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FEATURE ARTICLE

PEER REVIEWED

Recognizing Dangerous Poisonings in Primary Care: Part 3, Cardiovascular Drugs

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The 5 most common causes of poisoning-related fatalities in the United States are antidepressants, antihistamines, cardiovascular drugs, opioids, and pesticides.[1] Drug poisonings, particularly mild cases, are often exceptionally difficult to recognize. Slightly dilated pupils, mild tachycardia and hypertension, slight fever, and tachypnea are all constitutional symptoms that fit myriad working diagnoses, but autonomic instability is a hallmark of drug poisonings. Motor stiffness and hyperreflexia are frequently seen with a number of drug poisoning syndromes, although not with pesticide poisoning.[2,3]

This 6-part review article series helps sort out some of the more common symptoms, interactions, and therapeutic considerations in the clinical approach to a patient whom you suspect may be experiencing the effects of the most common types of poisoning.

This article, the third in the series, covers cardiovascular drug poisonings. Other articles in the series cover antidepressants, antihistamines, opioids, and pesticides, and one article specifically covers serotonin syndrome.

Calcium-Channel Blockers

Calcium-channel blockers (CCBs) comprise a medication class with many different applications in treating conditions such as angina, coronary vasospasm, arrhythmias, hypertension, cardiomyopathy, Raynaud phenomenon, migraine, and subarachnoid hemorrhage.[4,5]

The 3 major CCB classes to consider are the phenylalkylamines (ie, verapamil), the benzothiazepines (ie, diltiazem), and the dihydropyridines (ie, amlodipine, clevidipine, felodipine, isradipine, nifedipine, nicardipine, nimodipine, nisoldipine).

CCBs inhibit movement of extracellular calcium through the calcium channels contained within the cell membrane. CCBs preferentially block L-type voltage-gated calcium channels. L-type calcium channels mediate excitation and coupling of skeletal, smooth, and cardiac muscle types, as well as hormone secretion in endocrine cells. Thus, CCBs act on the vascular smooth muscle of arteries and cause vasodilation. CCBs do not work on venous smooth muscle.[6] CCB also have negative chronotropic and negative inotropic effects. These effects are prominent with verapamil and diltiazem.

As the use of CCBs for treating hypertension has increased, so have toxic exposures and deaths, either accidental or intentional. The toxic clinical manifestations vary depending on the specific agent, the presence of coingestants, and the presence of underlying heart disease. In 2011, CCBs were involved in 62% of all fatalities attributed to cardiovascular agents.[7] Clinical manifestations can affect the cardiovascular, central nervous, gastrointestinal, and metabolic systems.

Cardiovascular effects are the most troubling in terms of toxicity and range from hypotension to bradydysrhythmias that can include varying degrees of atrioventricular (AV) block or asystole. Central nervous system effects are diverse and include altered mental status, coma, and seizures. Gastrointestinal tract effects can consist of nausea, vomiting, ileus, obstruction, bowel ischemia, and infarction. And metabolic consequences can include hyperglycemia and lactic acidosis.

Hypotension and bradycardia that are not responsive to traditional supportive measures may require the use of calcium as an antidote. Calcium can be administered either as the chloride salt or gluconate salt but must be given cautiously in patients on digoxin because of the risk of profound bradycardia and in patients without central venous access because of the risk of tissue necrosis if calcium is extravasated. In addition, both glucagon and epinephrine have been reported to increase blood pressure in patients with refractory hypotension.[8]

β-Blockers

As a class, β-blockers are used to treat hypertension, arrhythmias, angina, congestive heart failure, essential tremor, and glaucoma, and for migraine prophylaxis.[4,5,8]

β-blockers inhibit the action of endogenous catecholamines (epinephrine and norepinephrine). The 3 subtypes of β receptors are β_1, β_2 and β_3. β_1 receptors act to produce positive chronotropic, dromotropic, and inotropic effects, as well as increased amylase secretion; β_2 receptors act to produce smooth muscle relaxation (eg, bronchodilation); and β_3 receptors produce lipolysis and promote relaxation of the detrusor muscle in the bladder.

β_1 receptors are found in the heart and kidneys. β_2 receptors are found in gastrointestinal tract, lungs, uterus, vascular smooth muscle, and skeletal muscle. β_3 receptors are located in adipose cells. In 2011, β-blockers were involved in 21% of all fatalities attributed to cardiovascular agents.[7] The 3 most common β-blockers involved were metoprolol, atenolol, and propranolol. The usual β-receptor specificity seen at therapeutic doses is lost in the setting of overdose. Propranolol and labetalol have membrane-depressant effects that further inhibit myocardial contractility and conduction. Because propranolol is lipid-soluble, it can penetrate the blood-brain barrier and may cause seizures and coma. The pharmacokinetics of β-blockers vary considerably, and the duration of the overdose may range from minutes to days. Clinical manifestations can affect the cardiovascular, central nervous, pulmonary and metabolic systems.

Cardiovascular effects such as hypotension and bradycardia are the most common. AV block, intraventricular conduction disturbance, cardiogenic shock, and asystole may occur with severe poisoning. The electrocardiogram frequently reveals nodal bradycardia, first-degree AV block, a slightly lengthened QRS complex, and prolongation of the PR and QTc intervals. Common

arrhythmias include ventricular tachydysrhythmias, multifocal ventricular extrasystoles, and, in severe poisoning, asystole. Central nervous system toxicity can include seizures and coma.[9] Bronchospasm is most common in patients with reactive airway disease.

Metabolic abnormalities include hypoglycemia and hyperkalemia. Special attention should be paid to the potential masking effect of β-blockers in patients with diabetes. In nonoverdose situations, β-blockers can obscure the sympathetic (noradrenergic) activation that occurs during hypoglycemia. In acute β-blocker overdose, this symptom masking is only exacerbated, potentially causing leading to a failure to recognize the characteristic symptoms of hypoglycemia and the need for glucose infusion. Bradycardia and hypotension that are resistant to traditional supportive measures may call for the use of glucagon and/or epinephrine infusion. QRS widening may respond to sodium bicarbonate.[8]

Digoxin

In 2011, when cardiovascular agents were involved in fatalities, the third most common agent (12.5% of cases) was digoxin.[7] Digoxin is derived from the plant *Digitalis purpurea*, also known as foxglove. Like other cardiac glycosides, it is a potent inhibitor of the cardiac myocyte sodium-potassium ATP pump. It is used to treat cardiac conditions such as atrial fibrillation, atrial flutter, and congestive heart failure.[4,5,8]

Digoxin toxicity can be of either the acute or chronic type.[4] The symptoms of chronic poisoning include drowsiness, nausea, vomiting, anorexia, diarrhea, disturbed color vision (patients often see yellow or green halos around objects), confusion, dizziness, agitation, and depression. Ventricular ectopy and arrhythmias are common. Chronic toxicity is frequently seen in patients with impaired renal function; the onset is insidious, and visual disturbances predominate. Weakness, sinus bradycardia, atrial fibrillation with slow ventricular response or junctional escape rhythm, and ventricular arrhythmias (ventricular bigeminy or trigeminy, ventricular tachycardia, bidirectional tachycardia and ventricular fibrillation) are common. Accelerated junctional tachycardia and paroxysmal atrial tachycardia with block are frequently seen. With acute overdose, vomiting, hyperkalemia, sinus bradycardia, sinoatrial arrest, and second- or third-degree AV block are common. Hypokalemia, if present, may worsen the tachyarrhythmias in either case.

The therapeutic window for digoxin is narrow, and there is considerable overlap between therapeutic (0.5-2.0 ng/mL) and toxic levels (1.2 ng/mL and above), although serum concentration does not necessarily correlate with toxicity. However, levels greater than 10 to 12 ng/mL are clearly diagnostic for acute toxicity. With acute poisoning, initial toxic gastrointestinal tract effects occur at 2 to 4 hours, peak serum levels at 6 hours, and life-threatening cardiovascular complications at 8 to 12 hours. The antidote to digoxin toxicity is Digoxin immune fab or digoxin-specific antibody.[9]

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