# PEARLS, PITFALLS, AND UPDATES IN TOXICOLOGY

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Advances in clinical toxicology are occurring rapidly, such as defining new approaches to clinical problem-solving, elucidating basic mechanisms of drug-induced toxicity, and developing new therapies. The pearls in this article are approaches to clinical problem-solving pertaining to the following: the role of the laboratory in the evaluation of the poisoned patient, the assessment and treatment of a hemodynamically compromised patient, and the psychologic injuries that may occur as a result of hazardous materials incidents. Several adverse effects of poisoning and drug interactions are described as pitfalls: complications of poisoning, recognition of adverse drug reactions, and the serotonin syndrome. Updates in therapeutic advances are also described regarding the emerging role of *N*-acetylcysteine, the new psychotropic medications, and new antidotes.

## PEARL: ROLE OF THE LABORATORY IN THE EVALUATION OF THE POISONED PATIENT

Poisoning is a dynamic process that can rapidly change for the worst. Recognizing the subtle signs of poisoning is often the key to good clinical outcomes. In addition to physical findings, routine diagnostic tests can be used by the examining physician as early warning signs of poisoning.

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Our initial impression (likely diagnosis) of a patient is based on specific history and physical findings obtained at the bedside. Are diagnostic tests that do not improve our initial bedside impression of any value? The utility of a diagnostic test is measured by its ability to improve on this initial hunch by confirming the diagnosis or excluding possible causes. Diagnostic tests are also useful when they help judge the severity of the disease, predict the subsequent clinical course, or guide therapy. Therapeutic decisions are best made with information reflecting the patient's current condition. Diagnostic tests that reflect end-organ toxicity provide a measure of the severity of the active disease. The tests may also improve on the diagnosis, provide clues of impending deterioration, or guide therapeutic decisions. Therefore, basic diagnostic testing of poisoned patients does not begin with the comprehensive drug screen, but with routine tests that detect end-organ toxicity including electrolytes, blood urea nitrogen, creatinine, glucose, ECG, and acetaminophen level.

Serum electrolytes, blood urea nitrogen (BUN), creatinine, glucose, and 12-lead ECG will detect end-organ toxicity regardless of the specific toxin. These diagnostic tests can detect "laboratory toxidromes." Toxidromes identify end-organ effects characteristic of certain classes of toxins. They guide further diagnostic workup and treatment decisions. Common laboratory toxidromes are metabolic acidosis, adrenergic toxicity, and sodium channel blockade.

## Metabolic Acidosis

Metabolic acidosis is defined as a serum bicarbonate of less than 24 mEq/L. A measured serum bicarbonate is one of the most useful diagnostic tests because it is an early warning sign of many metabolic poisons, including the following: toxic alcohols (methanol and ethylene glycol); inhalants (carbon monoxide, cyanide, hydrogen sulfide); iron and INH; salicylates; hypoglycemics (metformin and phenformin); and paraldehyde. Most poisonings that result in acidosis produce an anion gap; however, a normal anion gap acidosis can occur with these same toxins.[43] Additional diagnostic testing focuses on identifying the cause of the acidosis and detecting those diseases with specific therapies. Examples include serum salicylate level, arterial blood gas, serum osmolality, toxic alcohol screen, serum lactate and urinalysis for ketones, calcium oxalate crystals, and Wood's lamp fluorescence. Laboratory data must be examined for evidence of diabetic ketoacidosis or uremia.

### *Adrenergic Response*

Physiologic responses to excess catecholamines are hyperglycemia, metabolic acidosis, hypokalemia, and leukocytosis.[24] In response to adrenergic stimulation, the liver releases glucose from glycogen stores to provide adequate fuel for "fight or flight." Cellular activity is increased by stimulation of cAMP. Anaerobic metabolism produces metabolic acidosis when cellular oxygen demands increase beyond available supplies. Increasing sodium/potassium adenosine triphosphatase (ATPase) membrane pump activity moves potassium into cells, thus lowering serum potassium levels. Many toxins cause laboratory abnormalities from excessive adrenergic stimulation including the following: cocaine, amphetamine, phenylpropanolamine, ephedrine/pseudoephedrine, theophylline, caffeine, phencyclidine, and sedative-hypnotic withdrawal. Diagnostic tests focus on detecting end-organ toxicity, such as myocardial ischemia, dysrhythmias, rhabdomyolysis, or hyperkalemia.

If adrenergic stimulation is extreme, a serious hypermetabolic state ensues. Excessive adrenergic stimulation uncouples the release of energy from electron transport and the capture of energy as ATP. Even though uncoupled, cell activity continues, oxygen is consumed, and electron carriers release energy. The energy is not captured as ATP but is released as heat. ATP stores quickly decline, cells malfunction, and membrane pumps fail. The laboratory profile of "uncoupling" reveals metabolic acidosis and hyperkalemia. The resulting hyperthermia, muscle injury, and hyperkalemia can be fatal. Testing includes creatine kinase and electrocardiography looking for evidence of rhabdomyolysis, hyperkalemia, or dysrhythmias.

### Sodium Channel Blockade

Sodium channel blockade is a life-threatening toxic effect of several important poisons:

- Cyclic antidepressants
- Phenothiazines
- Antidysrhythmics (Ia and Ib)
  - Procainamide
  - Quinidine
  - Encainide/flecainide
  - Propafenone
- Propranolol
- Cocaine
- Propoxyphene
- Chloroquine
- Antihistamines (diphenhydramine, orphenadrine, chlorpheneramine, pyrilamine)

The 12-lead ECG provides important clues to cardiac end-organ toxicity. Sodium channel blockade manifests as conduction abnormalities or hypotension. Early changes include prolonged QRS duration (>0.10 second) and rightward axis of the terminal 40 milliseconds.[72, 105] The presence of an R wave in aVR and S wave in I and aVL suggest sodium channel blockade from cyclic antidepressants.[105] The QRS duration and R wave in aVR can be prognostic of complications in addition to suggesting the diagnosis.[15, 65]

Other useful information can be obtained from routine diagnostic tests. For example, both hyponatremia and hypernatremia accompany lithium-induced renal toxicity.[3] In acute digoxin toxicity, the elevated serum potassium is more reflective of toxicity than the serum digoxin level.[14] Hypoglycemia may explain altered mental status or raise suspicion of oral hypoglycemic overdose. Detecting impaired renal function may guide further therapy, such as need for dialysis. The ECG also detects dysrhythmias and ischemia needing immediate attention. Poisoning by potassium efflux blockers is reflected by prolonged QTc.[52]

Further diagnostic testing is individualized to each patient and is based on clues from diagnostic tests, history, and physical examination. For example, an unconscious patient found beside an empty bottle of antifreeze should prompt the physician to order an ethylene glycol level regardless of other diagnostic test results. Another example is the person "found down" who will need specific testing that will detect complications of poisoning, such as creatine kinase (CPK) for rhabdomyolysis and a chest radiograph for aspiration pneumonitis.

### What Is the Best Use of the Toxicology Laboratory?

The emergency physician should use the laboratory to identify drugs and toxins present in sufficient quantities to:

1. Explain clinical findings, for example, coma with an elevated phenytoin level.
2. Predict deterioration or complications, for example, elevated theophylline level and risk of seizures.
3. Guide specific therapies, for example, *N*-acetylcysteine use with potentially toxic acetaminophen levels.

Qualitative drug screening is of little benefit for decision making in acute toxic emergencies, whereas quantitative drug levels can be useful.[23, 104] Quantitative levels are useful for acetaminophen, aspirin, theophylline, iron, lithium, anticonvulsants, ethanol, isopropanol, ethylene glycol, methanol, and digoxin toxicity. It is extremely important to verify the units of measure (e.g., mg/L or mg/dL) to avoid misunderstanding the results. A serum acetaminophen level is part of the routine toxicology screen because acetaminophen-containing products are ubiquitous to medicine cabinets, and no clinical toxidrome is evident for early detection. In addition, *N*-acetylcysteine is most effective if administered before end-organ toxic effects.

We should carefully consider the use of the urine drug screen (UDS) as a diagnostic test in the acutely poisoned patient. Most often, the clinical examination provides more useful information for diagnosis and treatment than a comprehensive drug screen.[23, 71] A common misconception is that the comprehensive drug screen is a black box analyzer that spits out "the answer" from a drop of blood. In fact, urine is the most useful sample for screening for the presence of drugs or metabolites. Detection of drugs in the urine means that the patient was exposed (not necessarily in toxic amounts or even on the day of the illness) to that drug. It does not confirm that the clinical findings at that moment are related to a drug exposure. Because many emergency drug screens seek only 8 to 10 common drugs, a negative screen does not rule out poisoning as the cause of a patient's illness. On the other hand, the UDS may identify (1) substance abusers that need chemical dependency interventions, (2) patients exposed to cocaine presenting with new onset seizures or ischemic chest pain, or (3) the presence of unsuspected drugs in critically ill patients with unexplained illness. In summary, the comprehensive drug screen's usefulness is limited in the management of acutely poisoned patients.

## PEARL: APPROACH TO THE HEMODYNAMICALLY COMPROMISED PATIENT

The emergency physician must make quick decisions based on limited information to resuscitate a poisoned patient with severe hemodynamic compromise. The complexity of cardiovascular poisoning and the need to act quickly in a life-threatening situation is a dilemma. The tendency is to "cookbook" established treatment protocols. Advanced cardiac life support (ACLS) protocols developed by the American Heart Association were intended for treating typical life-threatening cardiac emergencies from coronary artery disease but frequently are inappropriate for treating hemodynamic compromise from poisoning. With poisoning, complex receptor interactions, altered ion channel function, and meta-

bolic derangements adversely effect the cardiovascular system.[80] Choosing the most precise therapy is essential because adding cardioactive resuscitation drugs to this toxic milieu can be detrimental.

Hemodynamic compromise from poisoning causes shock. Shock is inadequate delivery of oxygen to tissues. The viability of cells and eventually the entire organism is jeopardized by inadequate oxygen delivery. Shock is classified as hypovolemic, cardiogenic, or distributive.[75] Many diseases, such as hemorrhage, massive myocardial infarction, and sepsis, fit nicely into one of these three categories. Unfortunately, most cardiovascular toxins cross the boundaries of this classification and cause several effects simultaneously. Toxins may simultaneously cause gastrointestinal hemorrhage and dehydration (hypovolemia), pump failure (cardiogenic), or vasomotor paralysis and venous pooling (distributive).[80]

With such complex interactions underway, how do we find the most precise therapy? Because no randomized controlled trials are available to guide therapy for most cardiovascular toxins, therapeutic recommendations are based on our understanding of physiologic responses, animal models, observational studies, and case reports.[30, 31, 57, 89, 98, 100] By using the current understanding of a toxin's expected cardiovascular derangements, initial interventions can be precise even without invasive hemodynamic monitoring. Considering the physiologic effects of each component of the oxygen delivery formula can be very helpful in this regard. Oxygen delivery ($DO_2$) is determined by the product of blood oxygen content and cardiac output:

$$(DO_2 = \text{oxygen content (hemoglobin} \times 1.36 \text{ mg } O_2/g + \text{dissolved oxygen}) \times \text{cardiac output (heart rate} \times \text{stroke volume}))^{[75, 80]}$$

With this knowledge, it is easier to recognize when more than ACLS protocols are needed (Table 1). For example, oxygen content can be impaired by abnormal hemoglobins (carboxyhemoglobin or methemoglobin) or anemias (hemolytic or acute blood loss). For many toxins, diminished stroke volume, which is determined by the vigor of contraction (contractility), left ventricular filling pressure (preload), and peripheral resistance or vascular tone (afterload) causes cardiac compromise.[75, 80] Of these components, impaired contractility is the most important cause of cardiac compromise for many toxins by either direct (sodium channel blockade and calcium channel blockade), indirect (metabolic derangements [toxic alcohols], or myocardial ischemia [cocaine]) effects. Hemodynamic compromise from a dysrhythmia is often obvious after analyzing the ECG, although heart rate changes may be only reflex responses to other hemodynamic abnormalities.

The ultimate goal of therapy is to improve oxygen delivery to tissues. There are obvious limitations to this method, but it is intended to demonstrate that not all hypotension is treated with just intravenous (IV) fluids and dopamine. More effective therapies are indicated without invasive hemodynamic monitoring if the expected toxic effects are appreciated. In addition, it is more difficult to assess end-organ perfusion in poisoning because bedside evidence of perfusion (level of consciousness or metabolic acidosis) may be caused by direct toxic effects and not poor perfusion. Therefore, basing initial treatment decisions on expected alterations in components of the oxygen delivery formula can be helpful until more precise information is available from invasive hemodynamic monitoring.

Finally, Table 1 can be used to determine the most helpful initial therapies. Theophylline causes decreased cardiac output by gastrointestinal fluid losses and decreased vascular tone from $beta_2$-adrenergic stimulation. The best strategy

**Table 1.** EFFECTS OF POISONING ON OXYGEN DELIVERY

| | Oxygen Content | | Cardiac Output | | | |
|---|---|---|---|---|---|---|
| | | | | Stroke Volume | | |
| | Hemoglobin Concentration | Oxygen Saturation | Heart Rate | Preload | Afterload | Contractility |
| Theophylline | ø | ø | ↑ $beta_1$ adrenergic stimulation; baroreceptor reflex | ↓: GI losses | ↓: $beta_2$ adrenergic stimulation | ø |
| Verapamil | ø | ø | ↓: impaired AV nodal conduction | ø | ↓: vasodilatation | ↓: impaired excitation-contraction |
| Beta-adrenergic blocker | ø | ø | ↓: $beta_1$ blockade | ø | ↑: unopposed alpha effect following $beta_2$ blockade | ↓: Impaired excitation-contraction and sodium channel blockade |
| Cyclic antidepressants | ø | D: respiratory failure from CNS depression | ↑: anticholinergic stimulation | | ↓: vasodilation ($\alpha$ blocker); depletion of norepinephrine | ↓: Sodium channel blockade |
| Iron | ↓: GI blood loss | ø | ↑: response to hypovolemia | ↓: GI losses and third spacing | | ↓: ?direct myocardial toxic injury |
| Rattlesnake envenomation | ↓: hemolysis | ø | ↑: response to hypovolemia | ↓: third spacing | ↓: third spacing | ↓: cardiodepressant toxins |
| Carbon monoxide | ↓: relative anemia | ↓: respiratory failure from CNS depression | ↑: response to tissue hypoxia | | ↓: vasodilation (mimics nitric oxide) | ↓: CO-myoglobin binding, causing myocardial ischemia |

ø = no effect; ↑ = increased; ↓ = decreased; GI = gastrointestinal.

for correcting hypotension would include IV fluids and drugs that decrease $beta_2$ stimulation (propranolol) or that act opposite of $beta_2$ stimulation, such as alpha-adrenergic agents (phenylephrine). Although by different mechanisms, the calcium channel blockers', beta-adrenergic blockers', and cyclic antidepressants' most important adverse effect on oxygen delivery is decreasing myocardial contractility.[57, 89] Strategies for improving contractility from calcium and beta-blocker toxicity include administration of calcium, glucagon, adrenergic agonists, amrinone, and insulin.[57] Sodium bicarbonate is used to improve contractility for cyclic antidepressant poisoning. In addition, norepinephrine is likely a better vasopressor for cyclic antidepressant-induced hypotension because it is caused by decreased vascular tone from blocking norepinephrine reuptake and antagonizing alpha-adrenergic receptors. Iron poisoning and rattlesnake envenomation have similar adverse effects because both cause tremendous third-spacing of fluids, gastrointestinal fluid losses, and depress mycocardial contractility.[30, 100] Treatment requires large volumes of IV fluids and specific antidotes (deferoxamine chelation and rattlesnake antivenin). Oxygen therapy is essential to reverse carbon monoxide's toxic effects on all components of oxygen delivery.[98] For example, hyperbaric oxygen will improve cardiac contractility by allowing oxygen to bind to myoglobin, and it is likely more beneficial for reversing hypotension than a vasopressor.

## PEARL: HAZARDOUS MATERIAL INCIDENTS AND PSYCHOLOGIC INJURY

> A large cloud of smoke drifts into a warehouse and causes mild irritant gas symptoms. No one seeks medical care. One hour later, the fire department releases a statement that cyanide was burning in the building. Over the next several minutes, 60 people complain of headache, chest tightness, dizziness, difficulty breathing, and nausea.

Dramatic images of large black, billowing clouds of smoke, firefighters dressed in "moonsuits," and television coverage of neighborhood evacuations accompany many large chemical accidents. Along with the drama, facts about the incident are conflicting or unknown. These are sources of anxiety and fear among emergency responders, victims, nearby residents, and even the entire community. Acute anxiety reactions and the syndrome of mass psychogenic illness are common in chemical accidents, and it is often difficult to distinguish from systemic effects of acute poisoning. When large numbers of people are affected, the entire emergency response and hospital resources can be overwhelmed. In our attempt to "do the best for the most," we must learn to respond to this reaction.

The public and science (medicine)* have differing perceptions regarding health risks from chemical exposure.[88] Appropriate intervention requires understanding both perspectives. The public is keenly aware of the dangers of toxic chemicals because seldom does a day go by without some newsworthy story warning us of our risks. The public perceives exposures to chemicals as "all or none." Once exposed, certain lasting toxic effects occur or a time bomb ticks

*We make the assumption that most physicians think as scientists. Skepticism is a part of the critical appraisal skills of a scientist. Overall, physicians' perceptions are closer to a scientist's than to the public's when examining a problem not involving self or family.

within waiting to cause harm. To the scientist, "exposure" is only contact with a chemical, and "risk of harm" considers the dose-response of the chemical. Scientists live with uncertainty because scientific truth is only an approximation of the truth based on the current best evidence. From a scientist's perspective, it is impossible to achieve zero health risk from chemical exposure in our technologic society. Low risk is often an acceptable alternative and reassuring. The public's opinion of risk is not based on relative risks, odds ratios, $LD_{50}$, or critical appraisal of scientific evidence but primarily on trust and fear.[88] From the public's view, any risk is of grave concern. The public wants conclusions based on certainty and demands zero risk from chemicals. There is no safe dose from this perspective, and those exposed in chemical accidents feel victimized and have a sense of "no control." Unfortunately, science's (medicine's) pursuit of the truth has tended to ignore the public's perception and needs. Ignoring their concerns has resulted in poor communication and created a climate of distrust, outrage, and fear with emotional reactions well out of proportion to the magnitude of the risk.

Psychogenic-induced symptoms seem very real to the victims and are similar to those expected by a toxic exposure. Headaches; faintness; dizziness; nausea; chest tightness; difficulty breathing (hyperventilation); irritation of eyes, nose, or throat; weakness, and extremity numbness are the most frequent complaints.[18] Attempting to identify true toxicity from a powerful emotional reaction can be extremely difficult. Symptoms are contagious and can spread rapidly through a group of people in a room, building, or community. This response is a well-known syndrome called mass psychogenic illness, environmental somatization syndrome, or epidemic hysteria.[18, 46] Some key elements in mass psychogenic illness are as follows[18]:

- Sudden onset of relatively severe symptoms particularly after leaving the alleged source of exposure
- Transmission of illness by sight or sound
- Symptoms occurring after learning of suspected exposure or seeing someone else with illness
- Rapid spread and remission
- Diversity of symptoms without physical signs or laboratory findings
- Relapse of symptoms when group congregates

A large number of people with emotional reactions can overwhelm the entire emergency response system and hinder timely treatment to those with true toxic emergencies. But if indistinguishable, patients must be triaged as toxic emergencies. As the incident evolves, accurate information and a period of observation will usually clarify the situation. The syndrome is most effectively treated when it is rapidly recognized.[85] Symptoms are spread by sight and sound, so disband the group as quickly as possible and remove them from the "action" of lights, sirens, and fully encapsulated responders.[85] Decrease rumors and fear by attempting to address the victim's concerns and provide information about the incident. Emphasize the certainties of the situation, but do not downplay or minimize the patients' concerns. It is not the symptoms but the explanation of the symptoms that is questionable. Never label the symptoms as psychogenic because affected individuals will reject alternative explanations and "cling tenaciously to the idea that their illness is purely physical."[18, 46] Recognize that symptoms may recur. Give patients local resources for more information and explicit follow-up instructions, with actions to take, should symptoms return.

## PITFALL: COMPLICATIONS OF POISONING

Complications from poisoning, rather than direct toxic effects, are the cause of morbidity and mortality for many critically ill patients. The most common complications are aspiration pneumonitis, anoxic encephalopathy, rhabdomyolysis, and compartment syndrome. Since the comatose cannot complain, an active search for clues will detect early complications and provide the best possible clinical outcome.

### *Aspiration Pneumonitis*

Aspiration pneumonitis should be suspected in all critically ill poisoned patients because it is a common cause of morbidity and mortality.[1] The diagnosis may be difficult in the emergency department (ED) because the chest radiograph may lag 12 to 24 hours behind the aspiration event. Aspiration occurs as a result of (1) toxin-induced loss of airway protective reflexes that allows stomach contents and secretions to enter the airway system, (2) toxin-induced slowing of gastrointestinal motility and gastric emptying allowing large volumes of gastric secretions to remain in the stomach, (3) gastric distention from bag-valve-mask ventilation, and (4) complications of gastric-emptying procedures (gastric lavage and syrup of ipecac). Aspiration pneumonitis has a mortality of 30% to 60%.[27] It results in the associated complications of prolonged intubation and mechanical ventilation. It increases the risk of secondary bacterial invasion of the lungs, causes prolonged hypoxemia, and may progress to adult respiratory distress syndrome (ARDS). Preventing aspiration and aggressively treating the effects of toxic lung injuries are paramount in preventing ARDS.

Every effort should be made to identify high-risk patients because aspiration is, at times, preventable. Many poisoned patients have altered mental status and loss of airway protective reflexes. In toxicologic emergencies, intubation is often necessary for aspiration protection and not for compromised ventilation or oxygenation. Rapid sequence intubation must be performed with meticulous technique to avoid aspiration. Special precautions are required for physically restraining an unintubated patient with altered mental status. Restraining a supine patient in four-point leather restraints, spread eagle on the stretcher, makes aspiration likely should emesis occur. Restraining a patient on his or her side is a safer position. Alternatively, a patient may be secured to a backboard such that the patient and the backboard are free from attachments to the gurney and easily moveable should the patient need repositioning for airway protection.

Risks of aspiration should be considered when contemplating gastric-emptying procedures. The efficacy of gastric lavage on clinical outcome is questionable and it may cause aspiration in susceptible patients.[61, 69, 77] Carefully consider the risks before proceeding with gastric lavage and treat it as a procedure with specific techniques and expected complications.

1. Protect the airway.
2. DO NOT sedate or intubate a patient just to perform gastric lavage.
3. Intubate patients with any signs of lost airway reflexes or decreasing level of consciousness before the procedure.
4. Place patient in Trendelenburg position and left-side–down decubitus position.
5. Use small aliquots of normal saline (200 to 500 mL) and keep track of input and output.

## Anoxic Encephalopathy

Poisoning causes global anoxia from prolonged shock, respiratory failure, or direct toxic metabolic effects. Prolonged severe hypoxia results in coma and loss of brainstem reflexes.[64] Profound central nervous system (CNS) depression with fixed, dilated pupils, absence of brainstem reflexes, and isoelectric EEG can even mimic brain death following some poisonings.[13, 78, 102] These patients have a reversible metabolic encephalopathy and have been reported to recover fully.[73, 92, 107] If the coma is caused by anoxia, then the prognosis is poor. Clinical predictors of outcome for nontraumatic comatose patients or postresuscitation patients are not reliable when applied to poisoned patients.[37, 81] Prolonged resuscitation efforts may be justified despite apparent severe neurologic injury. Especially in the ED, the diagnosis of brain death should be made cautiously.

## Rhabdomyolysis

Rhabdomyolysis is skeletal muscle injury caused by too much muscle activity (status seizures or agitation from cocaine), too little activity (pressure necrosis from barbiturate coma), or direct cellular injury from toxins (ethanol or carbon monoxide).[29, 42] Muscle cells malfunction resulting in excess intracellular calcium, cell membrane breakdown, and leakage of cellular components (creatine phosphokinase, myoglobin, and potassium) into the blood.

Suspicion of rhabdomyolysis in all comatose patients is important because subtle findings may be the only clue. Areas of pressure necrosis initially appear only reddened, but with time can progress to full-thickness skin injury. Skin and muscle injury develops over prominent bony areas (particularly buttocks, heels, knees, and back) and in extremities. The urine appears tea colored when myoglobin is present. Serial serum CPK measurements are most helpful in identifying this disorder. Elevated or rapidly rising CPK levels are diagnostic for muscle injury.

The goal of therapy is to prevent the secondary effects that follow rhabdomyolysis.[29, 60] Cardiac sudden death from hyperkalemia and acute renal failure from myoglobinuria are most important. Cardiac monitoring, serial serum potassium levels, and optimal fluid management are basic management recommendations. Treatment with mannitol, urine alkalinization, hemofiltration, and hemodialysis are also recommended.

## Compartment Syndrome

Rhabdomyolysis may not always be generalized muscle injury but can be a local injury within a fascial compartment.[29, 67] Compartment syndrome is the increased pressure within a fascial compartment that compromises distal blood flow. Irreversible muscle damage may occur within 6 to 12 hours. The comatose poisoned patient may develop compartment syndrome after lying on an extremity or from direct pressure injury. Commonly, compartments in the hand, arm, forearm, buttocks, thigh, or leg are involved. Making the diagnosis requires close examination of all compartments, reassessment, serial CPK levels, and early surgical consultation for evidence of ischemia.

## PITFALL: RECOGNIZING ADVERSE DRUG REACTIONS

All too often, patients' expectations are usually not met these days by just reassurance or suggesting life-style changes. A prescription is almost expected with each therapeutic encounter, and often the physician is more than eager to oblige. A medication is administered to manipulate or "poison" cellular functions in a very specific way. This manipulation hopefully alleviates suffering or cures disease. Often we think of a medication's mechanism of action as its only effect, but this is too simplistic. For example, cyclic antidepressants not only block reuptake of norepinephrine and serotonin, their therapeutic actions, but are sodium channel antagonists, anticholinergic, antihistamine, alpha-adrenergic antagonists, and potassium efflux antagonists. Complexity increases as we add the effects of two, three, or more medications. Seldom do they ignore each other's actions but interact by addition, synergism, potentiation, or antagonism. Adverse drug reactions and interactions are inevitable when multiple medications are prescribed.* Do we consider adverse drug reactions as the cause of new symptoms or a deteriorating preexisting condition, particularly in patients with long medication lists? If not recognized, symptoms of adverse reactions may be treated with even more medications thus complicating the situation further.

### The Medication List

Give the medication list the same attention as an abnormal vital sign. Try to validate it and scrutinize it for explanations of the current acute illness. Consider interactions, overdose, or withdrawal as a cause of the acute illness. Above all, consider the consequences of adding an additional medication to the list. The medication list must include over-the-counter (OTC) medications, home remedies, vitamins, borrowed/shared medications, herbal products, and supplements for weight loss or enhancing performance. A patient's daily medication regimen may include multiple brand names of the same medication. This is especially true for pain relievers or "arthritis" medications. A patient may take generic ibuprofen in the form of Motrin, Advil, Nuprin, and Excedrin IB to relieve aching joints.

### The Elderly

Adverse drug reactions are common in the elderly. The elderly consume one third of all prescribed medications and on an average take four to five prescribed medications and two OTC medications.[8] Five percent to 10% of hospital admissions have been attributed to a drug-induced illness.[9, 28] Prescribing a medication to an elderly patient who is currently taking three or more prescribed medications poses significant risk for an adverse drug reaction.[11, 44, 50] Three percent to 50% of elderly patients given prescriptions in the ED have a potential drug interaction.[11, 44, 50]

Aging causes decreased functional reserves of the cardiovascular, renal, and

*For the purpose of this discussion, adverse drug effects refers to both drug-drug interactions and adverse drug reactions. The most accurate definitions are *drug interactions*: the adverse effects created by simultaneous administration of two or more medications; *adverse drug reactions*: undesirable drug effects from administration of a medication.

hepatic systems. Medications act as physiologic stressors that further diminish an organ's functional reserve. These physiologic changes alter drug absorption, distribution, metabolism, and elimination.[21, 40, 109] In addition, receptor sensitivity to some drugs is altered as aging occurs.[38] Underlying disease processes, particularly congestive heart failure, hypertension, diabetes, and renal disease, increase the risk of adverse drug reactions.[44] Adverse drug effects commonly present as lethargy, "stroke," delirium, depression, worsening dementia, orthostatic hypotension, syncope, dysrhythmias, falls, urinary retention, or incontinence.

Acute alteration of mental status in the elderly is caused by many disease processes. Vascular and infectious causes are often considered, but adverse drug effects may be overlooked.[4, 63] For example, aspirin use in the elderly is very common. Declining hepatic function and continued salicylate use can lead to accumulation. Chronic salicylism often presents as acute alteration of mental status and is frequently misdiagnosed as cerebrovascular disease.[4] An additional example comes from the additive effects of multiple anticholinergic medications. Using OTC cough and cold medications, antihistamines, antispasmotics, antiparkinson, antidepressants, and antipsychotics can produce an additive anticholinergic effect.[39, 99] Altered mentation from the anticholinergic syndrome may be overlooked because blunted cardiovascular receptor sensitivity from aging causes the central anticholinergic effects in the absence of peripheral anticholinergic signs.[38]

Studies have defined medications that often cause adverse drug effects and should be entirely avoided in the elderly (Table 2).[10, 44, 50, 103] Always consider the risk of serious adverse drug effects, options of safer alternatives, and proven benefits versus risks of treatment for all medications prescribed to elderly patients.

### Recommendations

Recognition:

- Treat the patient's medication list as a vital sign.
- Always consider adverse drug reactions in the differential diagnosis of acute disease, especially altered mental status and especially in the elderly.
- Subtle signs of toxicity, such as peripheral anticholinergic effects, may not be present with central anticholinergic toxicity.
- Remember OTC medications are not considered medications by most patients.

Prevention

- Look at patient's medication list for potential interactions when prescribing a new medication (computer software programs are available to detect potential interactions).[45]
- Caution patients about potential side effects and interactions.
- Clearly define a therapeutic endpoint of your treatment.
- The more prescriptions, the more likely an adverse reaction will occur.

## PITFALL: THE SEROTONIN SYNDROME

Serotonin is a biogenic amine neurotransmitter similar to norepinephrine and dopamine. Its CNS effects modulate eating, sleeping, sexual behavior, circa-

**Table 2.** MEDICATIONS WITH HIGH INCIDENCE OF ADVERSE REACTIONS

**Sedation/altered mental status**
- Long-acting benzodiazapines
- Meprobamate
- Short-acting barbiturates
- Narcotics
  - Propoxyphene
  - Pentazocine
- Antipsychotics
  - Haldol
  - Thioridazine
- Muscle relaxants
  - Cyclobenzaprine
  - Carisiprodol
- Salicylates
- Lithium
- Cimetidine

**Additive anticholinergics**
- Cyclic antidepressants
- Cyclobenzaprine
- Antispasmotics
- Antihistamines
- Antiparkinsons
- Antipsychotics

**Syncope/near-syncope**
- Antihypertensives
- Antidysrhythmics (Ia and Ic)
- Digoxin
- Diuretics
  - Hydrochlorothiazide
- Hypoglycemics
  - Chlorpropamide

**Orthostatic hypotension**
- Cyclic antidepressants
  - Doxepin
- Phenothiazines
  - Thioridazine
- Antihypertensives
  - Methyldopa
  - Hydrochlorothiazide
- Alpha-adrenergic blockers (e.g., terazosin)

**Worsening hypertension**
- OTC cough and cold medications
  - Phenylephrine
  - Pseudoephedrine
  - Phenylpropanolamine
  - Ephedrine

**GI complications**
- GI Bleeding
  - Nonsteroidal antiinflammatory drugs
  - Corticosteroids
- Constipation
  - Opioids
  - Anticholinergics

**Renal toxicity**
- Analgesic nephropathy
  - Nonsteroidal antiinflammatory drugs
- Urinary retention
  - Anticholinergics

**Medications with narrow therapeutic index**
- Lithium
- Digoxin
- Theophylline
- Salicylates

**Examples of important drug-drug interactions**
- Terfenadine and erythromycin/ketoconazole/ciprofloxacin/clarithromycin
- Cisipride and erythromycin/ketoconazole/ciprofloxacin/clarithromycin
- Acetaminophen and chronic ethanol abuse
- Seizures
  - Theophylline and ciprofloxacin
  - Theophylline and erythromycin
- SSRI and MAOI or demerol or lithium or dextromethoraphan
- Warfarin and fluconazole or metranidazole or erythromycin

Many of these medications have (1) a high incidence of adverse reactions, (2) no proven effectiveness, or (3) safer alternatives.

*Data from* Beers MH, Ouslander JG, Rollingher I, et al: Explicit criteria for determining inappropriate medication use in nursing home residents. Arch Intern Med 151:1825, 1991; Goldberg RM, Mabee J, Chan L, et al: Drug-drug and drug-disease interactions in the ED: Analysis of a high-risk population. Am J Emerg Med 14:447, 1996; Herr RD, Caravati EM, Tyler LS, et al: Prospective evaluation of adverse drug interactions. Ann Emerg Med 21:1331, 1992; Willcox SM, Himmelstein DU, Woolhandler S: Inappropriate drug prescribing for the community-dwelling elderly. JAMA 272:292, 1994.

dian rhythm, and neuroendocrine functions.[41] Pharmaceuticals with actions at serotonin neurons have flooded the market owing to the increased appreciation of its role in depression. Serotonin syndrome is a potentially severe adverse drug reaction caused by excessive serotonin availability in the CNS. Increased serotonin at the synapse is the result of increased production, decreased breakdown, decreased reuptake, or increased receptor activity. This hyperserotinergic state is a constellation of signs and symptoms (Table 3).[25, 70, 96]

The onset is usually rapid after a recent addition or increase in dosage of a serotinergic agent. Most cases result in mild to moderate symptoms that resolve in 24 to 72 hours. Rhabdomyolysis, renal failure, hepatic failure, and death can occur. It can be easily confused with other conditions, for example, sepsis, metabolic/endocrine disturbances, withdrawal syndrome, or neuroleptic malignant syndrome (NMS). Serotonin syndrome is somewhat similar to NMS, therefore the diagnosis of serotonin syndrome should be suspect when a neuroleptic has been started or increased in dosage before the onset of symptoms. Serotonin syndrome usually has an onset of several hours, in contrast to NMS which develops over 3 to 9 days and evolves over 24 to 72 hours after initiation of therapy or change in neuroleptic dose. In addition, NMS is always associated with neuroleptic medications, lead pipe rigidity, and patients usually do not exhibit severe myoclonus or nystagmus.

The most important aspect of treatment is recognizing the syndrome. Treatment involves discontinuation of the serotinergic agent and supportive therapy, including mechanical ventilation, temperature control, sedatives, and muscle relaxants. Beneficial effects have been reported with the use of some serotonin receptor antagonists, propranolol, and cyproheptadine, in animal studies and isolated case reports.[25, 70]

The incidence is unknown, but reports are increasing yearly. This rise in cases is not only caused by the increased use of pharmaceuticals with serotonergic activity but also to clinicians' awareness of the syndrome. Emergency physicians should take note of previous reports implicating interactions between selective serotonin reuptake inhibitors, mononamine oxidase inhibitors, and tricyclic antidepressants. Additionally, patients using one of the previous three classes of drugs along with either meperidine, pentazocine, dextromethorphan, L-tryptophan, lithium, buspirone, bromocriptine, phenylpropanolamine, pseudoephedrine, cocaine, or other sympathomimetics are at risk of developing the serotonin syndrome.[70, 95] Some authorities have suggested that the Libby Zion case, which precipitated a review of resident supervision with far-reaching impact, represents a case of fatal serotonin syndrome.[6] Interactions between imipramine, phenelzine, and meperidine may have resulted in the death of this

**Table 3.** SIGNS AND SYMPTOMS OF SEROTONIN SYNDROME

| | |
|---|---|
| Neurobehavioral | Neuromuscular |
| Mental status changes | Myoclonus |
| Agitation | Hyperreflexia |
| Confusion | Tremor |
| Seizures | Muscle rigidity (especially of lower extremities) |
| Autonomic | Ataxia |
| Hyperthermia | Nystagmus |
| Diaphoresis | |
| Diarrhea | |
| Tachycardia and hypertension | |
| Salivation | |

18-year-old woman who presented with fever and agitation. She was admitted to the hospital through the ED with a diagnosis of viral syndrome with hysterical symptoms and died 7 hours after arrival. In addition to recognizing the serotonin syndrome in patients using combinations of these medications, the emergency physician must use caution when prescribing to avoid predisposing a patient to this potentially fatal drug interaction.

## UPDATE: THE EMERGING ROLE OF *N*-ACETYLCYSTEINE

Emergency physicians are familiar with *N*-acetylcysteine (NAC) therapy for acetaminophen poisoning, and a standard protocol is well established. Despite its familiarity, new data, new products, and new ideas have caused confusion regarding appropriate treatment of acetaminophen poisoning.

The nomogram determines the need for therapy by estimating the risk of developing hepatotoxicity after an acute acetaminophen ingestion. The nomogram is valid for a specific population of patients with a single serum acetaminophen level obtained 4 hours or greater after an acute overdose.[82, 91] The nomogram was not intended for, nor has it been validated for, chronic poisoning, multiple acute ingestions, extended release preparations, or those with potentially high-risk conditions (chronic ethanol abuse, malnutrition, or p450-inducing medications). Be cautious of decisions derived from generalizing the nomogram to these populations.

NAC was approved in 1985 for the treatment of acute acetaminophen poisoning. A 72-hour oral protocol is the "standard" therapy in the United States. No controlled studies exist that compare the 20-hour European protocol, the 48-hour IV protocol, the 72-hour oral protocol, the discontinuation of NAC when acetaminophen level is zero protocol, or other "short course" protocols.[79, 90, 91, 106] None of these protocols is proven superior to any other.

A patient receiving NAC early after an ingestion is at low risk of developing hepatotoxicity.[79, 90, 91] Initiating NAC therapy within 8 hours of ingestion is protective of hepatotoxicity regardless of the serum acetaminophen level.[91] All protocols suggest NAC is efficacious for this group of patients. A comparative study of short course NAC with the standard protocol seems reasonable in this group.

Initiating NAC more than 8 hours after ingestion affords less antidotal protection.[79, 91] In addition to delayed NAC therapy, chronic ethanol abuse, or use of enzyme-inducing medications may increase the risk of hepatotoxicity.[22, 83] In a prospective controlled trial, initiating NAC late in the course (mean time 56 hours) and continuing until clinical progress improved survival in patients with fulminant hepatic failure.[56] Initiating NAC later than 24 hours after ingestion and continuing therapy past 72 hours is today considered beneficial and should be part of the treatment for patients with hepatotoxicity.[56, 66]

The process of Food and Drug Administration (FDA) approval of an IV preparation of NAC has been ongoing for many years. Frustrated by the long delay to release this preparation, many physicians have resorted to administering the oral preparation IV.[17, 108] Obviously, clinicians could be taking a risk because the oral preparation is not guaranteed to be pyrogen-free, and adverse immunologic responses have been reported.[17, 33, 35] Although potentially risky, reported experiences demonstrate relatively minor adverse reactions.[17, 35, 108] Certain patients may benefit from IV administration, despite the risk. Candidates for IV administration of NAC are those with probable toxicity by the nomogram and persistent vomiting that prevents oral NAC therapy and those with severe

hepatotoxicity that are too ill to take oral medications. Clinicians considering IV administration should consult a medical toxicologist for advice regarding the appropriateness. Data about IV NAC are currently being prepared for resubmission to the FDA so approval is still some time away.

Today, the 72-hour oral protocol is the "standard" of care for most cases of acute acetaminophen poisoning. Alterations from this protocol should be carefully considered in consultation with a medical toxicologist. Challenging the "standard" with good clinical studies is necessary to improve on the treatment of acetaminophen poisoning with NAC.

## UPDATE: THE NEW PSYCHOTROPIC MEDICINES

### Antidepressants

Depression is a common and disabling disease. At least 17% of the population will suffer major depression in their lifetime.[58] Depression is under-recognized and undertreated despite significant advances in effective therapeutic methods. The disease is associated with loss of productivity in the workplace, a high incidence of comorbid psychiatric disorders, and a high rate of health care utilization. Emergency physicians frequently encounter patients who use antidepressant medications and who have overdosed.

The study of neurotransmitters in the brain has resulted in the discovery of numerous receptors and subtypes for serotonin, glutamate, dopamine, and norepinephrine. Brain levels of serotonin (5-HT) are decreased in depressed patients. Serotonin receptors have been classified into four major subtypes, 5-$HT_{1-4}$. Decreased stimulation of the 5-$HT_{1A}$ receptor results in depressive symptoms. Early-generation antidepressant treatment modalities include tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), which rather nonselectively increase levels of neurotransmitters and exhibit numerous side effects through complex receptor pharmacology. Later-generation antidepressant therapy includes a class of agents that selectively inhibit the reuptake of serotonin. These selective serotonin reuptake inhibitors (SSRIs) include paroxetine (Paxil), fluoxetine (Prozac), and sertraline (Zoloft). These agents effectively treat depression with fewer adverse reactions than the older TCAs.[87]

The SSRIs are safer in overdose than TCAs or MAOIs. Henry and coworkers[49] reviewed overdose deaths caused by antidepressant therapy over a 6-year period in Scotland. Data were reported as the number of deaths per number of prescriptions, deaths per defined daily doses, and the absolute number of deaths. In all categories, TCAs resulted in the highest mortality figures in overdose, followed by MAOIs, and finally, mortality associated with SSRIs was least. The CNS and cardiovascular toxicities so common with TCAs or MAOIs rarely occurs with SSRIs. In a series of 234 cases of fluoxetine overdose, half the patients remained asymptomatic.[16] Symptomatic patients developed tachycardia, drowsiness, tremor, and nausea. Three of the five patients with tachycardia were taking other proarrhythmic drugs. There were no deaths. Serious toxicity in overdose is unlikely. Some case reports of SSRI overdose, usually with coingestants, document problems with seizure, tachycardia, and agitation, but these reports are limited in number and in general SSRIs do not pose a major threat.[20, 53] An SSRI overdose victim who presents to the ED should be carefully interviewed regarding possible coingestants, examined, evaluated with an ECG, and observed for a few hours. If no symptoms or signs of toxicity are observed after 1 to 3 hours, the patient may be released from further medical observation.

A group of other antidepressant medications referred to as atypical, or novel, antidepressants includes trazodone (Desyrel), nefazodone (Serzone), and venlafaxine (Effexor). Trazodone was the first antidepressant available that was not considered lethal in overdose unless significant coingestants were also present. Trazodone inhibits serotonin reuptake and antagonizes 5-$HT_2$ receptors. Trazodone possesses minimal anticholinergic and cardiotoxic properties. Nefazodone is a recently introduced atypical antidepressant chemically related to trazodone with a similar mechanism of action. Its side effect profile may result in slightly less sedation.[97] Overdose experience is limited but the toxicity profile appears to be similar to trazodone.[12] Venlafaxine is a novel antidepressant believed to act by selectively inhibiting reuptake of serotonin and norepinephrine with little effect on other neurotransmitters. Patients who have been refractory to other therapies sometimes respond to venlafaxine. Overdose experience is limited but seizures, hypotension, and death have all been reported.[32, 36, 59]

### Neuroleptics

The management of schizophrenia with antipsychotic medication provides enormous benefit to many patients. Despite this success, neuroleptic drugs have serious limitations. First, they are not always effective; second, positive psychopathological symptoms may benefit more than negative, or deficit, symptoms; and third, side effects and toxicities often limit their administration. Two drugs, clozapine (Clozaril) and resperidone (Risperdal), have recently been introduced into psychiatric practice.[54] Their mechanism of action involves potent inhibition of 5-$HT_2$ and dopamine $D_2$ receptors. These drugs appear to be associated with fewer adverse neurologic events and may be more effective in treating the negative symptoms than the traditional neuroleptics.[47]

Experience with clozapine overdose and adverse effects reveals that seizures occur frequently. Numerous case reports and postmarketing surveillance document this toxicity.[74] Seizures can develop within 1 hour after overdose, and one report describes respiratory arrest in a 5 year old.[101] Experience with risperidone overdose is more limited than with clozapine. Lethargy and tachycardia have occurred.[62] Another major toxicity that occurs with long-term clozapine administration is agranulocytosis.[2] The cumulative risk of agranulocytosis at 1 year is approximately 1%. Deaths from infectious complications have occurred. Patients are followed closely while using clozapine, and white blood cell counts are monitored every 1 to 2 weeks. Emergency physicians need to be alert to the potential for seizures in clozapine or risperidone overdose, and patients on long-term clozapine therapy are at risk for clozapine-induced agranulocytosis.

## UPDATE: ANTIDOTES

### Flumazenil

Flumazenil is an imidazobenzodiazepine derivative that antagonizes the CNS effects of benzodiazepines. Through competitive antagonism of GABA receptors, flumazenil reverses the sedation and respiratory depression induced by benzodiazepine toxicity. Current indications for the use of flumazenil include reversal of conscious sedation procedures and reversal of toxicity in benzodiazepine overdose. IV administration is individualized according to the desired level of consciousness. Onset of action occurs at 1 to 2 minutes with a peak effect at

5 to 10 minutes and a duration between 1 and 5 hours. Although flumazenil is not approved for use in pediatrics, its use has been reported.[76]

The use of flumazenil administration in patients with suspected benzodiazepine overdose is limited by side effects, especially when coingestants are involved. Seizures occur at a rate of 1% to 2%.[94] Seizures have been reported in children and adults.[68] Fatal status epilepticus is a recognized complication.[34, 48] Factors associated with an increased likelihood of precipitating seizures include a history of seizure disorder, chronic benzodiazepine usage, concomitant tricyclic antidepressant ingestion, and mixed overdose.[93] Ventricular dysrhythmias and benzodiazepine withdrawal have also occurred.[26, 86]

The administration of flumazenil is warranted under some circumstances.[51] When acute benzodiazepine overdose is suspected by history and confirmed by physical examination findings, flumazenil administration may reverse sedative effects to confirm the diagnosis and eliminate the need for endotracheal intubation and mechanical ventilation. There should be no evidence for coingestion of a proconvulsant or a proarrhythmic agent, and the patient must not be physically dependent on benzodiazepines. A pretreatment ECG may help identify patients with occult cyclic antidepressant overdose. An example of a circumstance warranting flumazenil administration is represented by a toddler who accidentally ingests several tablets of diazepam and presents with significant sedation and respiratory depression, which may be reversed by small, incremental doses of flumazenil. Intensive care monitoring of the patient will still be required because resedation may occur, but in this circumstance successful reversal of sedation has confirmed the diagnosis and obviated the need for mechanical ventilation.

## Nalmefene

Nalmefene is an investigational opiate antagonist structurally similar to naloxone. Competitive inhibition at opiate $\mu$ and $\kappa$ receptors reverses opiate-induced sedation and respiratory depression. The advantage of nalmefene over naloxone is a longer duration of action. In a study of 53 ED patients with suspected opiate toxicity, nalmefene successfully reversed opiate-induced sedation in the 24 patients who were confirmed to be opiate-positive by a laboratory toxicology screen.[55] There were no serious adverse effects. A potential consequence of nalmefene administration is iatrogenic induction of opiate withdrawal syndrome, which would be prolonged in comparison to the same complication induced by naloxone. Efficacy and safety need further study before widespread use can be recommended.

## 4-Methylpyrazole

4-Methylpyrazole (4-MP) is an alcohol dehydrogenase inhibitor that is currently under investigation for use as an antidote in methanol and ethylene glycol intoxication. Alcohol dehydrogenase (ADH) initiates the metabolism of methanol and ethylene glycol, which eventually results in formation of the toxic metabolites of formic acid and oxalic acid, respectively. Ethanol similarly inhibits ADH, preventing formation of toxic metabolites thus allowing time to prepare for hemodialysis. Ethanol administration is technically difficult owing to individual variations in metabolism, and the patient's condition may deteriorate as a result of ethanol-induced sedation, whereas 4-MP would not result in these problems.

A multicenter clinical trial to further evaluate the safety and efficacy of 4-MP is currently in progress.

### Fab Fragment (Antigen-Binding Fragment) Antidotes

Drug-specific antibodies have been used in humans to treat toxicity caused by digoxin and colchicine.[5, 7] Fab fragments have also been used to treat snake envenomation by crotalids, or pit vipers (rattlesnake, copperhead, and water moccasin) in the United States.[19, 84] Animal studies reporting the use of Fab fragments in poisoning by tricyclic antidepressants, phencyclidine, and paraquat are in progress.

Fab fragments are a small portion of the IgG molecule and contain antigen-binding sites that bind drug or protein to prevent toxicity. The resultant antibody-toxin complex is excreted by the kidney. These fragments are derived from animals (e.g., sheep, rabbits) who are immunologically challenged with a synthesized antigenic protein complex containing the toxin that functions as a hapten. This protein complex is injected into the animals. Serum is collected and purified to extract the IgG portion, which exhibits activity against the toxin. The Fc portion of the IgG molecule is cleaved and removed from the preparation. The Fc portion of the IgG molecule is immunogenic, and its removal enables human administration without the development of anaphylaxis or serum sickness. Herein lies the major advantage of Fab fragments over other antibody preparations, such as the standard equine-derived polyvalent crotalid snake antivenin, which retain the immunogenic Fc fragment thus inducing anaphylaxis and serum sickness. Because Fab fragments are produced in small amounts, only drugs and venoms that are toxic in small doses may be effectively treated. Despite this limitation, the development of antibody treatment for poisoning and toxic envenomations will continue. Fab fragment therapy for digoxin toxicity has improved patient outcomes. Should the newly developed crotalid Fab therapy prove effective, as will likely occur, snake bite victims will benefit as well.

## SUMMARY

Pearls and pitfalls learned from our practical experiences caring for poisoned patients are presented. Clinical pearls include the following: using diagnostic tests to detect end-organ toxicity, applying physiologic principles to the management of hemodynamically unstable poisoned patients, and dealing with psychologic injuries from hazardous materials incidents. Recognizing serious complications from poisoning and adverse drug effects, including the serotonin syndrome, are offered as pitfalls. Pharmaceutical companies are rapidly developing and marketing new therapies. Therefore, updates on the evolving role of NAC as an antidote for acetaminophen poisoning, new psychotropic medications, and new antidotes were included in this article. These pearls, pitfalls, and updates are intended to provide practical information that is readily applicable to the clinical practice of emergency medicine.

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