

Delayed Poisoning Emergencies

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Poisoning and overdose can take many forms. In some cases, the toxic material or overdosed drug causes immediate symptoms. In others, exposure to a substance can cause no immediate symptoms, but may lead to an increase in lifetime risk of cancer or blood, liver or lung disease. Yet another possibility is that the drug or chemical may produce mild or no immediate symptoms, but may cause harm within hours or a few days if not treated.

In acute poisoning cases with immediate symptom onset, the need for intervention is usually clear. But in delayed, or subacute, poisoning, an EMT's major contribution will be recognizing the potential for delayed toxicity. Some of these delayed poisoning cases are readily treatable if recognized.

EMS may also be alerted some time after the ingestion or exposure, when the victim presents with symptoms after previously appearing well. These cases can be challenging, since the risk to the patient is not immediately obvious. Knowing that toxicants have potential for delayed toxicity may help during scene survey for evidence of materials involved. Field treatment in the otherwise asymptomatic patient may be minimal. The challenge is recognizing the problem.

General Mechanisms of Delayed-Onset Toxicity

Certain drugs and chemicals are known to cause delayed-onset toxicity, but some common mechanisms can lead to delayed onset of symptoms from other drugs and chemicals as well. Absorption of most drugs occurs across the lining of the small intestine. In order for drugs or chemicals to be absorbed, they must first be dissolved; therefore, the onset of effects from a solid dosage form will be slower than a liquid dosage.

Ingestion of large amounts of solid tablets or capsules containing solid granules can cause aggregates to form into large masses in the stomach, known as concretions or bezoars. Because only the surface of this mass is available to dissolve, the effects may be delayed in onset and may last longer than expected.

Another cause of delayed poisoning syndromes is the nature of the pharmaceutical dosage form: enteric-coated and sustained-release products. Both are quite common dosage formulations for prescription and over-the-counter medications, and are engineered to improve product safety or make dosage administration more convenient. Enteric-coated tablets are designed to dissolve only in the more alkaline small intestine and not in the acidic stomach. Aspirin and iron tablets are common enteric-coated tablets, and both can be irritating to the stomach lining. Enteric coating prevents release of the drug in the stomach where side effects can occur and allows dissolution in the small intestine where absorption occurs. In overdose, absorption of these or other enteric-coated tablets will be delayed until they pass into the small intestine. Symptoms can therefore also be delayed.

Sustained-release products allow for slower absorption of the drug over time and therefore increase the dosing interval. Longer dosing intervals make taking medication more convenient for patients. Because the drug is released slowly, peak drug concentrations in blood and target organs occur later than in immediate-release formulations, and symptom onset may be delayed. Sustained-release products may also predispose an overdose patient to delayed deterioration. A patient may be mildly symptomatic, but quite stable, and suddenly deteriorate later as absorption of the drug continues. This delayed toxicity can occur with the tricyclic

antidepressants in general, but also with the sustained-release forms of a calcium channel blocker. In cases of sustained-release product overdose, delayed-onset toxicity may occur in the 4-6 hour range and up to 24 hours or more post-ingestion, depending on the drug.

Children and High-Risk Substances

Children under age six are in various stages of growth and development. When children are crawling, they can find potentially poisonous products, including drain cleaners, that are stored under the kitchen sink. As soon as they are able to stand, they can reach poisonous products like furniture polish on low-lying tables and find medications in purses or on bedside tables. When they begin climbing, they can reach medicine on countertops or open the medicine cabinet.

Reactions to absorbing a poisonous substance vary, depending on the product and the route of ingestion. Some children may vomit or become drowsy or sluggish. Some of the substance may remain around the child's mouth and teeth. There may be burns around the lips or mouth from corrosive items; or you may be able to smell the product on the child's breath.

Other substances commonly ingested by children under six years of age include cosmetics, cleaning products, analgesics and cold preparations. Prescription and over-the-counter medications accounted for more than one-half percent of pediatric deaths as a result of poisoning from 1995 to 1998. Substances associated with the greatest risk of death include cocaine, anticonvulsants, antidepressants and iron supplements.

Illegal Drugs

When children consume illegal drugs, there are several implications for field management. Ingested heroin may cause deep coma that is unresponsive to usual doses of naloxone. Prolonged airway management, high doses of naloxone and ultimately a continuous naloxone infusion may be necessary. Absorption of large amounts of cocaine can cause initial agitation and psychosis, hyperthermia, seizures, dysrhythmias and profound hypertension, followed by hypotension.

Serious cocaine toxicity can be challenging to manage. Signs and symptoms of cocaine overdose include: agitation, paranoia, bizarre behavior, PVCs, tachycardia, hypertension, hyperthermia and seizures. After assessing airway, breathing and circulation, the next goal is to manage agitation. Once agitation is controlled, the heart rate and blood pressure follow. Larger overdoses that might follow body packing have more profound effects on the central nervous and cardiovascular system. Even here, if the patient is agitated, psychotic or seizing, start with sedation, along with supplemental oxygen and cooling measures. Sedation alone might control other symptoms. If the patient is already unconscious, or if sedation fails to control tachycardia or blood pressure, another approach is needed. A narrow complex tachycardia may not respond to adenosine because the problem is excessive myocardial stimulation (increased automaticity), not reentry. For the same reason, synchronized cardioversion won't convert a narrow complex tachycardia caused by cocaine. If sedation and control of hyperthermia don't work to control tachycardia, further drug therapy or overdrive pacing may be needed in the emergency department. If this narrow complex tachycardia is accompanied by hypotension, IV saline boluses can be tried, as long as there is no significant pulmonary edema.

In less severe cocaine toxicity, the pediatric patient may experience chest pain. This is significant, because cocaine can cause coronary artery vasospasm and myocardial ischemia,

just like a cholesterol plaque or a thrombus. Treat with supplemental oxygen and sublingual nitroglycerin, just like any other suspected myocardial ischemia in the adult patient.

Medications and Vitamins

Medicines can be dangerous if taken in the wrong amount. Children are especially at risk because of their immature body systems and low body weight. Some of the most dangerous medicines for children include those for heart disease, high blood pressure and diabetes. In some cases, a single pill can be fatal.

Some of the more commonly ingested medicines and vitamins by children include heart or blood pressure drugs, tranquilizers, nerve pills, cough and cold medicines, iron, pain relievers, diabetes medicines and children's vitamins.

Iron

Adult-strength iron supplements are extremely dangerous for children; only a few pills can cause bleeding in the stomach. From 1986-1997, poison control centers in the United States received reports of more than 110,000 incidents of children under age six accidentally swallowing iron tablets. Some of the children were hospitalized ; more than 35 died.

Similar to acetaminophen, iron toxicity has a multiphasic syndrome. There are mild early symptoms, a largely asymptomatic period, then the manifestation of multiorgan toxicity. These phases tend not to be very distinct. The tricky thing about iron ingestion, particularly in children, is the apparently nonthreatening dosage form in which iron can appear. Prenatal vitamins and multivitamins with iron are good examples of widely used supplements that can cause iron overdose in children. Prescription forms of iron include Fergon (ferrous gluconate), Feosol and other brand names (ferrous sulfate). The toxicity of these iron supplements depends upon their elemental iron content, which varies from one dosage form to another. Identifying the exact dosage form of iron involved will allow the emergency department to calculate the dose of elemental iron ingested and predict to some extent the potential severity of the ingestion. In general, patients with suspected iron ingestions, especially children, should be transported and carefully evaluated for early signs of shock.

An untreated iron overdose can be quite toxic, especially in children. Within about six hours of ingestion, symptoms of nausea, vomiting, diarrhea, hematemesis (vomiting blood) and melena (black stool) develop. Iron is particularly irritating to the gastrointestinal (GI) tract, so if there are no early GI symptoms after presumed iron ingestion, the dose was probably low enough to avoid serious toxicity later. These early GI symptoms may appear to resolve after 6-24 hours. However, the next phase of untreated iron toxicity is metabolic acidosis, liver failure and coma. If the patient survives this initial insult, a final outcome of untreated iron toxicity is scarring of the damaged stomach lining with pyloric obstruction. These symptom phases are not necessarily distinct and may overlap.

Signs of shock in children may be subtle at first. Less vigorous behavior, tachycardia, tachypnea, delayed capillary refill and dry mucosa are fairly reliable signs of compromised perfusion. Changes in expected behavior for the child's age is the most sensitive sign of early shock. Supplemental oxygen and IV saline boluses of 20 ml/kg are the primary treatment. Although sodium bicarbonate is useful in metabolic acidosis in the field. A calculated bicarbonate dose can be given once blood pH is measured in the emergency department. Iron

overdose (or toxic ingestion in general), then, is one more possibility as a cause of shock in children, along with dehydration, sepsis and occult trauma (like child abuse).

Acetaminophen

Acetaminophen poisoning signs and symptoms are usually delayed. There are two reasons for this delay: The most important is that the drug undergoes metabolism to a toxic product that causes injury once a sufficient amount has been formed. Second is that acetaminophen is readily available over the counter in many single and combination products in an extended-release form.

Acetaminophen usually causes no immediate symptoms following overdose. Co-ingestants, like alcohol or other drugs, may produce symptoms independent of acetaminophen. If untreated, an acetaminophen overdose will cause vague symptoms like nausea, vomiting, anorexia and abdominal pain after about 24-48 hours. These symptoms are return of nausea, vomiting and abdominal pain, jaundice, right upper quadrant abdominal pain, and tenderness and fatigue. Unlike infectious causes of acute hepatitis, like hepatitis A, there is no fever. Once the chemical hepatitis symptoms develop, reversal of the course of liver toxicity is less successful. The liver damage can result in acute liver failure and may require liver transplantation or lead to death. The key to acetaminophen toxicity treatment is early recognition by SAMPLE history, physical evidence at the scene or blood concentration measurement in the emergency department.

If the product containing acetaminophen is not one of the sustained-release forms, the dose sufficient to cause liver injury can be estimated. In general, a single dose of greater than 140 mg/kg of acetaminophen can be hepatotoxic. This is about 9-10 grams in an average-sized adult. After a single overdose, the blood concentration of acetaminophen peaks within a few hours; thus, four hours after the overdose, the blood level can be used to estimate the risk hepatotoxicity and guide further treatment. Treatment for acetaminophen overdose is to supply the body with a sulfur-containing chemical called N-acetylcystine. This chemical combines with the toxic metabolite of acetaminophen to prevent it from interacting with liver cells and causing liver damage, but it is most effective before the liver damage phase begins. It is less effective once liver damage begins. Induced vomiting and gastric lavage are relatively ineffective if initiated later than one-half to one hour after ingestion. There is also the risk of pulmonary aspiration. Orally administered activated charcoal is a safer alternative to vomiting or lavage and will bind the ingested drug in the stomach and small intestine to prevent absorption, A high index of suspicion is important from an EMS perspective. Recognizing the potential of an acetaminophen overdose and the approximate dose will be useful historical information.

Prehospital care includes:

- Stabilize immediate life-threatening conditions and initiate supportive care, including IV fluids, oxygen and cardiac monitor.
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- Administer oral-activated charcoal if the time of ingestion is unknown, the patient ingested extended-relief acetaminophen, or possibility of a drug co-ingestion exists. Oral-activated charcoal avidly adsorbs acetaminophen and should be administered if the patient presents within 1–2 hours of ingestion or later, especially if a GI motility-inhibiting co-ingestant may have been involved.
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- Assess for evidence of other life-threatening co-ingestions. Good SAMPLE history collection and scene size-up are important.

Hypoglycemic Agents

The diabetic patient may take the usual dose of insulin and then forget to eat an adequate amount of food to balance the body's use of glucose. The blood glucose drops, they become symptomatic with altered level of consciousness and require oral or IV glucose to correct the problem. After successful treatment, these patients may prefer not to be transported. In this setting, with a clear history, an otherwise competent and well-informed patient can be safely be left at home. However, when the use or abuse of the oral hypoglycemic drugs cause hypoglycemia, there is the added risk of recurrent profound hypoglycemia. There are several new oral hypoglycemic drugs on the market. These, along with the older drugs, can cause delayed-onset hypoglycemia after ingestion, as well as recurrent hypoglycemia after treatment. This is also true for single tablet ingestion in children. Because of the delay in onset of hypoglycemia and the recurrence of hypoglycemia after treatment, these patients should be transported to the emergency department, where they should be observed for up to 24 hours.

Treatment of hypoglycemia from oral hypoglycemic drug overdose is the same for any other cause: D50W 25 gram IV, or oral glucose if the patient is awake enough to protect his/her airway and tolerate oral liquids. One easy way to judge whether a patient is capable of taking oral liquids is to have the patient sit upright, unsupported, and drink unassisted. If they can go through these motor skills without help, they can probably protect their airway. The IV dose of 25 grams (50 ml) of D50W is the adult dose. In children older than two years, the dose is 1 ml/kg of D50W up to 50 ml.

For accidental overdose or oral hypoglycemic drugs or other causes of hypoglycemia in children younger than two years, the dose has to be modified. D50W is a hypersomolal solution. The osmotic pressure, which is much greater than body fluids, draws water across cell membranes into the blood following intravenous administration of D50W. The problem in very young children, mostly neonates, is that this change in blood osmotic pressure can cause intracranial bleeding. Because of this, the concentration of glucose has to be reduced. So, for children under two years, the D50W is first diluted in half with saline to make D25W. The dose of D25W is 2 ml/kg.

Monoamine Oxidase Inhibitors

Antidepressants like monoamine oxidase inhibitors (MAOI) and tricyclics (TCA) are notorious for delayed onset and delayed deterioration in overdose. The MAOI have many drug-drug interactions and in overdose cause a hyperadrenergic state of hyperthermia, agitation, tachycardia, hypertension, dysrhythmias and seizures similar to cocaine and methamphetamine overdose. The MAOI agents currently available in the U.S. include phenelzine sulfate (Nardil), tranylcypromine sulfate, (Parnate), isocarboxazid (Marplan) and selegiline (specific for the monoamine oxidase-B enzyme), all of which irreversibly bind to monoamine oxidase (MAO). Reversible inhibitors of MAO are available in Europe (e.g brofaromine, cimoxatone, clorgyline, lazabemide, moclobemide). Substances like St. John's wort that may have MAOI-like activity are frequently used for self-treatment of depression. For food and drug interactions, the SAMPLE history must include a careful search for potential offending agents, including over-the-counter preparations.

Ingestion of an MAOI can induce a complex array of hypermetabolic signs that include fever, tachycardia, generalized muscle rigidity, tachypnea, metabolic acidosis, hypoxemia and hypercapnia. Acute overdose usually does not produce a hypertensive crisis, unless the patient provokes the interaction.

Early mild symptoms include irritability, anxiety, flushing and sweating. Moderate symptoms include anxiousness, restlessness, and fever. Severe symptoms may include severe fever, seizures and sleepiness. Late in the course, the patient may become hypotensive and comatose.

MOAIs may have drug interactions with serotonin reuptake inhibitors, several analgesics (particularly meperidine) and tyramine-containing foods. Any drug that releases catecholamines may precipitate life-threatening events in individuals also using MAOIs.

Prehospital care includes stabilization of vital signs, treatment of seizure activity and attention to airway maintenance. If the patient is hyperthermic, decreasing the temperature is imperative. Fluid therapy is of paramount importance, as patients may be significantly dehydrated from hyperthermia. Intravenous benzodiazepines are useful for agitation and seizure control, they also may help control the hypertension. Activated charcoal (Liqui-Char) may be useful for limiting systemic burden of the ingested substance, especially if administered within 1-4 hours of ingestion. For maximum effect, administer within 30 minutes of ingesting the poison.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) cause the overwhelming majority of antidepressant poisoning resulting in morbidity and mortality. Of the newer generation cyclic antidepressants, only amoxipine and maprotiline have strong potential to cause serious morbidity. TCAs produce a wide variety of toxic effects. The most severe toxicity occurs in the cardiovascular system, peripheral nervous system (PNS) and central nervous system (CNS).

TCAs also cause anticholinergic effects. Distinguishing between anticholinergic and hyperadrenergic effects in an acutely ill patient can be difficult. Both cause mental status changes, but anticholinergic effects produce delirium (confusion, hallucinations), while hyperadrenergic effects can cause violent agitation. Both cause papillary dilation (mydriasis), tachycardia and hypertension followed by hypotension and seizures. One difference may be skin moisture. Hyperadrenergic effects can cause marked diaphoresis; anticholinergic effects can cause marked diaphoresis; anticholinergic effects cause dry, red skin. Initial care includes airway management, cooling measures, IV fluid hydration (in the absence of pulmonary edema) and seizure or agitation control with midazolam. Tachycardia may be the first evidence of toxicity in TCA overdose. The tachycardia may begin as narrow complex, then start to widen. The initial management of tachycardia after TCA overdose, especially with a widened QRS, is hyperventilation and/or sodium bicarbonate. One reason this is thought to work is that alkalization of the blood helps clear TCA from the blood by reducing its binding to plasma proteins. The sodium ion specifically helps to reverse the sodium channel blocking effects of TCAs on myocardial cells. As with cocaine dysrhythmias, the dose is 1 mEq/kg.

Cardiovascular toxicity results from direct myocardial depression, cardiac conduction disturbances, effects on peripheral vasomotor tone and changes in the autonomic nervous system. TCAs block norepinephrine reuptake in the CNS and PNS (autonomic ganglia). Initially,

this may result in hypertension and tachycardia; however, with prolonged blockade of reuptake, norepinephrine is depleted from the presynaptic nerve terminal (most norepinephrine released is from a recycled neurotransmitter), which results in refractory hypotension and bradycardia.

Symptoms typically progress rapidly. Onset of signs and symptoms often occurs within two hours following ingestion, and life-threatening effects are almost always evident six hours post-ingestion. Not uncommonly, patients present asymptotically or minimally symptomatic and progress to life threatening cardiovascular and neurological toxicity within one hour.

The ECG is the single most important test for diagnosis and prognostication. In one study, a QRS greater than 0.10 predicted seizures in 34% of patients, and a QRS greater than 0.16 predicted ventricular arrhythmias in 50%. Case reports have described ECGs in TCA toxicity mimicking acute myocardial infarction and the Brugada syndrome.

Patients with suggested TCA ingestion should be immediately transported to the hospital. Rapid, cataclysmic clinical deterioration may occur shortly after overdose.

Environmental Poisonings

Children have physiologic and behavioral characteristics that make them vulnerable to damage from environmental chemicals. Among the characteristics leading to children's sensitivity are their limited diets, dividing cells, differentiating organs and organ systems, slow or absent detoxification mechanisms, long life expectancy with the resulting ability to express damage with delayed consequences, and the severe metabolic demands of growth.

Lead Poisoning

High lead levels in the body can result in problems with the brain, kidneys and bone marrow (soft tissue inside bones). Symptoms of high lead levels can include belly pain, headaches, vomiting, confusion, muscle weakness, hair loss or anemia (low red blood cell count). More than 4% of children in the United States have lead poisoning. Rates of lead poisoning are even higher in large cities and among people with low incomes. Lower levels of lead in the body may still cause problems; having trouble paying attention, behavior problems, learning difficulties and a fall in the intelligence quotient of young children.

Hazardous Materials with Delayed-Onset Toxicity

Hydrofluoric Acid

Hydrofluoric acid is unique among acids for its clinical effects. Unlike bases, acids generally cause a proteinaceous coagulum in skin that limits further penetration unless concentrations are high or contact times are prolonged. Bases liquefy tissue by hydrolyzing the fats in adipose tissue and cell membranes and tend to produce deeper burns for a shorter period of contact. Hydrofluoric acid is unique because of the fluoride ion. There is less coagulation necrosis of skin, and deeper penetration occurs than with other acids. Also, the fluoride ion associates with calcium ions that can cause bone demineralization at the burn site or deplete calcium from blood and cause cardiac dysrhythmias. Hydrofluoric acid toxicity could occur from inhalation of or skin exposure to hydrogen fluoride gas, skin or eye contact with the aqueous acid solution, or potentially from intentional or accidental ingestion of the acid.

Physical evidence of acid exposure to the skin depends upon the concentration. Concentrations greater than 50% cause immediate pain, and victims will know to seek help. Concentrations

below 50% may not cause immediate symptoms, especially concentrations in the range of 20%--25%. These lower concentrations can cause skin burns and even systemic toxicity; but may not produce symptoms for several hours after exposure. Early intervention may reduce the need for difficult medical therapies later. Water decontamination is the first priority. After a thorough water wash, applying a calcium salt in solution or dissolved in a water-soluble gel can help to prevent further absorption of the fluoride ion, which can go on to cause systemic toxicity. The calcium salt used has been calcium gluconate mixed with surgical lubricant. The sooner this can be done, the more likely it will bind up the fluoride ion.

The significance of recognizing the hazard of delayed-onset toxicity from hydrofluoric acid and implementation of early skin decontamination is that it may reduce the need for other more complicated treatments later. Once the fluoride ion has penetrated the skin, calcium gluconate may need to be injected in and around the skin site to prevent further tissue destruction or systemic toxicity. For hand burns, an intra-arterial infusion of calcium may be needed to treat extensive burns. Cardiac dysrhythmias from systemic fluoride toxicity may need treatment with intravenous calcium chloride.

Acetonitrile and Methanol

Industrial chemicals and chemicals used in household products may also present with delayed-onset toxicity. Acetonitrile is used in acrylic nail remover and industrial applications. When ingested or inhaled, one product of acetonitrile metabolism is cyanide. The onset of cyanide toxicity takes several hours following an acute exposure to the liquid or vapor. Clinically, cyanide toxicity will present as metabolic acidosis without hypoxia by pulse oximetry. Early symptoms will reflect tissue hypoxia due to the inability of organs to extract oxygen from the blood. Initially, there may be dyspnea, chest pain, headache or altered mental status. Later, there can be coma, hypotension, and dysrhythmias. Evidence at the scene that acetonitrile is the toxicant will guide treatment for cyanide toxicity, which may not be detected without suspecting it among the many causes of metabolic acidosis and specific laboratory tests.

Delayed onset of methanol toxicity also results from metabolic products. Ethanol and methanol are first metabolized to aldehydes, then to organic acids in the liver, making them another cause of metabolic acidosis. Unlike acetonitrile, methanol causes inebriation, just like ethanol. Other than accidental ingestion, it is the intoxicating effects that may be sought which lead to toxicity later. The end product of methanol metabolism is formic acid. This is responsible for the metabolic acidosis, as well as damage to the optic nerves (which can lead to blindness) and altered mental status.

Summary

The American Association of Poison Control Centers (PCCs) has a nationwide toll-free number for contacting regional poison centers. To be automatically connected to a local poison center, call 800/222-1222. EMS providers should follow local protocols to determine how to contact PCCs, either directly or through on-line medical control. Most experts agree that PCCs are a reliable and current source of information on the assessment and treatment of poisoning emergencies.