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Medication Overdoses in the Emergency Department: Oral Hypoglycemic Agents, Atypical Antipsychotic Agents, Beta-Blockers, Calcium Channel Blockers, and Digoxin

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The number of medication toxicities has been steadily increasing while atypical antipsychotic overdoses are managed with supportive care. Pharmacists in particular play a pivotal role in identifying presenting symptoms and recommending appropriate treatment options in toxicological emergencies.

Introduction

While incidences of toxic exposure to medications may be intentional or unintentional, trends are indicative of a rise in medication overdoses. Emphasis on opioid and prescription analgesic abuse remains a high priority. However, several other medication classes may be overlooked. In 2004, there were upwards of 10,000 cases of oral hypoglycemic overdose used in the treatment of diabetes. A significant number of atypical antipsychotic overdoses were reported from 2001 to 2005, some of which ended in fatality. Beta-blockers and calcium channel blockers show a combined incidence of over 30,000 overdoses, 57 of which were fatal. \textsuperscript{5,19,20} The cardiac glycoside digoxin has also been associated with severe toxic events and patient fatalities. Pharmacists, as drug experts, should be aware of toxicity potential for all medications and should be prepared with the knowledge for treatment.

Medication Overdoses in the Emergency Department:

Oral Hypoglycemic Agents, Atypical Antipsychotic Agents, Beta-Blockers, Calcium Channel Blockers, and Digoxin

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

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Objectives

After completion of this program, the reader should be able to:

1. Explain the pathophysiology behind oral hypoglycemic agents, atypical antipsychotic agents, beta-blockers, calcium channel blockers, and digoxin.
2. Describe the presenting symptoms associated with the aforementioned drug classes in an overdose.
3. Discuss recommended treatment options in cases of toxicity.
4. Describe the pharmacist's role in treating toxicological emergencies.

Abstract

The number of medication toxicities has been steadily increasing with more patients presenting to the emergency department for both intentional and unintentional overdoses. Oral hypoglycemics, atypical antipsychotics, beta-blockers, calcium channel blockers and digoxin overdoses are some of the more common medication toxicities health care professionals may see in practice. Toxic doses of oral hypoglycemic agents, beta-blockers, calcium channel blockers and digoxin have more definitive options for treatment, while atypical antipsychotic overdoses are managed with supportive care. Pharmacists in particular play a pivotal role in identifying presenting symptoms and recommending appropriate treatment options in toxicological emergencies.

Oral Hypoglycemics

Epidemiology

Type 2 diabetes mellitus (DM2) is a disease on the rise, affecting over 190 million patients in 2006, with a projected population of over 325 million by 2025. In the attempt to treat DM2, the use of oral hypoglycemics has steadily risen with the disease prevalence. A variety of medication classes are available including sulfonylureas, biguanides, meglitinides, thiazolidinediones and alpha-glucosidase inhibitors. While such therapy choices are appropriate for controlling blood glucose levels in the insulin-resistant patient, several of these classes have been shown to reach toxic levels, thereby causing severe adverse effects. Biguanides, for example, accounted for 40 percent of the 10,000+ cases, as did sulfonylureas; a majority of which were seen in children.\textsuperscript{2,3}

Mechanism

As there are several classes of oral hypoglycemics, it is important to make distinctions by which their mechanisms work so that toxic levels can be more readily identified and treated. Sulfonylureas work by lowering potassium channel permeability in pancreatic beta cells, leading to release of intracellular calcium and release of insulin-containing granules. The result is a lowered threshold at which insulin will be secreted in the presence of glucose.\textsuperscript{7} It should be noted that the second generation sulfonylureas, including glyburide, glipizide, and glimepiride, have a shorter half-life (t1/2) and duration of action (DOA).\textsuperscript{2} Meglitinides work similarly in lowering the potassium channel permeability allowing for intracellular calcium to depolarize pancreatic beta cells. By stimulating the Peroxisome Proliferator Activated Receptor-gamma (PPAR-gamma) in adipose, skeletal muscle, and liver tissue, thiazolidinediones promote the expression of glucose controlling genes in the presence of insulin.\textsuperscript{9} In order to increase insulin sensitivity, biguanides will increase the ability to metabolize glucose, and decrease glyco genolysis, the breakdown of glycogen to form glucose.\textsuperscript{10} Alpha-glucosidase inhibitors will slow the enzymatic breakdown of carbohydrates, thereby lowering the rise in post-prandial blood glucose levels. By this process, glycosylated hemoglobin will be decreased.\textsuperscript{11}

Presenting Symptoms of Toxicity

Upon over-ingestion of oral hypoglycemics, patients will tend...
to have similar presentations, yet the specific drug class will be distinguishable upon the presence of unique symptoms. As could be expected, patient presentation is associated with a hyperinsulinemic/hypoglycemic state. In sulfonylurea toxicity, for example, it is common to see neuroglycopenia (glucose deficiency in the brain), coma and seizures, all associated with low glucose levels. Additionally, counter-regulatory hormone effects in response to the low glucose may induce diaphoresis and tachycardia. An acute state may occur in as little as one to eight hours, where a chronic toxicity may be delayed over several days. Meglitinides will present similarly to sulfonylureas, however, they are associated with a quicker onset of action (30 minutes versus one to eight hours) in an acute situation.

Patients with increased levels of thiazolidinediones will show no acute symptoms of toxicity, as they are dependent on the presence of insulin to exert their effects. In a chronic overdose, there would be an elevation of transaminases as well as alkaline phosphatase levels, indicating hepatic toxicity. Also associated with thiazolidinediones is an increased prothrombin time (PT) and international normalized ratio (INR), in addition to the expected hypoglycemic sequelae such as bradycardia, coma and hypotension.

Biguanides are unique in that they have the potential to cause lactic acidosis. It is common for patients with overdoses (or even as side effects in normal doses) to present with gastrointestinal (GI) discomfort, abdominal pain, nausea, vomiting and diarrhea. Alongside tachypnea, hypotension, hypothermia and confusion (commonly associated with hypoglycemia), it is possible to see renal failure and cardiovascular effects such as ventricular arrhythmias and vascular resistance with biguanides.

Diagnosis and Treatment

While no single test may be used to diagnose a patient presenting with oral hypoglycemic toxicity, a combination of subjective and objective information may be used to assess an individual’s status. There are many common presenting symptoms such as hypoglycemia, and some distinct tests that set drug classes apart. For example, liver function tests may be appropriate for suspected thiazolidinedione toxicity, or arterial blood gas levels in the instance of biguanides. Timeline may also be a factor in determining the class of drug, whether the onset was acute such as with some sulfonylureas, or chronic, which is more commonly associated with thiazolidinediones.

In treating the sulfonylurea and meglitinide classes, it is important to first give the patient quickly metabolized carbohydrates in the form of oral glucose or intravenous (IV) dextrose. A 50 mL bolus of 50 percent dextrose (DS50W) and dextrose containing IV fluids should be administered. The possibility for recurrent hypoglycemia exists in which the pancreas will release insulin in response to the IV dextrose. Upon refractory hypoglycemia, use of alternative therapy is required. The second option for sulfonylurea-induced hypoglycemia is octreotide, a somatostatin analog that inhibits glucagon and insulin secretion. By binding to somatostatin-2 receptors on pancreatic beta cells, it inhibits G-protein coupled voltage gated calcium channels from being opened. This inhibition of calcium influx will stop further insulin release by pancreatic beta cells. Octreotide is U.S. Food and Drug Administration (FDA) approved for the treatment of various endocrine related disease states such as acromegaly and pancreatic tumors; however, it has not been FDA approved as an antidote for sulfonylurea toxicity. Subcutaneous and intravenous routes of administration have equivalent bioavailability with peak effects occurring after 30 minutes. Adult dosing of octreotide ranges from 50 to 100 mcg subcutaneously every six to 12 hours, while pediatric dosing requires 1 to 2 mcg/kg up to 50 mcg every six to 12 hours. Glucagon may also be used for the treatment of sulfonylurea overdose, as it will promote the breakdown of glycogen and synthesis of glucose to combat low glucose levels. Glucagon, however, may also influence the release of insulin. Studies were not found to provide evidence of glucagon or octreotide as effective treatment options in meglitinide overdose. Activated charcoal will bind to meglitinide entities and is most effective early on in treatment.

In the instance of lactic acidosis with excess biguanide ingestion, the primary goal in treating the patient is acid-base restoration, which can be achieved with the use of sodium bicarbonate (1-2 mEq/kg). Activated charcoal may be administered to the patient, even late in an overdose, as biguanides will still be present in the gastrointestinal tract. In an emergency situation where renal function is critically impaired, hemodialysis may be initiated alongside sodium bicarbonate.

Thiazolidinediones, which are known to cause hepatic toxicity, are most appropriately treated with drug discontinuation. Neither pioglitazone or rosiglitazone were found to be dialyzable through either conventional (coefficient of ultrafiltration <8 mL/hour/mm), high permeability (coefficient of ultrafiltration >8 mL/hour/mm) or peritoneal dialysis.

Atypical Antipsychotics

Epidemiology

Atypical antipsychotic medications, including clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole, have become widely popular in treating schizophrenia and related psychiatric disorders. These drugs have a more favorable adverse effect profile compared to the traditional antipsychotics, contributing to their preference over other medications. However, overdose of antipsychotic medications is common, and in rare cases even fatal. From 2001 to 2005, 156,431 ingestions were reported to the Toxics Exposure Surveillance System (TESS), an organization maintained by the American Association of Poison Control Centers. Of the 156,431 cases reported, 8,894 had major effect outcomes and 403 resulted in death. Total fatalities to date due to atypical antipsychotic drug overdose are unknown.

Mechanism

Atypical antipsychotic medications are tricyclic dibenzoazepines that have unique receptor binding affinities and more favorable side effect profiles. The atypical agents are...
defined clinically as having minimal or no extrapyramidal symptoms at appropriate therapeutic doses and have less potential to cause tardive dyskinesias and elevation of serum prolactin concentrations. Atypical antipsychotics are dopamine D2 receptor antagonists and serotonin 5HT2A receptor antagonists. The decreased incidence of extrapyramidal side effects is attributed to the decreased affinity of the atypical antipsychotics to the D2 receptor. The “negative” symptoms of schizophrenia, including avolition, anhedonia, alogia and social withdrawal, are alleviated due to the drugs’ 5HT2A antagonistic activity. However, aripiprazole differs from other atypical antipsychotics because it is a partial agonist at the D2 and 5HT1A receptors and an antagonist at the 5HT2A receptors. Typical side effects that would be expected of these drugs include orthostatic hypotension due to α-adrenergic receptor blockage, sedation, sinus tachycardia and urinary retention (associated with clozapine, olanzapine, quetiapine).

Presenting Symptoms of Toxicity
Toxic doses in patients are highly variable because an overdose may occur at therapeutic or supratherapeutic doses. The most serious presenting symptoms involve the central nervous system (CNS) and cardiovascular system. A patient may present with pronounced sedation, most common with clozapine and quetiapine, due to blockade of CNS histamine H1 receptors. Tachycardia, mild hypotension and QT prolongation may also be present. Another serious and potentially fatal symptom of overdose is neuroleptic malignant syndrome (NMS) which is characterized by hyperthermia, autonomic instability, neuromuscular rigidity and altered mental status. Patients will most likely seem agitated, have muscular rigidity and may present with additional extrapyramidal effects such as Bradykinesia and tremor. Lastly, antimuscarinic delirium may also be present in toxicity due to antagonism of central and peripheral muscarinic receptors. Antimuscarinic delirium is most commonly seen with clozapine, olanzapine and quetiapine, and less often seen with risperidone, ziprasidone and aripiprazole. Presenting symptoms of antimuscarinic delirium that may suggest overdose include: hyperthermia, tachycardia, blurred vision, flushed dry skin, absent bowel sounds, urinary retention, agitation, hallucinations, mumbling speech and repetitive picking behavior.

Diagnosis and Treatment
Diagnosing an overdose caused by atypical antipsychotics is primarily supported by gathering information in the patient’s clinical history, physical examination and presenting symptoms. Obtaining serum concentrations of antipsychotics is not helpful in guiding therapy because data listing toxic serum concentrations are not widely available and the concentrations are not definitively correlated with clinical signs and symptoms. Routine urine screens of commonly abused drugs do not detect antipsychotics and therefore are not helpful in managing toxic cases. Co-ingestion of other medications is common in overdose, especially with other psychotropic agents such as antidepressants, sedatives, hypnotics, anticholinergics, valproic acid and lithium. Co-ingestion of nonprescription analgesics such as acetaminophen and aspirin are also common. Obtaining a serum concentration of acetaminophen and salicylates should be considered in all toxic cases.

Supportive therapy is the cornerstone of treatment for patients with antipsychotic overdose. Use of supplemental oxygen in hypoxic cases and administration of thiamine and parenteral dextrose in altered mental status patients are typical first-line therapies in managing overdoses. All patients who are symptomatic should be continuously monitored for cardiac abnormalities and have an electrocardiogram (ECG), particularly focusing on QT prolongation. Moreover, serum electrolytes should be monitored and corrected, as hypokalemia and hypomagnesemia could exacerbate QT dysrhythmias. Hypotension due to peripheral alpha 1-blockage can be corrected using intravenous fluids. If required, vasopressors of choice include alpha-agonists, norepinephrine or phenylephrine.

Gastrointestinal decontamination procedures are rarely necessary with antipsychotic overdoses. Activated charcoal (1 g/kg by mouth or nasogastric tube) can be considered in a large or multi-drug overdose within an hour of ingestion as long as the patient does not present with sedation or vomiting. While the administration of activated charcoal is time sensitive, the antimuscarinic effects and slowed gastric emptying caused by the antipsychotic may improve the beneficial effects of activated charcoal.

Pronounced anticholinergic symptoms are common with atypical antipsychotics. The cholinesterase inhibitor physostigmine has been used successfully in overdosed patients, particularly in improving agitated delirium. Physostigmine should be given in 0.5 mg increments every three to five minutes under close patient observation. Other cholinesterase inhibitors such as edrophonium, neostigmine and pyridostigmine should not be used to improve anticholinergic delirium because these drugs do not cross the blood-brain barrier.

Beta-Blockers and Calcium Channel Blockers

Epidemiology
Beta-blockers (BB) and calcium channel blockers (CCB) are used to treat various medical conditions such as hypertension, angina pectoris, supraventricular tachycardias, tremors, anxiety and others. According to the American Association of Poison Control’s 2007 records, 10,084 exposures to CCBs were reported, of which 435 were classified as moderate to major toxicity and 17 exposures resulted in death. The National Poison Data System (NPDS) reported nearly 20,000 exposures to BBs in 2007, of which 200 to 400 cases were classified as major toxic events with over 40 deaths. Interestingly, propranolol accounts for a majority of self-induced poisonings, which may be attributed to its use in treating anxiety, stress and migraine patients.

Mechanism
Although BBs and CCBs have differing mechanisms of action, both are involved in interfering with calcium flux across cell membranes. BBs are β-blockers, which inhibit the sympathetic nervous system, causing a decrease in cardiac output. This decrease in output is due to a decrease in heart rate and contractility, as well as a decrease in peripheral vasodilation. CCBs, on the other hand, are calcium channel blockers, which prevent calcium from entering the muscle cell. This decrease in calcium results in decreased muscle contractility, which leads to decreased cardiac output. Both of these mechanisms can lead to hypotension, bradycardia, and decreased cardiac output, which can be life-threatening in overdose cases.

Toxic doses of BBs can result in hypotension, bradycardia, and decreased cardiac output. In overdose cases, this can lead to hypotension, bradycardia, and decreased cardiac output. In overdose cases, this can lead to hypotension, bradycardia, and decreased cardiac output. In overdose cases, this can lead to hypotension, bradycardia, and decreased cardiac output. In overdose cases, this can lead to hypotension, bradycardia, and decreased cardiac output. In overdose cases, this can lead to hypotension, bradycardia, and decreased cardiac output.
membranes. Cardiovascular function is dependent on calcium flow across cell membranes to regulate cardiac automaticity, myocardial conduction and contraction, vascular tone and insulin secretion.

Beta-blockers selectively antagonize β-adrenergic receptors that are linked to Gs proteins. Three subtypes of the β-receptor are known: β₁-receptors regulate myocardial tissue and effect rate of contraction, β₂-receptors regulate smooth muscle tone and influence vascular and bronchiolar relaxation and β₃-receptors are thought to effect lipolysis with some influence on cardiac inotropy. Under normal conditions, these Gs proteins stimulate the increase of intracellular cyclic adenosine monophosphate (cAMP) with subsequent increase of calcium flow through L-type calcium channels and release of calcium from the sarcoplasmic reticulum. The increase in intracellular calcium is directly proportional to the overall strength of contraction brought on by the interaction between actin and myosin. Beta-blockers competitively inhibit β-receptors, therefore indirectly decreasing cAMP production and intracellular calcium levels. This mechanism results in decreased cardiac automaticity, slowed conduction and decreased contractility. Over 15 BBs are on the market today, many of which have variable selectivity for β-receptor subtypes and fewer which have α-receptor antagonistic activity, also referred to as intrinsic sympathomimetic activity. Other properties of individual BBs that are important to note in toxic cases are the lipid solubility and sodium channel blocking activity. Highly lipophilic agents, such as propranolol, can cross the blood-brain barrier resulting in CNS effects.

Calcium channel blockers have the same overall pharmacological result as beta-blockers with a slight difference in mechanism. CCBs directly inhibit calcium influx by blocking voltage-gated L-type calcium channels located in myocardial cells, smooth muscle cells and β-islet cells of the pancreas. Two types of CCBs are known and exhibit different selectivity for cardiac versus vascular channels. The dihydropyridine (DHP) CCBs, which include amlodipine and nifedipine, preferentially act on peripheral vasculature. Antagonism of calcium channels in the peripheral vasculature results in decreased coronary vascular resistance, increase in coronary blood flow and overall vasodilation. Verapamil and diltiazem make up the non-dihydropyridine (Non-DHP) CCBs that are somewhat less selective and target both cardiac tissue and peripheral vasculature. The results of the non-dihydropyridines acting in cardiac tissue include decreased nodal conduction and decreased myocardial contractility. Moreover, decreased insulin secretion is an outcome of CCB activity in the pancreas.

Presenting Symptoms of Toxicity
Patients experiencing toxic doses of either BBs or CCBs may present with symptoms within two to three hours of ingestion. Immediate-release preparations develop toxicity within six hours and toxicity from sustained-released products may be delayed for six to 12 hours. In general, toxicities usually present as an extension of the drug’s therapeutic effects. Specifically, bradycardia and hypotension caused by myocardial depression and peripheral vasodilation are expected. Early or mild symptoms may include dizziness, fatigue and lightheadedness that may manifest as lethargy and altered mental status. Common ECG findings during BB toxicities are first-degree atrioventricular (AV) block and interventricular conduction delays; ECG findings for CCB toxicities are sinus bradycardia, AV blocks, complete heart block, junctional rhythm and QT prolongations.

While the clinical manifestations for BB and CCB overdose are similar, there are subtle differences that may suggest poisoning in one class over the other. Hyperglycemia is expected to present more with CCBs, particularly with serious verapamil, diltiazem and DHP overdoses, whereas hypoglycemia is common in BB toxicity. Mild hypokalemia and hypocalcemia have been reported in CCB overdose, but are not reliable differentiating factors. CCB toxicity can lead to hypoperfusion and end-organ ischemic complications such as non-cardiogenic pulmonary edema, seizures, myocardial infarction and renal failure. Beta-blocker toxicities can also have dangerous complications such as rhabdomyolysis, renal failure, seizures and bowel infarction.

Diagnosis and Treatment
Diagnosing toxicities due to BBs and CCBs is primarily supported by clinical manifestations, continuous cardiac monitoring with an ECG and serum glucose concentrations. While obtaining serum glucose concentrations is not definitively diagnostic, this value may warrant further treatment. In reported cases, patients who required vasopressors, a pacemaker or who died of overdose had an initial mean serum glucose concentration of 188 mg/dL compared to an average of 122 mg/dL in those not requiring intervention. These findings may be useful in determining the initial severity of toxicity.

Managing BB and CCB overdoses can be accomplished in a similar manner, as their mechanisms are physiologically comparable. Pharmacological therapies will be discussed in further detail in the following paragraphs. When toxicity is suspected through clinical manifestations, an ECG should be obtained and repeated every one to two hours, along with attention to airway, breathing and circulation. Supplement oxygen as clinically necessary and obtain intravenous access. Initial resuscitation fluid bolus with 10 to 20 mL/kg of intravenous crystalloids, likely normal saline, is recommended for hypotensive patients, however be aware that poisoning may produce drug-induced inotropic failure, making fluid overload a concern. Gastrointestinal decontamination is recommended to prevent delayed cardiovascular toxicity, especially with CCBs. Multiple-dose activated charcoal (MDAC) is recommended ideally within one hour of ingestion at an initial dose of 1 g/kg followed by 0.5 g/kg if the patient shows signs of continuing absorption. Whole-bowel irrigation (WBI) should be used in the presence of suspected overdose with sustained-release CCBs. Whole-bowel irrigation with polyethylene glycol solution at 1 to 2 L/h orally or via nasogastric tube is recommended and should be continued until the rectal effluent is clear.
Pharmacological Treatments

Atropine
Atropine is an initial treatment of choice to be administered in patients with symptomatic bradycardia. Although atropine was ineffective in improving heart rate in clinical cases of CCB overdoses, atropine should still be considered based on its availability and familiarity. Doses can be administered at 0.5 to 1 mg IV every two or three minutes up to a maximum dose of 3 mg. In severely poisoned patients, treatment failure with atropine is expected, however initial treatment with calcium may improve the efficacy of atropine.

Catecholamines
Catecholamines are administered to act as agonists at \( \beta \)-adrenergic receptors in the myocardium or at \( \alpha \)-adrenergic receptors in the peripheral vascular smooth muscle in order to improve heart rate, contractility and peripheral vasoconstriction. However, the effects of catecholamines on \( \beta \)-adrenergic receptors may be blunted due to the excessive \( \beta \)-receptor blockade from the drug overdose. No single agent has been proven to be consistently effective in all clinical cases due to the variability of the patient and involved receptors. Epinephrine has shown to improve heart rate and blood pressure the most and is a reasonable choice for either a BB or CCB overdose. Dopamine and norepinephrine are also logical choices; especially in CCB toxicities. Using a combination of inotropes and vasopressors will most likely be necessary.

Calcium
Calcium is a logical treatment option for BB and CCB toxicity with the intention of increasing extracellular calcium, allowing calcium influx through unblocked L-type channels. Calcium ions can correct the negative inotropy, delayed conduction, and hypotension in poisoned patients, but have a limited effect on heart rate. Ideal doses of calcium are not yet established, but the attention and selection of a specific calcium salt is critical for dosing. Calcium chloride contains three times the amount of elemental calcium as calcium gluconate and is therefore preferred, although there is no difference in efficacy. Literature suggests initial intravenous infusion of approximately 13 to 25 mEq of calcium over five minutes, which equates to 10 to 20 mL of 10 percent calcium chloride or 30 to 60 mL of 10 percent calcium gluconate. The initial infusion can be followed by either repeat boluses every 15 to 20 minutes up to three or four doses or a continuous infusion of 0.5 mEq/kg/hr of calcium. It is important to note that calcium chloride has a high potential to cause tissue damage if extravasated, therefore it is best if administered through a central venous catheter.

Glucagon
Glucagon is the therapy of choice in BB overdose because it has both inotropic and chronotropic effects independent of activating \( \beta \)-adrenergic receptors. Ideal doses of glucagon are not yet established and maximum doses are undefined. An appropriate starting dose is a bolus of 5 to 10 mg (150 mcg/kg) over one to two minutes followed by a continuous infusion of 2 to 10 mg/hour once a response occurs. The glucagon infusion could also be started at the "response dose," which means the hourly infusion rate is set equal to the initial cumulative dose required to obtain a response. Because nausea and vomiting can occur with bolus doses of glucagon over 50 mcg/kg, airway protection is necessary to prevent aspiration. Hyperglycemia and mild hypocalcemia can also be expected and should be treated appropriately.

Hyperinsulinemia Euglycemia
Hyperinsulinemia euglycemia (HIE) therapy has become particularly more prominent in the treatment of CCB toxicity, but is also clinically used in BB overdose. Insulin facilitating myocardial utilization of carbohydrates is the foundation for the theory behind using insulin in treating BB and CCB overdose. Under healthy conditions, myocardial tissue relies on free fatty acids to fuel its metabolic needs. Drug poisoning shifts its need to be more carbohydrate dependent. Toxic levels of BBs and CCBs also inhibit calcium-mediated insulin secretion from the \( \beta \)-islet cells in the pancreas, therefore myocardial cells become dependent upon concentration gradients for glucose uptake rather than insulin-mediated active transport. Studies involving verapamil toxicity showed improved glucose uptake with insulin administration and consequently improved contractility. Again, ideal doses have not been established but typical therapy begins with a bolus of 1 unit/kg of regular human insulin with 25 to 50 mL of DSOW IV, followed by insulin infusion 1 units/kg/hr and dextrose infusion at 0.5 g/kg/hr. Glucose should be monitored every 30 minutes for the first four hours and titrated to maintain euglycemia. A response to HIE therapy may be delayed for 15 to 60 minutes. It is also important to monitor glucose and electrolyte levels for several hours after insulin is discontinued.

Phosphodiesterase Inhibitors
Phosphodiesterase inhibitors (PDIs) such as amrinone and milrinone are typically used as second-line agents in BB and CCB toxicity. Phosphodiesterase inhibitors inhibit the breakdown of cAMP by phosphodiesterase, thereby increasing cAMP concentrations, increasing intracellular calcium and improving inotropy. Case reports suggest an initial bolus dose of 1 mg/kg of amrinone or 2 minutes followed by a continuous infusion of 5 to 20 mg/kg/min.

Phosphodiesterase inhibitors have been clinically successful when used in combination with another inotrope, such as glucagon. Glucagon stimulates cAMP production while PDIs inhibit its breakdown, increasing the overall effects of cAMP. However, PDIs nonselectively inhibit phosphodiesterase in the vascular smooth muscle, causing smooth muscle relaxation, peripheral vasodilation and hypotension. The nonselective behavior of PDIs makes it a second-line agent and should only be used in patients who have hemodynamic monitoring, as the additive hypotension could be dangerous in BB and CCB poisoning.

Methylene Blue
Methylene blue (MB) is an experimental antidote for refractory vasodilatory shock from dihydropyridine overdoses, particularly amiodipine. Methylene blue is thought to interfere with guanylate cyclase activity and endothelial nitric
oxide synthase activity, preventing the cGMP production and vasodilation effects of amiodipine.\textsuperscript{23,24} Literature that supports the use of MB in refractory vasodilatory shock is limited to retrospective case reports.\textsuperscript{23} Patients in two case reports were administered MB 14 and 16 hours post ingestion. They received 2 mg/kg IV of MB over 20 minutes followed by 1 mg/kg/hr after not responding to normal saline, calcium gluconate, glucagon, dopamine, norepinephrine and high-dose insulin euglycemia therapy.\textsuperscript{23,24} One hour after MB administration, the case patients responded with an elevation in blood pressure and heart rate.\textsuperscript{23,24} Clinically, methylene blue may be a newer option for antidotal treatment of vasodilatory shock from dihydropyridine overdoses, however the literature is limited to use in amiodipine overdoses and no ideal doses of MB have been established.

**Digoxin**

**Epidemiology**

An estimated 4 to 5 percent of digoxin users per year experience toxicity.\textsuperscript{25} In 2011 alone, there were 2,513 reported exposures to cardiac glycosides resulting in toxicity. The majority of cases were the result of an adverse event with prescribed use of a cardiac glycoside. Of the reported exposures, the majority of cases were classified as being moderately severe in nature, with 27 cases resulting in death.\textsuperscript{6} Each of these incidents is estimated to have cost the U.S. health care system between $1,500 and $6,500.\textsuperscript{25}

**Mechanism**

Cardiac glycosides as a class exhibit their function by inhibiting the Na\textsuperscript{+}/K\textsuperscript{+} ATPase in myocytes. Pump inhibition will cause an increase in sodium concentration within the cell.\textsuperscript{26,27} This results in an increase in the resting membrane potential of the myocyte, allowing voltage-gated calcium channels to open and triggering calcium release from the sarcoplasmic reticulum.\textsuperscript{26} Additionally, the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchange pump will be affected by the change in sodium’s electrochemical gradient, thus inhibiting its ability to drive calcium from the cell. The overall increase in intracellular calcium concentration results in positive inotropy.\textsuperscript{27}

In a toxic situation, the high sodium levels can cause phase IV depolarization to lengthen and increase the resting membrane potential. This allows cardiac cells to fire off their own action potential, and may lead to the development of arrhythmias.\textsuperscript{28}

**Presenting Symptoms of Toxicity**

In addition to heart arrhythmias, toxic effects may be observed in other organs throughout the body due to the presence of Na\textsuperscript{+}/K\textsuperscript{+} ATPase pumps in a multitude of cells. Symptoms caused by digoxin toxicity include gastrointestinal issues, such as nausea, vomiting, and anorexia, and neurological symptoms, including confusion, disorientation, lethargy, delirium, weakness, and vision disturbances.\textsuperscript{25,26,28} Chronic toxicity is typically observed in practice.\textsuperscript{6} These patients more frequently exhibit neurological symptoms than those suffering from acute overexposure, who commonly demonstrate the gastrointestinal side effects. In either situation, an ECG, may illustrate extrasystoles, ST depression, and minor degrees of AV node block, among other issues.\textsuperscript{28}

**Diagnosis and Treatment**

It is important for pharmacists to be able to recognize and properly treat patients that are exhibiting symptoms of digoxin toxicity, as treatment should be provided as soon as possible. Although acute cases of toxicity may occur, in which a patient may ingest excessive amounts of digoxin at one time, most patients with digoxin toxicity experience chronic toxicity. In this instance, adverse events are exhibited after multiple ingestions of the medication, during which the digoxin accumulates as a result of impaired drug clearance. As such, there is a gradual increase in serum digoxin concentration until toxic levels are achieved. Thus, serum digoxin levels may be beneficial, but should be obtained after six hours of ingestion to avoid misleading results in cases of acute ingestion.\textsuperscript{26} If the overdose is known to be acute and has occurred within two hours, cleansing the gastrointestinal system through the use of multiple doses of activated charcoal may be a valid option.\textsuperscript{26,28} Gastric lavage should be utilized with care, as it may worsen cases of bradycardia. Additionally, if a patient is experiencing hypokalemia, this condition should be corrected.\textsuperscript{28}

Treatment options for the patient’s arrhythmia will be dependent upon how the patient is displaying, so this must be treated on an individual basis.\textsuperscript{26} High levels of potassium will hinder digoxin binding to the Na\textsuperscript{+}/K\textsuperscript{+} ATPase, and therefore may be useful in treating mild cases of overexposure.\textsuperscript{26,28} It should also be noted that hyperkalemia can be problematic to the patient’s health, and should be monitored.\textsuperscript{28}

First-line therapy, when available, is Digoxin-Fab. This medication is a highly utilized treatment method that functions as a specific digoxin-binding antibody, thus decreasing the amount of free digoxin to bind to the Na\textsuperscript{+}/K\textsuperscript{+} ATPase. Digoxin-Fab is indicated in both acute and chronic toxic emergencies.\textsuperscript{29} The onset of action is reported to occur in less than 30 minutes.\textsuperscript{29} A 40 mg vial of Digoxin-Fab will bind approximately 0.5 mg of ingested digoxin.\textsuperscript{25} Therefore, the required dose of Digoxin-Fab is dictated by the amount of consumed digoxin that must be nullified.\textsuperscript{28} Health care professionals should remember that any time this drug is utilized, there is the potential of developing a severe immunological reaction to the administered antibodies. Immune responses to the antidote should be closely monitored.\textsuperscript{30}

In an acute crisis where an unknown amount of digoxin has been ingested, 20 vials are typically sufficient for treatment. They may be administered either all at once as a single dose or divided into two equal doses. In the case of dividing into two equal doses, one dose is administered and the patient’s response is monitored to determine if the other half is required.

In an acute situation in which the amount of consumed digoxin is known, the corresponding dose of Digoxin-Fab can be calculated. Initially, the total body load of consumed digoxin should be determined using one of the following equations, depending upon the prepared formulation of digoxin:
Once the value for total body load has been found, the number of vials of Digoxin-Fab that are necessary can be calculated as follows:

\[
\text{Digoxin-Fab required for treatment (mg) = Total body load (mg)} / 0.5
\]

\[
\text{Vials of Digoxin-Fab to be used = Digoxin-Fab required for treatment (mg) / 40 mg/vial}
\]

In this manner, the math can quickly be completed to determine the appropriate way to treat an overdose patient. The pharmacist must utilize care in these situations, however, due to the possibility of unreliable patient accounts regarding the amount of drug ingested.

In a situation involving chronic overexposure, six vials is usually adequate to treat a patient. Calcium is typically contraindicated in patients suffering from digoxin toxicity, because an excess of calcium can throw the heart into a non-contractile state as a result of overstimulation. This is sometimes known as a "stone heart" state. Despite this, calcium is sometimes desired in the treatment regimen to counteract the patient's hyperkalemia. In a recent retrospective observational study conducted by Levine and colleagues, patient outcomes were evaluated in cases of digoxin toxicity in which calcium treatment was utilized. Overall, all mortality between both those who received calcium and those who did not were similar. These findings suggest that calcium may not be harmful in digoxin overdose situations, and that the health care practitioner must use professional judgment when considering calcium as a treatment option to combat hyperkalemia.

Supportive care should be provided for the patient in addition to one or more of the above treatment methods. This will provide the patient with the best possible odds of surviving the digoxin overdose with minimal lasting effects.

**Role for Pharmacists**

Toxicity can be the result of acute or chronic exposure, and may be either intentional or unintentional. In any scenario, pharmacists play a vital role in the health care team by helping to select, properly dose and oversee drug treatments. This becomes especially important in many of the previously listed cases, in which treatment strategies may include multiple drugs and may require monitoring various parameters in order to properly care for the patient.

**References**


**Medication Overdoses in the Emergency Department**

**Total body load (mg) = Total amount of digoxin capsules consumed (mg)**

**Total body load (mg) = Total amount of digoxin tablets consumed (mg) x 0.8**

**Emergency Medicine**
com/lco/action/doc/retrieve/docid/patch_f/6746.

30. Bosse GM, Pope MM. Recurrent digoxin overdose and treatment with
85.
Assessment Questions

1. Pronounced anticholinergic symptoms are common with atypical antipsychotic toxicity. What intervention can be used to manage these symptoms, especially agitated delirium?
   A. Physostigmine
   B. Edrophonium
   C. Neostigmine
   D. Pyridostigmine

2. How is an atypical antipsychotic overdose primarily diagnosed?
   A. By obtaining serum concentrations of the drug
   B. Collecting and analyzing patient's clinical history, physical examination, and presenting symptoms
   C. Conducting urine screens
   D. Monitoring changes in the ECG

3. A patient suffering from an atypical antipsychotic overdose typically presents with symptoms involving what system(s)?
   A. Cardiovascular
   B. Gastrointestinal
   C. Central nervous system
   D. A & C
   E. All of the above

4. What is the therapy of choice in treating beta-blocker toxicity?
   A. Atropine
   B. Glucagon
   C. Calcium
   D. Catecholamines

5. What is unique about the presentation of biguanide toxicity compared to other oral hypoglycemics?
   A. Elevated transaminases and alkaline phosphatase
   B. Hypoglycemia
   C. Lactic acidosis
   D. No acute symptom onset

6. Thiazolidinediones do not present with acute symptoms of toxicity because...
   A. They are considered to be a safer class of drugs
   B. They have a very short $t_{1/2}$
   C. They have very low bioavailability upon oral ingestion
   D. They require the presence of insulin to exert their effects

7. In treating the sulfonylurea and meglitinide classes, it is important to first give the patient
   A. Normal saline solution continuous IV
   B. Octreotide 50-100 mcg subcutaneously every 6-12 hours
   C. Quickly metabolized carbohydrates in the form of oral glucose or IV dextrose
   D. Sodium bicarbonate 1-2 mEq/kg

8. In the early stages of _____ toxicity, _____ may be administered because of the medication's tendency to remain in the gastrointestinal tract.
   A. Biguanide, Activated charcoal
   B. Thiazolidinedione, Sodium bicarbonate
   C. Thiazolidinedione, Octreotide
   D. Biguanide, Octreotide

9. JR, a 35-year-old male, arrives in the emergency room complaining of nausea and vomiting. It is determined that he has acute digoxin toxicity. He states that he has swallowed fifteen 25 mg tablets of digoxin. How many vials of Digoxin-Fab will JR likely need for treatment?
   A. 8 vials
   B. 15 vials
   C. 19 vials
   D. 22 vials

10. What ion is associated with “stone heart” state in digoxin toxicity?
    A. Sodium
    B. Potassium
    C. Magnesium
    D. Calcium

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Office of Continuing Education at the Raabe College of Pharmacy
Ohio Northern University
525 South Main Street
Ada, Ohio 45810

Program Title: Medication Overdoses in the Emergency Department: Oral Hypoglycemic Agents, Atypical Antipsychotic Agents, Beta-Blockers, Calcium Channel Blockers, and Digoxin
UAN: 0048-0000-14-197-HOl-P CEUs: 0.1

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid email address.

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<thead>
<tr>
<th>Program Content</th>
<th>Strongly Disagree</th>
<th>Strongly Agree</th>
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<td>The program objectives were clear.</td>
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<td>The program met the stated goals and objectives:</td>
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<td>Explain the pathophysiology behind oral hypoglycemic agents, atypical antipsychotic agents, beta-blockers, calcium channel blockers, and digoxin.</td>
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<td>Describe the presenting symptoms associated with the aforementioned drug classes in an overdose.</td>
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<td>Discuss recommended treatment options in cases of toxicity.</td>
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<td>Describe the pharmacist’s role in treating toxicological emergencies.</td>
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<td>The program met your educational needs.</td>
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Comments/Suggestions for future programs:

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Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C D  
2. A B C D  
3. A B C D E  
4. A B C D  
5. A B C D  
6. A B C D  
7. A B C D  
8. A B C D  
9. A B C D  
10. A B C D

Any questions/comments regarding this continuing education program can be directed to Lauren Hamman, Advanced Administrative Assistant for the Office of Continuing Education (email: l-hamman@onu.edu, phone 419-772-2280).

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