response is usually seen within 15 minutes. If there is no response, the bolus dose may be repeated. If there is hemodynamic improvement, a maintenance infusion should be initiated at 5 milligrams/kg per hour in adults and 0.05 milligram/kg per hour in children.

The main adverse effects of glucagon are vomiting and hyperglycemia; empirically give ondansetron, once it is determined that there is no QT_c prolongation, hypokalemia, or hypomagnesemia. Because of the large amounts of glucagon required, hospital supplies of the drug are often rapidly depleted; plan ahead and consider making arrangements (e.g., with nearby centers) for additional glucagon.

IV LIPID EMULSION THERAPY

Lipid emulsion therapy was first described in the management of local anesthetic toxicity. Lipid emulsions appear to create a pharmacologic sink for fat-soluble drugs.[57] Therapy may also provide fatty acid substrate for cardiac energy supply and improve myocyte function by increasing intracellular calcium levels. Lipid emulsion therapy prolonged survival in an animal model of verapamil poisoning,[58] and several case reports described benefit in CCB ingestions unresponsive to standard therapy.[59,60] There are many different commercial lipid emulsion preparations, with the major components typically being soybean oil, egg yolk phospholipids, and glycerin.

The recommended dose is a 20% lipid emulsion given as a 1.5 mL/kg bolus over 2 to 3 minutes, followed by a 0.25 mL/kg per minute infusion. If the blood pressure remains low, an additional 1.5 mL/kg bolus may be repeated followed by an increase in the infusion rate to 0.5 mL/kg per minute. The recommended upper limit for lipid emulsion infusion is about 10 mL/kg over the initial 30 minutes. If the patient's hemodynamic stability is dependent on continued lipid infusion, the treatment may be continued.[61] Case reports suggest that if sudden cardiac arrest occurs in the setting of overdose, a bolus can be given in the hope of restoring spontaneous circulation. In addition to interference with laboratory parameters (e.g., blood cell count, electrolytes, liver transaminases), there are rare adverse effects such as hypertriglyceridemia, hypoxemia (with high doses), and hyponatremia.[23]

EXTRACORPOREAL CIRCULATORY SUPPORT

With lack of response to aggressive medical therapy, consider circulatory support measures, such as the placement of intra-aortic balloon pumps, the use of left ventricular assist devices, and even extracorporeal membrane oxygenation, which may provide adequate blood pressure to allow clearance of the drug and resolution of symptoms.[23,62,63] Lipid emulsion therapy can cause complications with extracorporeal membrane oxygenation.[64] Contact the extracorporeal membrane oxygenation team before starting lipid emulsion, if extracorporeal membrane oxygenation is to be used. Due to CCB's large volume of distribution and high affinity for protein binding, hemodialysis and hemoperfusion are not beneficial in the treatment of CCB overdoses.[65]

DISPOSITION AND FOLLOW-UP

In general, patients usually manifest toxicity within 6 hours of ingestion of IR products. Therefore, those who are asymptomatic and who have normal vital signs and normal ECG after a 6-hour observation period can be discharged after appropriate psychiatric evaluation.[24] Toxicity may be delayed for up to 12 hours after ingestion of ER products.[8,9] **As a rule, patients who ingest potentially toxic amounts of ER products should be monitored for at least 24 hours.** Contact the regional poison control center for assistance with management.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 196

Antihypertensives

Frank LoVecchio
Dan Quan

INTRODUCTION

An estimated 29% of adults in the United States have hypertension; thus, antihypertensives are commonly found in patient homes.[1] Several classes of drugs used to treat hypertension are discussed in this chapter: diuretics, sympatholytic agents, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and vasodilators (**Table 196-1**). Calcium channel blockers and β-blockers, also used in the treatment of hypertension, are discussed elsewhere (see Chapter 195, "Calcium Channel Blockers," and Chapter 194, "Beta-Blockers").

For most of these agents, life-threatening toxicity is not expected in acute overdose.[2] In nearly all cases, good supportive care is adequate. The initial approach to the patient with potential overdose of an antihypertensive drug is fairly uniform. Secure the airway as necessary, establish IV access, provide continuous cardiac monitoring, and obtain an ECG. A bolus of crystalloid solution is first-line treatment for hypotension. If a vasopressor is required, a direct-acting drug such as norepinephrine is preferred. If pulmonary aspiration is not a concern, activated charcoal can be given within the first hour. Although there is usually no specific therapy for initial management of these drugs in overdose, the different classes of antihypertensives are distinct in their potential for causing metabolic derangements and adverse effects.

DIURETICS

Diuretics initially control hypertension by increasing elimination of salts, but their mechanism of action in long-term blood pressure control is not clear. All diuretics cause increased sodium elimination, which results in the potential for hyponatremia, hypokalemia, hyperkalemia, hypomagnesaemia, and hypovolemia.

Thiazides, like **hydrochlorothiazide**, inhibit sodium chloride reabsorption in the renal distal convoluted tubule. Decreased sodium reabsorption leads to increased excretion of potassium and the possibility of hypokalemia. Calcium regulation is also affected by thiazide diuretics via two separate mechanisms: (1) inhibition of vitamin D synthesis and thus decreased calcium absorption from the GI tract, and (2) increased

TABLE 196-1 Summary of Antihypertensive Drugs

Class	Drug	Mechanism of Action	Clinical Presentation With Toxicity	Comments
Diuretics	Chlorothiazide Chlorthalidone Hydrochlorothiazide Indapamide Metolazone	Inhibition of distal tubule sodium chloride absorption	Hypovolemia Hypokalemia Hypercalcemia	Metabolic complications, such as hypokalemia, glucose intolerance, and hyperuricemia seen with increased therapeutic thiazide doses.
	Bumetanide Furosemide	Inhibition of sodium-potassium-chloride symporter in renal loop of Henle	Hypovolemia Hypocalcemia Hypokalemia Hypomagnesemia	
	Amiloride Triamterene	Inhibition of sodium absorption and potassium elimination in renal distal collecting duct	Hypovolemia Hyperkalemia	
	Eplerenone Spironolactone	Mineralocorticoid antagonist	Hypovolemia Hyperkalemia	
Sympatholytics	Doxazosin Prazosin Tamsulosin Terazosin	α_1-Adrenergic receptor antagonist	Hypotension	Phenylephrine may be used for refractory hypotension.
	Clonidine Guanabenz Guanfacine	α_2-Adrenergic receptor agonist Imidazoline receptor agonist μ-Receptor opioid agonist	Hypotension Bradycardia Neurologic depression	Dopamine considered agent of choice for hypotension. Phenylephrine may be used for refractory hypotension.
	Oxymetazoline Tetrahydrozoline	Imidazoline receptor agonist	Hypotension Bradycardia Neurologic depression	
	Guanadrel Methyldopa Reserpine	Decreased norepinephrine release	Hypotension Bradycardia Hemolytic anemia (idiosyncratic reaction to methyldopa)	
Angiotensin-converting enzyme inhibitors	Benazepril Captopril Enalapril Fosinopril Moexipril Perindopril Quinapril Trandolapril	Inhibition of ACE Inhibition of bradykininase	Hypotension Hyperkalemia Angioedema (idiosyncratic) Cough (idiosyncratic)	Epinephrine, corticosteroids, and antihistamines have no proven benefit in ACEI-induced angioedema. Icatibant 30 milligrams SC or C1 esterase inhibitor [human] 1000 U IV appear effective in ACEI-induced angioedema.
Angiotensin receptor blockers	Candesartan Eprosartan Irbesartan Losartan Telmisartan Valsartan	Angiotensin II receptor antagonist	Hypotension Hyperkalemia Angioedema (less common than with ACE inhibitors)	Epinephrine, corticosteroids, or antihistamines have no proven benefit in ARB-induced angioedema.
Vasodilators	Hydralazine	Arteriolar vasodilation	Hypotension Lupus-like syndrome (idiosyncratic reaction to hydralazine)	
	Minoxidil	Arteriolar vasodilation	Tachycardia Increased myocardial oxygen demand	
	Sodium nitroprusside	Arteriolar and venous vasodilation (via nitric oxide release)	Hypotension Tachycardia Thiocyanate toxicity (after prolonged infusion) Cyanide toxicity (very rare)	Thiosulfate should be administered if cyanide toxicity is considered. Many pharmacies mix sodium nitroprusside and thiosulfate to avert cyanide toxicity.

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ACEI = angiotensin-converting enzyme inhibitors.

renal absorption of calcium. The net result, however, is calcium retention and potentially hypercalcemia.[3] Glucose intolerance is noted at higher doses.

Loop diuretics, such as **furosemide** and **bumetanide**, are used more frequently for control of edema and pulmonary congestion than for hypertension. Loop diuretics inhibit the activity of the sodium-potassium-chloride symporter (a type of cotransporter that facilitates transport across a plasma membrane) in the renal loop of Henle, where 25% of the filtered sodium load is typically reabsorbed. A secondary effect of the inhibition of this symporter is decreased calcium and magnesium reabsorption, which results in hypocalcemia, hypokalemia, and hypomagnesemia.

Triamterene, **amiloride**, **spironolactone**, and **eplerenone** are referred to as potassium-sparing diuretics for their ability to cause a sodium chloride diuresis without increased potassium secretion. Triamterene and amiloride inhibit sodium channels in the distal renal tubule and collecting duct, which play a role in both reabsorbing sodium and secreting potassium. These drugs may be used in conjunction with other stronger diuretics for management of hypertension. Triamterene has been associated with rare cases of crystalline nephropathy.[4]

Spironolactone and eplerenone are antagonists of mineralocorticoids such as aldosterone. Mineralocorticoid antagonists increase elimination of sodium and retention of hydrogen and potassium. Spironolactone is typically used to treat heart failure and hepatic cirrhosis. In the acute overdose setting, hyperkalemia and hypotension are the most serious clinical manifestations of these drugs.

Clinical manifestations of excessive diuresis include tachycardia, hypotension (orthostatic or supine), electrolyte abnormalities, and generalized weakness. The ECG may show changes caused by these electrolyte abnormalities (see Chapter 17, "Fluids and Electrolytes"). A widened QRS interval or peaked T waves may suggest hyperkalemia, such as from a potassium-sparing diuretic. A prolonged QT interval may indicate hypokalemia, hypomagnesemia, or hypocalcemia, which may be caused by a loop diuretic.

The first priority of therapy is restoration of plasma volume. Administer an isotonic crystalloid solution bolus, such as 0.9% saline. Treat electrolyte abnormalities, such as hyperkalemia, hypokalemia or hypocalcemia, with standard management and fluid resuscitation (see Chapter 17, "Fluids and Electrolytes").

In addition to causing direct toxicity, diuretics may potentiate toxicity from other medications. Mechanisms include decreased renal clearance of drugs or creation of a metabolic state that changes a particular drug's effect. **Diuretics and ACEIs can increase the risk of lithium toxicity** by reducing lithium elimination (see Chapter 181, "Lithium").[5] Hypokalemia from diuretics may exacerbate arrhythmias seen in chronic digoxin poisoning or other antiarrhythmics (see Chapter 193, "Digitalis Glycosides").

SYMPATHOLYTIC AGENTS

Catecholamines produced by the sympathetic nervous system play a key role in maintaining blood pressure. Drugs with action at α-adrenergic receptors are used to diminish peripheral sympathetic tone in order to decrease blood pressure. There are two subtypes of α-adrenergic receptors. Stimulation of the α_1-adrenergic receptors causes vasoconstriction of arterioles and veins, increasing peripheral vascular resistance and elevating blood pressure. Stimulation of the α_2-adrenergic receptors produces different effects in the peripheral and central nervous systems. In the peripheral nervous system, stimulation of the α_2-receptors produces vasoconstriction and increases blood pressure. In the CNS, stimulation of the α_2-receptors at presynaptic sympathetic terminals inhibits the release of catecholamines, thereby decreasing sympathetic tone, promoting peripheral vasodilation, and decreasing blood pressure.

DOXAZOSIN, PRAZOSIN, AND TERAZOSIN

Doxazosin, **prazosin**, and **terazosin** antagonize α_1-adrenergic receptors, reducing peripheral vascular resistance. Although the aforementioned drugs are used for the treatment of hypertension, other members of this class, such as **tamsulosin**, are used exclusively for management of benign prostatic hyperplasia and as an adjunct in nephrolithiasis management. Because an increase in peripheral vascular resistance is required to maintain blood pressure when changing from a supine to an upright position, it is not surprising that the most typical adverse effect observed with α_1-adrenergic antagonists is orthostatic hypotension, particularly within 30 to 90 minutes after ingestion, and is most prominent after taking the first dose.[6]

Although orthostatic hypotensive episodes may be associated with lightheadedness and adverse events such as falls resulting in hip fracture, patients rarely come to the ED with prolonged hemodynamic instability. Patients who do present with hypotension associated with α_1-adrenergic antagonist use should be placed supine and receive a crystalloid bolus. Based on the mechanism of action of these drugs, α_1-adrenergic agonists should be used if blood pressure does not improve with IV fluids.[7]

CLONIDINE

Clonidine is the most commonly used α_2-adrenergic agonist. Clonidine is available in an oral formulation and as a transdermal patch. This class of drugs, which also includes guanabenz and guanfacine, stimulates α_2-adrenergic receptors in the CNS, inhibiting release of catecholamines in the periphery, which results in decreased heart rate, contractility, and peripheral vascular resistance. Clonidine shares the imidazoline functional group with the nasal spray decongestant oxymetazoline and topical eye vasoconstrictor medication tetrahydrozoline. **Inappropriately ingesting oxymetazoline or tetrahydrozoline can result in toxicity similar to clonidine poisoning.**[8,9] In addition to hemodynamic effects, clonidine also possesses opioid agonist properties at the μ receptor.[10] For this reason, clonidine is used in some opioid-dependent patients to ameliorate symptoms of withdrawal.

Clonidine poisoning typically results from either intentional overdose or exploratory pediatric poisoning.[11,12] **Even a single tablet may cause significant symptoms in a child.**[13,14] Toxicity can develop from ingesting clonidine patches.[15,16] Compounded ointments used for chronic pain may contain clonidine; application of these patches to small children (or to adults in excessive quantity) may produce toxicity.[17-19]

Shortly after an ingested overdose of clonidine, the peripheral α_2-adrenergic stimulation may cause hypertension.[12,20] By the time of presentation, however, the clinical manifestations of central α_2-adrenergic stimulation and imidazoline toxicity are present with bradycardia, CNS depression, and hypotension.[11,21] Clonidine may produce miotic pupils in a manner similar to opioids.[22] Hypothermia may occur as a result of opioid or adrenergically mediated pathways. Somnolence is typical and may progress to apnea in severe cases.[8,11,23] Although clonidine is intended to be dosed twice daily, symptoms may last days with an overdose.

Focus on ventilatory and hemodynamic support in clonidine toxicity.[21,24] Clonidine-induced respiratory and neurologic depression has variable response to naloxone, and its use is unlikely to be helpful in adults[21,25-29]; however, it is considered to be more effective in children.[28] Bradycardia may be treated with atropine. When encountered, hypertension should be treated only if it is severe and prolonged, because hypertension may unpredictably give way to hypotension. If it is necessary to treat clonidine-associated hypertension, use a short-acting drug that can be quickly discontinued (e.g., nitroprusside). Hypotension associated with clonidine typically responds well to crystalloid fluid resuscitation.

METHYLDOPA

Methyldopa is also a centrally acting antihypertensive, although it has a unique mechanism. Methyldopa is a dopamine analog that, in the CNS, is converted in two steps to α-methylnorepinephrine, which in turn substitutes for norepinephrine in adrenergic neuron secretory vesicles. In the CNS, α-methylnorepinephrine stimulates presynaptic α_2-adrenergic receptors, reducing peripheral sympathetic tone. In therapeutic dosing, the peak effect of methyldopa is delayed for 6 to 8 hours, because time is required for methyldopa to pass into the brain and be converted to its active form. Methyldopa use is also associated with an autoimmune hemolytic anemia, which can occur during long-term therapeutic use.[30,31] If symptomatic hypotension is encountered in association with methyldopa, IV crystalloid solution should be administered. In cases

of refractory, severe hypotension, a direct-acting vasopressor such as norepinephrine should be administered.[32]

GUANADREL AND RESERPINE

Guanadrel and **reserpine** are antihypertensives that interfere with the release of catecholamines from synaptic terminals. Guanadrel, which has no intrinsic sympathetic activity, substitutes for norepinephrine in presynaptic storage vesicles. Reserpine inhibits formation of biogenic amine storage vesicles in central and peripheral neurons. In each case, there is a decreased capacity to release catecholamines in response to a sympathetic stimulus. Sympathetic tone is diminished, and peripheral vascular resistance decreases. There is little experience with these drugs in overdose. However, because the common mechanism of both drugs is a decrease in circulating catecholamines, it would seem reasonable to administer boluses of crystalloid as first-line therapy and to use a direct-acting vasopressor, such as norepinephrine or phenylephrine, to treat refractory hypotension.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin II raises blood pressure by several mechanisms, including triggering aldosterone release, increasing response to catecholamines, and acting as a direct vasoconstrictor. Angiotensin II is created in a two-step process. In the first step, renin, released by the kidneys, cleaves angiotensinogen, forming angiotensin I. The second step uses angiotensin-converting enzyme, which separates the carboxy terminus off angiotensin I, forming angiotensin II. Inhibition of this conversion at either step results in decreased blood pressure.

ACEIs are thought to slow the progression of diabetic glomerulopathy and have been shown to improve mortality and left ventricular function when administered after myocardial infarction. Members of this large class of drugs can be identified by their shared "-pril" suffix: **benazepril**, **captopril**, **enalapril**, **fosinopril**, **moexipril**, **perindopril**, **quinapril**, and **trandolapril**. Inhibition of angiotensin-converting enzyme results in decreased production of angiotensin II, which causes vasodilation. Despite their widespread use, these medications have not been associated with significant morbidity in overdose. ACEIs can cause hyperkalemia in therapeutic dosing. If hypotension is encountered, initial therapy focuses on basic management, including administration of boluses of crystalloid and vasopressors for refractory cases.

Captopril, and possibly other ACEIs, are thought to inhibit the metabolism of the enkephalins, a group of endogenous opioids. Naloxone, a μ-opioid antagonist, may reverse captopril-associated hypotension[33] but is not universally effective.[34]

ARBs produce vasodilatation and increase renal salt elimination. Members of this class end with the suffix "-artan" and include **losartan**, **candesartan**, **irbesartan**, **valsartan**, **telmisartan**, and **eprosartan**. When they are taken therapeutically, the peak antihypotensive effect of agents in this class is not observed for 4 weeks. Typically, these drugs are not associated with significant morbidity in overdose. There are no reported cases of isolated ARBs overdose causing life-threatening hypotension. Like ACEIs, ARBs can cause hyperkalemia, which results from decreased aldosterone production. This effect is typically seen in patients with renal insufficiency.[27]

Persistent dry cough occurs in 5% to 20% of patients treated with ACEIs.[35] Cough typically develops within a few weeks after ACEI therapy is started and is more common in women, and the rate of occurrence or severity does not correlate with dose. Cough will usually resolve in 1 to 4 weeks after the drug is stopped, although resolution may take up to 3 months for some patients. The only effective treatment is discontinuing the ACEI, substituting a different antihypertensive. ARBs are not associated with an increased incidence of chronic cough and may be used in patients with ACEI-induced cough.[36]

Angioedema is the most consequential adverse effect associated with ACEIs and ARBs (see Chapter 14, "Allergy and Anaphylaxis").[37-39] Angioedema is an idiopathic reaction that occurs in 0.1% to 0.7% of patients prescribed these drugs.[38,40] Because these agents are widely used, this small percentage represents a large number of events. Patients present with swelling of the lips, larynx, pharynx, tongue, or vocal cords, which can range in severity from mild to airway compromise. Symptoms develop over several hours and may not resolve for 24 hours or longer.[39] **The absence of urticaria, abdominal swelling, and genitourinary swelling differentiates ACEI-induced angioedema from histamine-mediated causes.**[41] The mechanism is thought to be related to inhibition of ACE-mediated degradation of bradykinin, a peptide associated with vasodilatation and tissue edema, and accumulation of substance P and other prostaglandins.[39,41] ARBs do not inhibit bradykinin, so the exact pathophysiology of angioedema associated with drugs from this class is not clear. **The mean time from first use to development of angioedema has been reported as about 2 years,**[42] **but angioedema can occur at any time during therapy,** with 12% of patients developing this reaction in the first week of ACEI use.

Management of ACEI-induced angioedema begins with evaluation of the airway. If the patient has difficulty breathing, stridor, or lingual or oropharyngeal edema, secure the airway, usually by intubation.[43] Fiberoptic-guided laryngoscopy is recommended because it requires minimal sedation and provides direct visualization in an edematous airway. **Regardless of the method employed, a skilled operator should secure the airway early because angioedema can progress rapidly and anatomic landmarks may become obscured.**

Allergic-reaction drugs, such as epinephrine, antihistamines, and corticosteroids, are often given but not likely beneficial because ACEI-induced angioedema is not mediated by histamines or immunoglobulins.[38] Agents reported beneficial in ACEI-induced angioedema include icatibant, a bradykinin-2 antagonist, at a dose of 30 milligrams SC[44]; C1 esterase inhibitor (human) 1000 units IV[45]; and fresh frozen plasma 2 units,[46,47] but the overall quality of evidence is mixed.[48,49]

Patients with milder symptoms should be observed and managed medically. There is no consensus regarding the disposition of patients with ACEI-associated angioedema who do not require ED airway intervention. Patients with milder swelling only around the lips or face should be observed for 6 to 12 hours and considered for discharge when swelling begins to regress.[41] Patients should be instructed that angioedema can recur if they continue to take the same agent or switch to another agent of the same class.[50,51] **After an episode of angioedema, the safest and recommended course of action is to discontinue all ACEIs and ARBs.**

VASODILATORS

HYDRALAZINE AND MINOXIDIL

Hydralazine is an antihypertensive agent most commonly used during pregnancy. Hydralazine relaxes arteriolar smooth muscle but does not affect venous smooth muscle or epicardial coronary arteries. Hydralazine is metabolized to an inactive compound by hepatic acetylation. Roughly half of Americans are fast acetylators and therefore require a higher dose to achieve a given clinical effect. The peak effect of the drug is seen 30 to 120 minutes after ingestion, although effects may last as long as 12 hours. The most common adverse effects of hydralazine overdose result from vasodilatation, but serious events are rare. Patients with hydralazine overdose with mild hypotension may develop ST-segment depression on ECG.[52] This myocardial ischemia is thought to result from a steal syndrome in which peripheral vasodilatation is accompanied by reflex tachycardia without an increase in epicardial blood flow, so that myocardial demand increases while coronary perfusion does not. Because of this reflex tachycardia, hydralazine should not be used for treatment of acute coronary syndrome or cocaine-associated chest pain.

Patients on continuous treatment with hydralazine are at risk for development of a lupus-like syndrome. The mechanism is thought to be formation of autoantibodies, but it is not known how hydralazine contributes to this process. Risk factors include high dose, female gender, slow-acetylator phenotype, and white ethnic background. Symptoms of this syndrome include arthralgia, arthritis, fever, and pericardial

effusion. Management includes administration of anti-inflammatories and discontinuation of the drug.

Minoxidil is a potent antihypertensive generally used only for resistant cases of hypertension. Minoxidil is better known for its topical formulation as a treatment for male pattern baldness. Minoxidil is metabolized to minoxidil sulfate, which in turn relaxes smooth muscle by opening potassium channels and causing hyperpolarization. Like hydralazine, minoxidil has little effect on venous smooth muscle. Peripheral vasodilatation results in reflex tachycardia and increased cardiac output. Reduced renal perfusion causes fluid retention. For this reason, minoxidil is usually prescribed with a β-blocker and diuretic. Overdose of minoxidil is associated with hypotension, common reflex tachycardia, and occasional myocardial ischemia in a manner similar to hydralazine.[53-56]

Hypotension from either hydralazine or minoxidil is treated with IV crystalloid fluids. Vasopressors should be avoided if possible, because severely poisoned patients may have coronary ischemia. If blood pressure is refractory to fluid resuscitation, an α_1-adrenergic agonist, such as phenylephrine or midodrine,[55] is preferable to a β-adrenergic agonist, in order to minimize tachycardia and prevent increased myocardial oxygen demand.

SODIUM NITROPRUSSIDE

Sodium nitroprusside is administered IV for hypertensive emergencies.[57,58] Nitroprusside derives its activity from the release of nitric oxide, an endogenous mediator of vasodilation, which stimulates smooth muscle guanylyl cyclase to produce cyclic guanosine monophosphate. The onset of action is roughly 30 seconds, and the offset is 3 minutes. Nitroprusside dilates both arteriolar and venous smooth muscle. In the ED, hypotension is the adverse effect most likely to be observed. If hypotension occurs, the infusion should be stopped immediately. If signs of cerebral hypoperfusion are present, place the patient supine or possibly in the Trendelenburg position. Because of the very brief duration of action of the drug, little else is generally necessary after discontinuing the drug.

When nitric oxide is released from nitroprusside, cyanide is produced as well. As long as the nitroprusside infusion rate is not above 2 to 5 micrograms/kg per minute, the cyanide is usually of little consequence, because it is immediately metabolized by rhodanese to thiocyanate, a much less toxic metabolite. At higher infusion rates over several days, the ability of rhodanese to detoxify cyanide may become overwhelmed.[59] Administration of sodium thiosulfate, which serves as a substrate for rhodanese, can be protective for patients requiring a high rate of nitroprusside administration. Cyanide toxicity may manifest as confusion, lactic acidosis, and progression to cardiovascular collapse. If the clinician is concerned about cyanide toxicity, the infusion should be discontinued, and sodium thiosulfate should be administered.

Over time, the thiocyanate generated by detoxification of cyanide can itself cause toxicity manifesting as nausea, fatigue, and CNS depression. Thiocyanate toxicity, although much more common than cyanide toxicity during nitroprusside treatment, is unlikely to occur in the ED. Thiocyanate, which is eliminated by the kidney with a half-life of 3 to 7 days, usually does not accumulate until infusion has continued for several days.[60] The most important predictors of toxicity are rate of production (nitroprusside infusion rate) and rate of elimination (renal function).

FENOLDOPAM

Fenoldopam is a selective dopamine-1 agonist used for hypertensive emergencies, although its clinical utilization in the United States has remained low.[61,62] Fenoldopam is administered parenterally and acts as a vasodilator and diuretic.[57,58] Fenoldopam has a half-life of approximately 5 minutes, and after infusion is instituted, steady-state serum levels are reached in about 30 to 60 minutes. If hypotension is encountered after fenoldopam administration, the infusion should be stopped immediately and a fluid bolus administered.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 197

Anticonvulsants

Frank LoVecchio

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 1938 and 1978 (**Table 197-1**). Since 1993, over 20 additional agents, termed the *second and third generations* of antiepileptic drugs, have been introduced into clinical use. 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 roughly 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.

The toxicity of two benzodiazepines used to treat seizures—clonazepam and clobazam—is discussed elsewhere (see Chapter 183, "Benzodiazepines")

This chapter reviews the pharmacology, clinical features, and treatment for toxicity of commonly used anticonvulsants. Disposition recommendations depend on the resolution of clinical toxicity, but patients with intentional overdose need mental health evaluation in the ED before discharge.

PHENYTOIN AND FOSPHENYTOIN

Phenytoin is a primary anticonvulsant for partial and generalized tonic-clonic seizures. In conjunction with rapidly acting anticonvulsants, it is useful in the treatment of non–drug-induced status epilepticus.[1] Phenytoin has been used to prevent seizures due to head trauma (in the immediate posttraumatic 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 associated with 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 is usually 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-life of 10 to 15 minutes. **The advantage of 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.**[2]

PATHOPHYSIOLOGY

Mechanism of Action Phenytoin exerts its anticonvulsant effects by blocking neuronal voltage-sensitive and frequency-dependent sodium channels, suppressing repetitive neuronal activity, and preventing the spread of a seizure focus.[3]

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, most 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 have 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.