# Four Steps to Diagnosing Drug Overdose

Bedside basics can help you determine what was ingested in order to quickly stabilize the patient.

**By Scott Goldstein, DO**

The morning starts as usual, with three patients to see: a 46-year-old with chest pain, a 25-year-old with back pain, and a 27-year-old schizophrenic brought in by friends who believe he may have overdosed but aren't sure what drug he might have taken.

One of the many challenges faced by today's emergency departments is a rising incidence of overdoses, both intentional and accidental, in the population as a whole but especially in schizophrenic patients.[1] Fortunately, there is a way to pursue the suspicion of overdose that's thorough enough to pick up any life-threatening ingestions but efficient enough to save both practitioner and patient time in the emergency department. The predictable actions of drugs on the body fall into six broad classifications—anticholinergic, cholinergic, hallucinogenic, opiate/narcotic, sedative/hypnotic, and sympathomimetic—called toxidromes (Table).[2] Temperature, heart rate, respiratory rate, pulse oximetry, and blood pressure are all clues to a specific toxidrome. Most toxicities from overdosing either an illicit or a prescribed drug can be treated symptomatically under the general guidance of the toxidromes. The caveat is that the picture may be clouded by multiple offending agents that bring different toxidromes into play if the patient has taken drugs from more than one class.

The physician's first task, of course, is to analyze the patient's vital signs for insight into how the body is reacting to whatever pathological process is happening. Almost all toxidromes use the vital signs in evaluating what the patient may have ingested. Once that has been done, there are four phases of testing that should be undertaken to narrow down the possible toxins and ensure that a life-threatening overdose is not about to go untreated. Those phases are the subject of this article.

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## FIRST: TEST BLOOD GLUCOSE

If there is any change in mental status, the first test should be a blood glucose level. This is one of the few times in current medicine when you can treat someone and see a therapeutic change within seconds—possibly avoiding intubation, unnecessary imaging, and days in the ICU. If a patient is obtunded, and the glucose is low, an ampule of dextrose should fix the problem.

Many drugs and substances can lower blood glucose—most obviously, the antidiabetic medications, such as biguanides and sulfonylureas, which have become ubiquitous as more and more people develop diabetes and live longer with the condition. Not only can patients overdose on their own diabetic medications, but their family members may also be at risk.

**>>FAST TRACK<<**

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Alcohol, so often used and abused as self-medication by individuals with psychiatric diagnoses, causes hypoglycemia by dysregulating pancreatic control of insulin release and decreasing glucose production by the liver.

Hypoglycemia has been associated with acetaminophen overdose in a few cases, possibly secondary to liver failure.[3]

## SECOND: GET AN ECG

Like the blood glucose level, the ECG is easily obtainable, readily available, and full of valuable infor-

**TABLE. Toxidromes as a Diagnostic Guide in Suspected Overdose**

| Toxidrome | Signs and symptoms | Vital sign | Classic agents |
|---|---|---|---|
| anticholinergic | delirium, flushed skin, dilated pupils, urinary retention, decreased bowel sounds, memory loss, seizures<br><br>(mnemonic: "hot as a hare, dry as a bone, red as a beet, blind as a bat, mad as a hatter") | tachycardia<br>hyperthermia<br>hypertension | atropine<br>antihistamines<br>scopolamine<br>tricyclic antidepressants |
| cholinergic | confusion, weakness, salivation, lacrimation, urination, defecation, gastrointestinal motility, emesis, diaphoresis, muscle fasciculations, miosis, seizures, "Killer Bs": bradycardia, bronchorrhea, bronchospasm | bradycardia<br>hypothermia<br>tachypnea | organophosphates<br>carbamates |
| hallucinogenic | disorientation, hallucinations, visual illusions, panic reaction, moist skin, hyperactive bowel sounds, seizures | tachycardia<br>tachypnea<br>hypertension | phencyclidine<br>lysergic acid diethylamide<br>cannabis |
| opiate/narcotic | altered mental status, unresponsiveness, miosis, shock, decreased respiration | bradypnea<br>bradycardia<br>hypothermia<br>hypotension | dextromethorphan<br>opiates:<br>morphine<br>propoxyphene |
| sedative/hypnotic | coma, stupor, confusion, sedation, CNS dsyfunction | apnea | ethanol<br>barbiturates<br>benzodiazepines<br>anticonvulsants |
| sympathomimetic | delusions, paranoia, diaphoresis, piloerection, mydriasis, hyperreflexia, seizures, anxiety | tachycardia<br>hypertension<br>hyperthermia | cocaine<br>amphetamines<br>methamphetamine<br>phenylpropanolamine<br>ephedrine<br>pseudoephedrine |

*Source*: Florida Poison Information Center, Jacksonville.[2]

mation for the treating physician about what drug or drugs may have been taken. Keep in mind the normal heart rate (60 to 100 bpm), the normal $QT_c$ (less than 0.45 s for men or 0.42 s for women) and the normal QRS (less than 0.12 s).

One of the main things to watch for is possible overdose with a tricyclic antidepressant (TCA). These drugs have a notoriously narrow therapeutic window and a dangerous potential for severe neurologic and cardiovascular toxicity, including

life-threatening arrhythmias.[4] The ECG can help with ruling TCA toxicity in or out and formulating a treatment plan.

The most common ECG finding in a TCA overdose is sinus tachycardia. If you see evidence of tachycardia and the suspicion for TCA overdose is high, look for additional ECG clues to the use of a TCA, such as a strong rightward axis or terminal R wave in aVR. The latter finding is very sensitive for TCA overdose and signals an urgent need for treatment, because it means that the drug has already affected the cardiac electrical system. Recent studies show that if the terminal R wave is greater than 3 mm, there is a higher risk of seizures.[4,5]

The QRS is another important place to look for electrocardiographic clues to a TCA overdose. Normal QRS is defined for general purposes as less than 0.12 s, but if TCA overdose is a concern, the threshold drops to 0.10 s. Numerous studies have shown that the risks of arrhythmia and seizure increase as the QRS increases, and markedly so once it exceeds 0.16 s, which occurs in about 50% of patients who have a wide QRS associated with TCA overdose.[6,7]

Any of the above abnormalities in a patient suspected of TCA overdose warrants treatment with sodium bicarbonate and admission to the ICU.

Clues to the presence of many potentially deadly cardiac medications can be picked up on the ECG, mostly by looking at the rate. The two most common are beta-blockers and calcium channel blockers—it's hard to go through a shift without seeing a patient on either of these medications. Both slow the heart rate, leading to bradycardia, first-degree heart block and prolonged QT interval. These similarities make it difficult to discern which type of drug is causing the changes, but the combination of hypotension with bradycardia and conduction abnormalities should always raise suspicion for cardiotropic drug overdose. The patient likely needs emergent treatment with either calcium (for hyperkalemia or calcium-channel overdose) or glucagon (for beta-blocker overdose). However, if the agent is unknown, it is always safe to treat symptomatically with atropine and cardiopulmonary support.

The ECG is just one of many screening tools for possible overdose and needs to be used in conjunction with all other tests. For example, a patient with bradycardia and hypoglycemia may have overdosed on a beta-blocker, since calcium channel blockers do not cause hypoglycemia. In contrast, bradycardia with hyperglycemia may signal an overdose of the calcium blocker nifedipine. All the information gathered needs to be used together to formulate a safe and effective plan.

## THIRD: CHECK THE ACETAMINOPHEN LEVEL

The acetaminophen level is not as easy to obtain as the bedside glucose or ECG, but it's very important because acetaminophen can be a silent killer—there is no toxidrome with acute ingestion. It is ubiquitous in today's society and should be considered in all intentional overdoses; liberal testing for it will help save many lives at modest cost.[8] When it is not picked up and treated early, acetaminophen toxicity takes a protracted, painful, and deadly course.

Even though there are no telltale signs, there are "phases" in acetaminophen overdose. The first phase consists of gastrointestinal upset with nausea and vomiting, usually in the first 24 hours. This is the most important phase to consider, since most overdoses and medical clearance cases come to the ED within this time frame.[9] The subsequent phases correlate with liver injury, spanning from right upper quadrant pain to jaundice, vomiting, and frank liver failure.

Always keep the time frame in mind. Acetaminophen has a half-life of four hours; after a toxic ingestion the level usually peaks at four hours.[3] When there is concern for acute acetaminophen toxicity, the level does not need to be tested until four hours have passed since ingestion, but treatment can begin immediately. If you suspect a chronic overdose spanning days to weeks, check the acetaminophen level and liver functions and institute treatment, if necessary, as soon as possible. If you are certain the ingestion is acute, you can plot the level against the Rumack-Matthew nomogram to see if it is in the toxic range, which mandates emergent treatment with acetylcysteine (Mucomyst) and admission.[10]

**>>FAST TRACK<<**

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## FOURTH: LOOK FOR AN ANION GAP

A basic metabolic panel (BMP) can provide valuable clues to the presence and effects of many medications

if you look at the totality of it, even though a single electrolyte or other value may not tell you much by itself. That makes the BMP one of the most effective assessment tools when overdose is suspected. If used well, it can make hours' worth of additional laboratory studies unnecessary.

The first and probably most important function of the BMP in these patients is to reveal an anion gap. If there is an anion gap, there is an acidosis, and if there is an acidosis, the number of possible causes is limited. The most commonly used formula is *sodium – (chloride + bicarbonate [total $CO_2$])*. If the result is greater than 12 to 15 mEq/L, there is an anion gap.[11]

A mnemonic often used in this context is MUDPILES—methanol, uremia, diabetic ketoacidosis, paraldehyde (or propylene glycol or phenformin), iron and/or isoniazid, lactic acid, ethanol, and salicylates—which covers the most likely perpetrators of an anion gap, but is by no means all-encompassing.[12] A positive anion gap can be seen with many drugs, including bromide, iodide, and lithium.[13] Other compounds, such as carbonic anhydrase, lysine, NADP+, or spirolactone, produce a hyperchloremic acidosis with minimal to no gap when overdosed. That is why determining the anion gap is useful in the asymptomatic patient but is not the definitive study of choice in the known overdose.

***Methanol.*** This toxic alcohol is converted into formic acid in the body via the alcohol dehydrogenase pathway, which leads to a buildup of unmeasured anions. If a patient presents early or has ingested only a small amount, there will be no anion gap, which means the diagnosis is based more on history and physical. Most of the physical examination findings are localized to the visual system, ranging from dilated pupils to "snowstorm blindness."

**>>FAST TRACK<<**

**A clinical picture featuring somnolence, vomiting, and abdominal pain may mean DKA rather than overdose.**

If there is high concern for methanol ingestion, you'll want to know the osmolar gap—(the difference between estimated serum osmolarity using the formula *2(Na) + glucose/18 + BUN/2.8 + ethanol/4.6* and the patient's actual, lab-measured serum osmolarity. A gap between these two values of more than 10 to 20 is considered abnormal.[14] Anything that increases serum osmolarity (usually alcohol) is concerning in overdose.

***Uremia.*** The definition of uremia seems to be changing on a regular basis due to advancements in medicine, but it can be basically described as illness accompanying kidney failure that cannot be explained by derangements in extracellular volume, inorganic ion concentrations, or lack of known renal synthetic products. Initially, acidosis develops in uremia as a consequence of the kidney's inability to excrete ammonium and the accumulation of various organic acids. Most commonly, uremia is found in the patient with chronic renal failure and diabetes mellitus. The uremic patient is usually sallow and thin, and presents with nausea and vomiting. One more clue, besides the anion gap, is that uremia is often accompanied by hypocalcemia, due to lower vitamin D levels and high phosphate levels.

***Diabetic ketoacidosis (DKA).*** A clinical picture featuring somnolence, vomiting, and abdominal pain may mean DKA rather than overdose. If it's DKA, the patient will have an anion gap and high glucose on BMP, usually over 200 mg/dL. Maintain a high level of suspicion for DKA, in which mortality is close to 100% without treatment. The combination of hyperglycemia, glycosuria, ketonuria, and a metabolic acidosis should be managed as diabetic ketoacidosis until proven otherwise.

***Paraldehyde.*** Used regularly in the 1960s to treat seizures and agitation, paraldehyde has fallen out of favor as a drug but is still used in resin manufacturing. It is excreted mostly by the lungs, which imparts a characteristic offensive odor to the breath of patients with paraldehyde poisoning. Other symptoms and signs are mild to moderate dehydration, hypotension, Kussmaul respirations, mental-status changes, heme-positive gastrointestinal contents, and pulmonary edema. The elevated anion gap is caused by production of acetic acid and chloracetic acid. Be aware that when the nitroprusside reaction test is used, paraldehyde may cause a false-positive reaction for ketones, leading to a misdiagnosis of another cause of mental status change.

***Isoniazid (INH).*** One of the many drugs used to treat tuberculosis, INH can be a cause of acidosis. Suspect INH overdose when a patient presents in status epilepticus with metabolic acidosis that appears unresponsive to conventional antiseizure medication—although that can be a tricky call, due to the acidosis caused by the seizures themselves. A detailed drug history from the family (don't forget

to ask about medications for other family members, too) and paramedics is often very helpful. The treatment is supportive in most cases, but up to 5 g of vitamin $B_6$ (pyridoxine) can be administered to stop refractory seizures.[15]

***Iron.*** Toxicity from iron is extremely detrimental and more common in children, thanks to the enticing candy-like appearance of some iron pills. It is corrosive to the gastrointestinal tract, leading to symptoms such as nausea and vomiting (with or without blood). On the cellular level, iron overdose impairs oxidative phosphorylation. After an asymptomatic period lasting up to 24 hours, due to the time it takes for the iron to be absorbed and transported to the body tissue, metabolic acidosis and cellular toxicity develop.[16] These patients are usually hypotensive and require aggressive intravenous fluids, critical monitoring and, in some cases, possibly chelation therapy with deferoxamine.

***Lactic acid.*** Type A lactic acidosis, caused by hypoperfusion, cell anoxia and anaerobic metabolism, is seen in many types of overdoses involving drugs of abuse or suicidal intent. Treatment is supportive (intravenous fluids, oxygen) while you identify the offending substance. The suspect list includes biguanides, cocaine, cyanide, niacin, nitroprusside, lactulose, ether, sorbitol, streptozosyn, theophylline and, of course, alcohol, which drives a large share of emergency department visits due to consequences ranging from motor vehicle accidents to violence to liver failure.

When a patient seems to be intoxicated, a good neurologic examination (with or without a CT scan) and observation are all that is needed. Debates abound over alcohol levels and their utility. The reality is that each person metabolizes alcohol differently and a level is just a number, not a sign of intoxication. If someone who is not a baseline alcoholic goes on a drinking binge and presents with an alcohol level of 150 mg/dL, he may be inebriated and need intubation for airway control. But a chronic alcoholic with the same blood-alcohol level will be in complete withdrawal, requiring benzodiazepines.

Most binge drinkers don't take in enough carbohydrates, leading to ketogenesis for energy. The anion gap seen in alcohol intoxication reflects a combination of lactic acidosis and ketosis (predominantly beta-hydroxybutyrate).

***Salicylates.*** Many prescription and nonprescription medications contain salicylates but may not be advertised as such, so accidental overdoses are quite common. The toxic effect of salicylate is multifactorial, involving various metabolic systems. Direct stimulation of the respiratory center increases respiratory rate and carbon dioxide excretion, causing respiratory alkalosis. Salicylates also inhibit the citric acid cycle and interfere with oxidative phosphorylation, leading to hyperpyrexia, increased oxygen consumption and depletion of hepatic glycogen stores. Following the respiratory alkalosis, usually seen early and with mild salicylism, the body goes into metabolic acidosis, due to the dysregulated citric acid cycle and increased oxygen consumption.

The toxic dose of salicylate depends on the timing and duration of ingestion (chronic versus acute). A chronic history is more common in elderly patients, who may take aspirin regularly for coronary artery disease or joint pain. It's important to bear in mind that the signs and symptoms of chronic toxicity, such as change in mental status, low-grade fever, dehydration, and renal dysfunction, can occur with even a mild increase in dosage, are usually subtle, and can be confused with those of various other processes, such as sepsis or pneumonia.[17]

Acute ingestion is defined as a single ingestion of non-enteric-coated acetaminophen within a 24-hour period. The toxic dose is anything over about 140 mg/kg in adults and children; this level is halved (70 mg/kg) in people with chronic disease. The blood salicylate level is available in most, if not all, hospital laboratories. The older ferric chloride urine test (Figure) reliably demonstrates recent salicylate ingestion, but gives no clue to the amount taken.

**>>FAST TRACK<<**

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Both acute and chronic salicylate overdose are treated with supportive care and fluids to maintain urinary alkalinization. Be careful, however, not to alkalinize the serum, which can worsen CNS toxicity.

## ADDITIONAL CONSIDERATIONS

In addition to the above workup, a human chorionic gonadotropin (hCG) test is mandatory for female patients. Any woman of childbearing age should have her pregnancy status checked regardless of her last menstrual period and sexual activity. For some women, the news of a pregnancy may trigger fear,

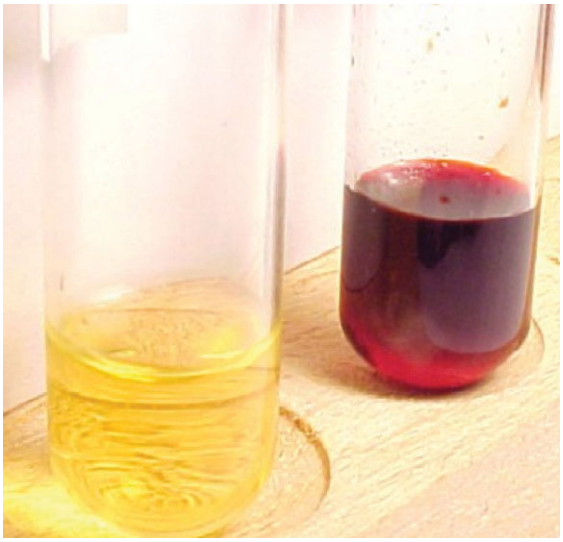

**FIGURE.** Ferric chloride test showing the change in urine color when the patient has recently ingested a salicylate.

shame, and suicidal ideation, and usually the most accessible mechanism is ingesting from whatever is in the medicine cabinet. Almost all overdoses are managed similarly for pregnant and nonpregnant women, but depending on the situation and drug (or drugs) ingested, a more aggressive approach may be taken with a pregnant patient out of concern for the uncertain status and possible compromise of the fetus. The resuscitation of the mother always takes precedence, regardless of fetal status.

The omission of a urine drug screen (UDS) from the workup discussed here may seem surprising, but every drug of potential abuse to which it is sensitive is treated symptomatically. A UDS takes time to obtain and perform, time that would delay a potentially life-saving intervention for a patient presenting with a specific toxidrome. Consider the possible scenarios: If the patient is medically stable, a positive UDS does not change that or the patient's likelihood of being medically cleared for a psychiatric evaluation. If there is respiratory depression from benzodiazepines, narcotics, or alcohol, the patient will be intubated for airway protection. If narcotics are high on the differential diagnosis list, the physical examination will give many clues (pinpoint pupils, decreased respiration, and hypotension) and naloxone can be attempted, with few side effects. If a patient ingested an opioid 24 hours ago, the UDS will be positive—but the patient will have no signs or symptoms of acute ingestion, because there is no acute ingestion. And agitation from phencyclidine (PCP) and sympathomimetics will be treated with sedation and cooling methods regardless of the agent involved.

Due to the many agents that can cause false positive and negatives, the UDS is a poor test, at best, that can lead to the wrong diagnosis or sway a provider into treating a result and not the patient.[18] □

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