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Critical Care Toxicology

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Critically poisoned patients are commonly encountered in emergency medicine. Exposure to potential toxins can occur by either accident (ie, occupational incidents or medication interactions) or intentionally (ie, substance abuse or intentional overdose). The outcome following a poisoning depends on numerous factors, such as the type of substance, the dose, the time from exposure to presentation to a health care facility, and the pre-existing health status of the patient. If a poisoning is recognized early and appropriate supportive care is initiated quickly, most patient outcomes are favorable. In modern hospitals with access to life support equipment the case fatality rate for self-poisonings is approximately 0.5%, but this can be as high as 10% to 20% in the developing world lacking critical care resources [1].

This article introduces the basic concepts for the initial approach to the critically poisoned patient and the steps required for stabilization. It introduces some key concepts in diagnosing the poisoning, using clinical clues and ancillary testing (ie, laboratory, ECG, and radiology). Finally, specific management issues are discussed.

Clinical evaluation

When evaluating a patient who has presented with a potential toxicologic emergency, the health care practitioner should not limit the differential diagnosis. A comatose patient who smells of ethanol may be harboring an

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intracranial hemorrhage; an agitated patient who seems anticholinergic may actually be encephalopathic from an infectious etiology. Patients must be thoroughly assessed and appropriately stabilized. Rarely is there a specific antidote for a poisoned patient; supportive care is the most important intervention.

All patients presenting with toxicity should be aggressively managed. Poisoned patients may seem to be in extremis (ie, brain dead), but most fully recover. The patient's airway should be patent and adequate ventilation ensured. If necessary, endotracheal intubation should be performed. Too often physicians are lulled into a false sense of security when a patient's oxygen saturations are adequate on high-flow oxygen. If the patient has either inadequate ventilation or poor airway protective reflexes, then the patient may be at risk for subsequent CO_2 narcosis with risk for worsening acidosis and the potential for aspiration. The initial treatment of hypotension for all poisonings consists of intravenous fluids. Close monitoring of the patient's pulmonary status should be performed to ensure that pulmonary edema does not develop as fluids are infused. The health care providers should place the patient on continuous cardiac monitoring with pulse oximetry and make frequent neurologic checks. Glucose should be checked at bedside in all patients with altered mental status. Poisoned patients should receive a large-bore peripheral intravenous line and all symptomatic patients should have a second line placed in either the peripheral or central venous system.

Many toxins can potentially cause seizures. In general, toxin-induced seizures are treated in a similar fashion to other seizures. Clinicians should ensure the patient maintains a patent airway and the blood glucose should be measured. Most toxin-induced seizures are self-limiting. For seizures requiring treatment, the first-line agent should be parenteral benzodiazepines. If benzodiazepines are not effective at controlling seizures, a second-line agent, such as phenobarbital, should be used. In rare poisoning cases (ie, isoniazid) pyridoxine should be administered. In cases of toxin-induced seizures, phenytoin is generally not recommended. It is usually ineffective and may add to the underlying toxicity of some agents, such as cyclic antidepressants, theophylline, cocaine, and lidocaine [2]. If a poisoned patient requires intubation, it is important to avoid the use of long-acting paralytic agents because these agents may mask seizures if they develop.

Rapid recognition of a toxidrome, if present, can help determine whether a poison is involved in a patient's condition and can help determine the class of toxin involved. Toxidromes are the constellation of signs and symptoms associated with a class of poisons. Table 1 lists selected toxidromes and their characteristics. Patients may not present with every component of a toxidrome and toxidromes can be clouded in mixed ingestions. Certain aspects of a toxidrome can have great significance. For example, noting dry axilla may be the only way of differentiating an anticholinergic patient from a sympathomimetic patient, and miosis may distinguish opioid toxicity from a benzodiazepine overdose. There are several notable exceptions to the

Table 1
Toxidromes

Toxidrome	Clinical effects
Opioid	Sedation, miosis, decreased bowel sounds, decreased respirations
Anticholinergic	Mydriasis, dry skin, dry mucous membranes, decreased bowel sounds, sedation, altered mental status, hallucinations, tachycardia, urinary retention
Sympathomimetic	Agitation, mydriasis, tachycardia, hypertension, hyperthermia, diaphoresis
Cholinergic	Miosis, lacrimation, diaphoresis, bronchospasm, bronchorrhea, vomiting, diarrhea, bradycardia
Serotonin syndrome	Altered mental status, tachycardia, hypertension, hyperreflexia, clonus, hyperthermia

recognized toxidromes. For example, several opioid agents do not cause miosis (ie, meperidine and tramadol). In most cases, a toxidrome does not indicate a specific poison, but rather a class of poisons.

Testing in the critically poisoned patient

When evaluating the critically ill poisoned patient, there is no substitute for a thorough history and physical examination. Numerous television medical shows depict a universal toxicology screen that automatically determines the agent causing a patient's symptoms. Unfortunately, samples cannot be simply "sent to the laboratory" with the correct diagnosis to a clinical mystery returning on a computer printout. Clues from a patient's physical examination are generally more likely to be helpful than a "shotgun" laboratory approach that involves indiscriminate testing of blood or urine for multiple agents [3].

When used appropriately, diagnostic tests may be of help in the management of the intoxicated patient. When a specific toxin or even class of toxins is suspected, requesting qualitative or quantitative levels may be appropriate [4]. In the suicidal patient whose history is generally unreliable or in the unresponsive patient where no history is available, the clinician may gain further clues as to the etiology of a poisoning by responsible diagnostic testing. In the intentionally poisoned patient, an acetaminophen level should be obtained to rule out coexisting toxicity.

Anion gap

A basic metabolic panel should be obtained in all suicidal poisoned patients. When low serum bicarbonate is discovered on a metabolic panel, the clinician should determine if an elevated anion gap exists. The formula most commonly used for the anion gap calculation is [5]

$$\left[Na^{+}\right] - \left[Cl^{-} + HCO_3\right]$$

This equation allows one to determine if serum electroneutrality is being maintained. The primary cation (sodium) and anions (chloride and bicarbonate) are represented in the equation [6]. There are other contributors to this equation that are unmeasured [7]. Other serum cations are not commonly included in this calculation, because either their concentrations are relatively low (ie, potassium) or assigning a number to represent their respective contribution is difficult (ie, magnesium, calcium) [7]. Similarly, there is also a multitude of other serum anions (ie, sulfate, phosphate, organic anions) that are also difficult to measure and quantify in an equation [6,7]. These unmeasured ions represent the anion gap calculated using the previously mentioned equation. The normal range for this anion gap is accepted to be 8 to 16 mEq/L [7], but some have recently suggested that because of changes in the technique for measuring chloride, the range should be lowered to 6 to 14 mEq/L [6]. An increase in the anion gap beyond an accepted normal range, accompanied by a metabolic acidosis, represents an increase in unmeasured endogenous (ie, lactate) or exogenous (ie, salicylates) anions [5]. A list of the more common causes of this phenomenon is organized in the classic MUDILES pneumonic as shown (the ''P'' has been removed from the older acronym of MUDPILES, because paraldehyde is no longer available):

Methanol
Uremia
Diabetic ketoacidosis
Iron, inhalants (ie, carbon monoxide, cyanide, toluene), isoniazid, ibuprofen
Lactic acidosis
Ethylene glycol, ethanol ketoacidosis
Salicylates, starvation ketoacidosis, sympathomimetics

It is imperative that clinicians who evaluate poisoned patients initially presenting with an increased anion gap metabolic acidosis investigate the etiology of that acidosis. Symptomatic poisoned patients may have an initial mild metabolic acidosis on presentation because of an elevation of serum lactate that can be caused by a number of processes before stabilization (ie, agitation, hypoxia, hypotension). With adequate supportive care including hydration and oxygenation, the anion gap acidosis should begin to resolve. If, despite adequate supportive care, an anion gap metabolic acidosis worsens in a poisoned patient, the clinician should consider toxins that form acidic metabolites (ie, ethylene glycol, methanol) [8]; toxins that themselves can worsen the acidosis as absorption increases (ie, ibuprofen) [9]; or toxins that cause lactic acidosis by interfering with aerobic energy production (ie, cyanide or iron) [10].

Osmole gap

The serum osmole gap is a common laboratory test that may be useful when evaluating poisoned patients. This test is most often discussed in the

context of evaluating the patient suspected of toxic alcohol (ie, ethylene glycol, methanol, and isopropanol) intoxication. Although this test may have use in such situations, it has many pitfalls and limitations to its effectiveness.

Osmotic concentrations are themselves expressed in both terms of osmolality (milliosmoles per kilogram of solution) and osmolarity (milliosmoles per liter of solution) [11,12]. This concentration can be measured by use of an osmometer, a tool that most often uses the technique of freezing point depression and is expressed in osmolality (Osm_M) [13]. A calculated serum osmolarity (Osm_C) may be obtained by any of a number of equations [14], involving the patient's glucose, sodium, and urea that contribute to almost all of the normally measured osmolality [15]. One of the most commonly used of these calculations is expressed below:

$$Osm_C = 2[Na^+] + [BUN]/2.8 + [glucose]/18$$

The correction factors in the equation are based on the relative osmotic activity of the substance in question [11]. Assuming serum neutrality, sodium as the predominant serum cation is doubled to account for the corresponding anions. Finding the osmolarity contribution of any other osmotically active substances that is reported in milligrams per deciliter (like blood, urea, nitrogen [BUN] and glucose) is accomplished by dividing by one tenth its molecular weight in daltons [11]. For BUN this conversion factor is 2.8 and for glucose it is 18. Similar conversion factors may be added to this equation to account for ethanol and the various toxic alcohols as shown below:

$$Osm_C = 2[Na^+] + [BUN]/2.8 + [glucose]/18 + [ethanol]/4.6 + [methanol]/3.2 + [ethylene\ glycol]/6.2 + [isopropanol]/6.0$$

The difference between the measured (Osm_M) and calculated (Osm_C) is the osmole gap (OG) and is depicted by the equation below [11]:

$$OG = Osm_M - Osm_C$$

If a significant osmole gap is discovered, the difference in the two values may represent presence of foreign substances in the blood [13]. Possible causes of an elevated osmole gap are listed as follows:

Acetone
Ethanol
Ethylene glycol
Isopropanol
Methanol
Propylene glycol

Unfortunately, what constitutes a normal osmole gap is widely debated. Traditionally, a normal gap has been defined as less than or equal to 10 mOsm/kg. The original source of this value is an article from Smithline and Gardner [16] that declares this number as pure convention. Further clinical study has not shown this assumption to be correct. Glasser and colleagues [17] studied 56 healthy adults and reported that they found the normal osmole gap to range from −9 to 5+ mOsm/kg. A study examining a pediatric emergency department population (N = 192) found a range from −13.5 to 8.9 [18]. Another study by Aabakken and colleagues [19] looked at the osmole gaps of 177 patients admitted to their emergency department and reported their range to be from −10 to 20 mOsm/kg. A vital point brought forth by the authors of this study is that the day-to-day coefficient of variance for their laboratory in regards to sodium was 1%. They believed this variance translated to a calculated analytic standard deviation of 9.1 mOsm in regards to osmole gap. This analytic variance alone may account for the variation found in patient's osmole gaps. This concern that even small errors in the measurement of sodium can result in large variations of the osmole gap has been voiced by other researchers [18,20]. Overall, the clinician should recognize that there is likely a wide range of variability in a patient's baseline osmole gap.

There are several concerns in regard to using the osmole gap as a screening tool in the evaluation of the potentially toxic-alcohol poisoned patient. The lack of a well-established normal range is particularly problematic. For example, a patient may present with an osmole gap of 9 mOsm, a value considered normal by the traditionally accepted normal maximum gap value of 10 mOsm. If this patient had an osmole gap of −5 just before ingestion of a toxic alcohol, the patient's osmole gap must have been increased by 14 mOsm to reach the new gap of 9 mOsm. If this increase was caused by ethylene glycol, it corresponds to a toxic level of 86.8 mg/dL [21]. In addition, if a patient's ingestion of a toxic alcohol occurred at a time distant from the actual blood sampling, the osmotically active parent compound has been metabolized to the acidic metabolites. The subsequent metabolites have no osmotic activity of their own and hence no osmole gap is detected [14,22]. It is possible that a patient may present at a point after ingestion with only a moderate rise in their osmole gap and anion gap. Steinhart [23] reported a patient with ethylene glycol toxicity who presented with an osmole gap of 7.2 mOsm caused by delay in presentation. Darchy and colleagues [20] presented two other cases of significant ethylene glycol toxicity with osmole gaps of 4 and 7, respectively. The lack of an abnormal osmole gap in these cases was speculated either to be caused by metabolism of the parent alcohol or a low baseline osmole gap that masked the toxin's presence.

The osmole gap should be used with caution as an adjunct to clinical decision making and not as a primary determinant to rule out toxic alcohol ingestion. If the osmole gap obtained is particularly large, it suggests an agent from the previous list may be present. A normal osmole should be

interpreted with caution; a negative study may not rule out the presence of such an ingestion; and the test result must be interpreted within the context of the clinical presentation. If such a poisoning is suspected, appropriate therapy should be initiated presumptively (ie, ethanol infusion, 4-methylpyrazole, hemodialysis, and so forth) while confirmation from serum levels of the suspected toxin are pending.

Urine drug screening

Many clinicians regularly obtain urine drug screening on altered patients or on those suspected of ingestion. Such routine urine drug testing is of questionable benefit. Kellermann and colleagues [24] found little impact of urine drug screening on patient management in an urban emergency setting, and Mahoney and colleagues [25] similarly conclude that toxic screening added little to treatment or disposition of overdose patients in their emergency department. In a study of over 200 overdose patients, Brett [26] showed that although unsuspected drugs were routinely detected, the results rarely led to changes in management and likely never affected outcome. In a similar large study of trauma patients, Bast and colleagues [27] noted that a positive drug screen had minimal impact on patient treatment.

Some authors do argue in favor of routine testing. Fabbri and colleagues [28] countered that comprehensive screening may aid decisions on patient disposition, resulting in fewer admissions to the hospital and less demand on critical care units. The screen used in their retrospective study tested for over 900 drugs and is not available to most clinicians. Milzman and colleagues [29] argued in favor of screening trauma victims, stating that the prognosis of intoxicated patients is unduly poor secondary to low Glasgow Coma Scores, although patient treatment and disposition did not seem to be affected [29].

The effect of such routine screening on patient management is low because most of the therapy is supportive and directed at the clinical scenario (ie, mental status, cardiovascular function, respiratory condition). Interpretation of the results can be difficult even when the objective for ordering a comprehensive urine screen is adequately defined. Most assays rely on the antibody identification of drug metabolites, with some drugs remaining positive days after use, and may not be related to the patient's current clinical picture. The positive identification of drug metabolites is likewise influenced by chronicity of ingestion, fat solubility, and coingestions. In one such example, Perrone and colleagues [30] showed a cocaine retention time of 72 hours following its use. Conversely, many drugs of abuse are not detected on most urine drug screens, including gamma hydroxybutyrate, fentanyl, and ketamine.

Interpretation is further confounded by false-positive and false-negative results. George and Braithwaite [31] evaluated five popular rapid urine screening kits and found all lacked significant sensitivity and specificity. The monoclonal antibodies used in these immunoassays may detect epitopes from multiple drug classes. For example, a relatively new antidepressant,

venlafaxine, produced false-positive results by cross-reactivity with the antiphencyclidine antibodies used in a urine test device [32]. False-positive benzodiazepine results were found in patients receiving the nonsteroidal anti-inflammatory drug oxaprozin who were screened using urine immunoassays [33]. Conversely, antibodies used in the immunoassays may not detect all drugs classified within a specific drug class. For example, one urine immunoassay does not detect physiologic doses of methadone. This assay detects codeine and its metabolites: morphine and morphine-3-glucuronide. Additionally, cross-reactivity of both prescription and over-the-counter medications used in therapeutic amounts for true illness may elicit positive screens. Diphenhydramine has been documented to interfere with one urine immunoassay for propoxyphene [34].

The use of ordering urine drug screens is fraught with significant testing limitations, including false-positive and false-negative results. Many authors have shown that the test results rarely affect management decisions. Routine drug screening of those with altered mental status, abnormal vital signs, or suspected ingestion is not warranted and rarely guides patient treatment or disposition.

Radiographic studies

The role of radiologic testing specifically in the diagnosis and management of the critically poisoned patient is limited. Radiologic testing is commonly used to diagnose complications associated with poisonings, such as aspiration pneumonitis and anoxic brain injury.

In some circumstances, plain radiography can assist in the diagnosis and management of poisonings if the substance in question is radiopaque. The primary use of radiography in the critically ill poisoned patient is in the detection and management of iron poisoning (Fig. 1) [35–37]. Attempts to use the presence or absence of radiopacities consistently to predict severe iron toxicity have not been successful [38,39]. Not all iron products are equally radiopaque; whereas ferrous sulfate and ferrous fumurate are typically radiopaque, other preparations may not be radiopaque [40]. For example, chewable iron supplements are unlikely to be seen on abdominal radiographs [37] secondary to both the low elemental content in these chewable products and as a result of their quick dissolution in the gastrointestinal tract [37]. In using abdominal radiographs in diagnosing iron poisonings, time from ingestion is important; as time passes visualization becomes more difficult [35].

Another situation where plain radiography may prove useful is with body packers. These couriers, also known as ''mules,'' swallow multiple packages of illicit drugs for the purposes of transporting without detection. The container of choice is often condoms, latex, or cellophane formed into balls or ovals that are 2 to 4 cm in size [41]. Besides the illegal nature of this occupation, there is a serious health risk to these patients who may suffer from

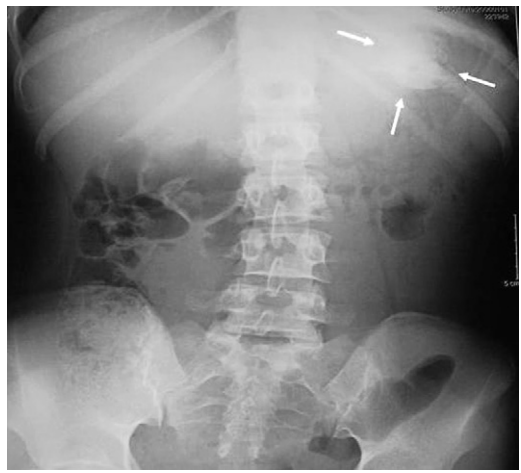

Fig. 1. A radiograph demonstrating a grouping of iron tablets in the stomach (*arrows*) following a suicidal ingestion of ferrous fumarate.

intestinal obstruction or from the direct effects of the illicit drugs themselves if the packages leak [42]. One study by Karhunen and colleagues [43] in Finland looked at a total of 82 patients admitted for abdominal radiographs because of suspected body packing. Twelve of these were read as positive, and nine of these proved to be true positives (75%). The three false-positives (3.6%) were thought secondary to constipation involving compact feces with increased radiodensity mimicking narcotic packages. There were 70 films that were read as negative with only one false-negative (1.2%) that was attributed to the inexperience of the radiologist. In a recent review of the literature, plain abdominal radiography was identified as the radiologic method of choice for finding these packets, as opposed to ultrasound and CT [41]. The authors based this decision on ease of use, availability, patient tolerance, and the relatively high sensitivity and specificity shown by the Karhunen study.

Besides these established examples, plain radiography of the abdomen has also been studied to identify other pills that may be radiopaque in acute overdose. Multiple studies regarding the radiopacity of ingested pharmaceuticals have not consistently supported the use of radiography in management of these patients. O'Brien and colleagues [44] studied the detect ability of 459 different tablets and capsules using plain radiography. The investigators used a ferrous sulfate tablet as a control grading the other tablets' radiopacity. These pills were then placed in the middle of a plastic container that contained 20 cm of water to simulate the human body density. Overall, of the wide variety of pills tested, only 29 drugs (6.3%) were graded as having the same or greater radiopacity as ferrous sulfate; 136 pills (29.6%) were regarded as having at least moderate opacity; and the largest

remaining portion of pills, 294 (64%), were regarded as no more than minimally detectable. The authors concluded that indiscriminate use of plain abdominal radiographs was not justified and that a negative film could not be relied on to rule out potential toxic pill ingestions, especially if there is time to allow the pills to dissolve.

Electrocardiogram

The interpretation of ECG in the poisoned patient can challenge even the most experienced clinician. There are numerous drugs that can cause ECG changes. The incidence of ECG changes in the poisoned patient is unclear and the significance of various changes may be difficult to define. Despite the fact that drugs have widely varying indications for therapeutic use, many unrelated drugs share common cardiac electrocardiographic effects if taken in overdose. Potential toxins can be placed into broad classes based on their cardiac effects. Two such classes, agents that block the cardiac potassium efflux channels and agents that block cardiac fast sodium channels, can lead to characteristic changes in cardiac indices consisting of QRS prolongation and QT prolongation, respectively. The recognition of specific ECG changes associated with other clinical data (toxidromes) can be potentially life saving [45].

Studies suggest that approximately 3% of all noncardiac prescriptions are associated with the potential for QT prolongation [46]. Myocardial repolarization is driven predominantly by outward movement of potassium ions [47]. Blockade of the outward potassium currents by drugs prolongs the action potential, resulting in QT interval prolongation and the potential emergence of T- or U-wave abnormalities on the ECG [48,49]. The prolongation of repolarization causes the myocardial cell to have less charge difference across its membrane, which may result in the activation of the inward depolarization current (early afterdepolarization) and promote triggered activity. These changes may lead to reentry and subsequent polymorphic ventricular tachycardia, most often as the torsades de pointes variant of polymorphic ventricular tachycardia [50]. The QT interval is simply measured from the beginning of the QRS complex to the end of the T wave. Within any ECG tracing, there is lead-to-lead variation of the QT interval. In general, the longest measurable QT interval on an ECG is regarded as determining the overall QT interval for a given tracing [51]. The QT interval is influenced by the patient's heart rate. Several formulas have been developed to correct the QT interval for the effect of heart rate (QTc) using the RR interval (RR), with Bazett's formula ($QTc = QT/RR^{1/2}$) being the most commonly used. QT prolongation is considered to occur when the QTc interval is greater than 440 milliseconds in men and 460 milliseconds in women, with arrhythmias most commonly associated with values greater than 500 milliseconds (Fig. 2). The potential for an arrhythmia for a given QT interval varies from drug to drug and

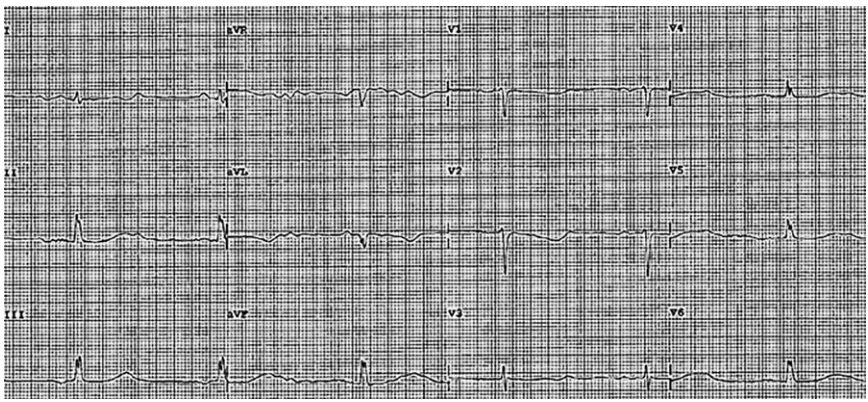

Fig. 2. ECG demonstrating sinus bradycardia with marked QT prolongation (660 ms) following an overdose of sotalol.

patient to patient [47]. Drugs associated with QT prolongation are listed in Box 1 [52].

Other etiologies involved in possible prolongation of the QT interval include congenital long QT syndrome, mitral valve prolapse, hypokalemia, hypocalcemia, hypomagnesemia, hypothermia, myocardial ischemia, neurologic catastrophes, and hypothyroidism [53].

The ability of drugs to induce cardiac Na^+ channel blockade and prolong the QRS complex has been well described in numerous literature reports (Fig. 3) [54]. This Na^+ channel blockade activity has been described as a membrane stabilizing effect, a local anesthetic effect, or a quinidine-like effect. Cardiac voltage-gated sodium channels reside in the cell membrane and open in conjunction with cell depolarization. Sodium channel blockers bind to the transmembrane Na^+ channels and decrease the number available for depolarization. This creates a delay of Na^+ entry into the cardiac myocyte during phase 0 of depolarization. As a result, the upslope of depolarization is slowed and the QRS complex widens [55]. In some cases, the QRS complex may take the pattern of recognized bundle branch blocks [56,57]. In the most severe cases, the QRS prolongation becomes so profound that it is difficult to distinguish between ventricular and supraventricular rhythms [58,59]. Continued prolongation of the QRS may result in a sine wave pattern and eventual asystole (Fig. 4). It has been theorized that the Na^+ channel blockers can cause slowed intraventricular conduction, unidirectional block, the development of a reentrant circuit, and a resulting ventricular tachycardia [60]. This can then degenerate into ventricular fibrillation. Differentiating a prolongation of the QRS complex because of Na^+ channel blockade in the poisoned patient versus other nontoxic etiologies can be difficult. Rightward axis deviation of the terminal 40 milliseconds of the QRS axis has been associated with tricyclic antidepressant poisoning [61,62]. The occurrence of this finding in other Na^+ channel blocking agents is unknown.

Box 1. K^+ efflux channel blocking drugs

Antihistamines
- Astemizole
- Clarithromycin
- Diphenhydramine
- Loratidine
- Terfenadine

Antipsychotics
- Chlorpromazine
- Droperidol
- Haloperidol
- Mesoridazine
- Pimozide
- Quetiapine
- Risperidone
- Thioridazine
- Ziprasidone

Arsenic trioxide
Bepridil
Chloroquine
Cisapride
Citalopram
Clarithromycin
Class IA antiarrhythmics
- Disopyramide
- Quinidine
- Procainamide

Class IC antiarrhythmics
- Encainide
- Flecainide
- Moricizine
- Propafenone

Class III antiarrhythmics
- Amiodarone
- Dofetilide
- Ibutilide
- Sotalol

Cyclic antidepressants
- Amitriptyline
- Amoxapine
- Desipramine
- Doxepin

- Imipramine
- Nortriptyline
- Maprotiline

Erythromycin
Fluoroquinolones
- Ciprofloxacin
- Gatifloxacin
- Levofloxacin
- Moxifloxacin
- Sparfloxacin

Hydroxychloroquine
Levomethadyl
Methadone
Pentamidine
Quinine
Tacrolimus
Venlafaxine

Myocardial Na^+ channel blocking drugs comprise a diverse group of pharmaceutical agents (Box 2).

Patients poisoned with these agents have a variety of clinical presentations. For example, sodium channel blocking medications, such as diphenhydramine, propoxyphene, and cocaine, may also develop anticholinergic, opioid, and sympathomimetic syndromes, respectively [63–65]. In addition, specific drugs may affect not only the myocardial Na^+ channels, but also calcium influx and potassium efflux channels [66,67]. This may result in ECG changes and rhythm disturbances not related entirely to the drug's Na^+ channel blocking activity. All the agents listed in Box 2 are similar in that they may induce myocardial Na^+ channel blockade and may respond to therapy with hypertonic saline or sodium bicarbonate [59,64,65]. It is

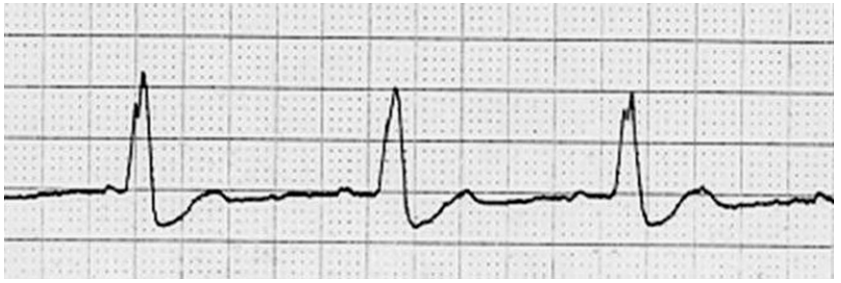

Fig. 3. A rhythm strip demonstrating marked QRS prolongation following a propoxyphene overdose.

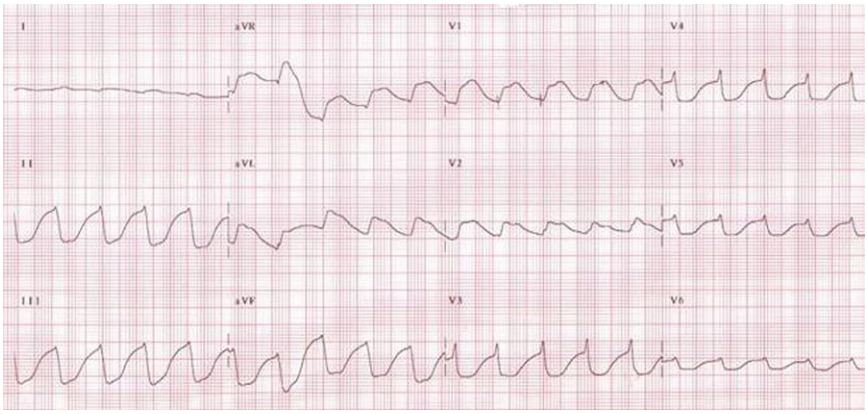

Fig. 4. An ECG demonstrating a sinusoidal wave pattern secondary to the sodium channel blockade induced by an acute overdose of hydroxychloroquine.

reasonable to treat poisoned patients with a prolonged QRS interval, particularly those with hemodynamic instability, empirically with 1 to 2 mEq/kg of sodium bicarbonate. A shortening of the QRS can confirm the presence of a sodium channel blocking agent. It can also improve inotropy and help prevent arrhythmias [54].

There are multiple agents that can result in cardiotoxicity and subsequent ECG changes from the changes noted previously to other alterations, such as bradycardia and tachycardia. Physicians managing patients who have taken overdoses on medications should be aware of the various electrocardiographic changes that can potentially occur in the overdose setting.

Management

After initial evaluation and stabilization of the critically poisoned patient as described previously, the physician can consider whether there is a need for the administration of specific therapies. Decontamination should be considered. Several poisons have specific antidotes that if used in a timely and appropriate manner can be of great benefit. Finally, the safe disposition of the patient must be determined (ie, monitored floor bed or ICU).

Approximately 80% of all poisonings occur by ingestion and the most common type of decontamination performed is gastrointestinal decontamination using a variety of techniques including emesis, gastric lavage, activated charcoal, cathartics, and whole-bowel irrigation. Poisonings may also occur by dermal and ocular routes, which necessitate external decontamination. Significant controversy exists concerning the need for routine gastric emptying in the poisoned patient. Current available evidence dissuades from the routine use of gastric decontamination. Gastric decontamination may be considered in select cases and specific scenarios. Before

Box 2. Na^+ channel blocking drugs

Amantadine
Carbamazepine
Chloroquine
Class IA antiarrhythmics
  Disopyramide
  Quinidine
  Procainamide
Class IC antiarrhythmics
  Encainide
  Flecainide
  Propafenone
Citalopram
Cocaine
Cyclic antidepressants
Diltiazem
Diphenhydramine
Hydroxychloroquine
Loxapine
Orphenadrine
Phenothiazines
  Medoridazine
  Thioridazine
Propranolol
Propoxyphene
Quinine
Verapamil

performing gastrointestinal decontamination techniques, the clinician responsible for the care of the poisoned patient must clearly understand whether the benefit of decontamination outweighs any potential harm.

The number of pharmacologic antagonists or antidotes available to treat the critically poisoned patient is quite limited (Table 2). There are few antidotes that rapidly reverse toxic effects and restore a patient to a previously healthy baseline state. Administering some pharmacologic antagonists may worsen patient outcome compared with simply optimizing basic supportive care. Antidotes should be used cautiously, with a clear understanding of indications and contraindications.

Atropine

Atropine is the initial drug of choice in symptomatic patients poisoned with organophosphates or carbamates. Atropine acts as a muscarinic

Table 2
Antidotes

Agent or clinical finding	Antidote
Acetaminophen	*N*-acetylcysteine
Benzodiazepines	Flumazenil
β-blockers	Glucagon
Cardiac glycosides	Digoxin immune Fab
Crotalid envenomation	Crotalidae polyvalent immune Fab
Cyanide	Hydroxocobalamin
Ethylene glycol	Fomepizole
Iron	Deferoxamine
Isoniazid	Pyridoxine
Methanol	Fomepizole
Methemoglobinemia	Methylene blue
Opioids	Naloxone
Organophosphates	Atropine Pralidoxime
Sulfonylureas	Octreotide

receptor antagonist and blocks neuroeffector sites on smooth muscle, cardiac muscle, secretory gland cells, and the central nervous system. Atropine is useful in alleviating bronchoconstriction, bronchorrhea, tenesmus, abdominal cramps, nausea, vomiting, bradydysrythmias, and seizure activity. Atropine can be administered by the intravenous, intraosseous, intramuscular, or endotracheal route. The dose varies with the type of exposure, requiring a few milligrams in mild cases and hundreds of milligrams in extreme cases [68]. For the mildly and moderately symptomatic patient, 2 mg for adults and 0.02 mg/kg for children (minimum of 0.1 mg) is administered every 5 minutes. In the severely poisoned patient, dosages may need to be increased and given more rapidly [69]. Tachycardia is not a contraindication to atropine administration in these patients. Drying of the respiratory secretions and resolution of bronchoconstriction are the therapeutic end points used to determine the appropriate dose of atropine. This is clinically apparent as the patient's work of breathing improves [68]. Atropine has no effect on the nicotinic receptors and has no effect on autonomic ganglia and neuromuscular junction [69]. Muscle weakness, fasciculations, tremors, and paralysis are not indications for further atropine dosing. It does have a partial effect on the central nervous system and is helpful in resolving or preventing seizures [70]. It is most effective in preventing seizures if given within 5 minutes of organophosphate exposure [71]. After 5 to 10 minutes anticholinergic treatment alone is not effective at terminating seizures and benzodiazepines must be added to treat seizures effectively [71,72].

Deferoxamine

Deferoxamine is an effective chelator of iron. Deferoxamine chelates iron and converts it to a water-soluble complex, ferrioxamine, which is

eliminated readily by the urine. Indications for deferoxamine infusion include significant clinical signs of iron toxicity, metabolic acidosis, shock, profound lethargy, coma, serum iron levels greater than 500 μg/dL, or a radiograph positive for multiple pills [73]. Deferoxamine should be infused intravenously at a starting rate of 15 mg/kg/h, not to exceed 1 g/h, over a total of 6 hours, followed by re-evaluation. Deferoxamine-induced hypotension may occur at fast rates, and adequate hydration should be ensured before infusion initiation [73]. As iron is chelated and excreted, urine may develop a characteristic rusty-red (vine rose) appearance.

Crotalidae antivenin

Use of antivenin in the appropriate doses can control local swelling and serious systemic effects (ie, coagulopathy) that occur in patients who have been envenomated [74]. Antivenin should not be used prophylactically because a significant number of snake bites are dry bites. There are numerous dosage regimens that vary with the degree of systemic toxicity and regional treatment preferences. Consultation with a poison center or a clinical toxicologist is advised for the most contemporary treatment recommendations.

Digoxin immune Fab

Digoxin-specific Fab fragments are antibody fragments produced by enzymatic cleavage of sheep IgG antibodies to digoxin. Fab fragments can reverse digitalis-induced dysrhythmias, conduction disturbances, myocardial depression, and hyperkalemia in severely poisoned patients [75]. Patients can have reversal of ventricular arrhythmia within 2 minutes and most patients have settling of toxic dysrhythmias within 30 minutes of Fab administration [76]. Within 6 hours 90% of patients have complete or partial response [75]. Animal studies and case reports have demonstrated the efficacy of Fab fragments to the cardiac glycoside contained in plants [77–79]. Digoxin-specific Fab fragment therapy should be administered in a digoxin poisoned patient for the following indications: (1) potassium greater than 5 mEq/L following acute ingestion, (2) hemodynamic instability, and (3) patients with potentially life-threatening dysrhythmias [76].

Although serum digoxin levels should not be the sole factor in determining the need to administer Fab, dosage calculations for Fab are based on the serum digoxin level, or estimated body load of digoxin. It is assumed that equimolar doses of antibody fragments are required to achieve neutralization. Forty milligrams of Fab (one vial) bind 0.6 mg of digoxin. When presented with a severely poisoned patient in whom the quantity ingested acutely is unknown, an empiric dose of 5 to 10 vials at a time should be given and the clinical response observed. If cardiac arrest is imminent or has occurred, the dose can be given as a bolus, but it should be infused

over 30 minutes in stable patients. For patients with chronic therapeutic overdoses the digoxin levels are often only mildly elevated and one to two vials of Fab may be sufficient [75]. The recommended dose for a given patient can be determined using the tables in the package insert or by contacting a regional poison center or toxicology consultant.

Flumazenil

Benzodiazepines are involved in many intentional overdoses. Although these overdoses are rarely fatal when a benzodiazepine is the sole ingestant, they often complicate overdoses with other central nervous system depressants (eg, ethanol, opioids, and other sedatives) because of their synergistic activity. Flumazenil finds its greatest use in the reversal of benzodiazepine-induced sedation from minor surgical procedures. The initial flumazenil dose is 0.2 mg and should be administered intravenously over 30 seconds. If no response occurs after an additional 30 seconds, a second dose is recommended. Additional incremental doses of 0.5 mg may be administered at 1-minute intervals until the desired response is noted or until a total of 3 mg has been administered. It is important to note that resedation may occur [80], and patients should be observed with close monitoring after requiring reversal. Flumazenil should not be administered as a nonspecific coma-reversal drug and should be used with extreme caution after intentional benzodiazepine overdose because it has the potential to precipitate withdrawal in benzodiazepine-dependent individuals or induce seizures in those at risk [80].

Fomepizole

Fomepizole (4-methyl-pyrazole) is an alcohol dehydrogenase inhibitor. It is administered in cases of suspected or confirmed ingestion and intoxication with ethylene glycol or methanol [81]. Fomepizole should be administered intravenously as a loading dose of 15 mg/kg, followed by doses of 10 mg/kg every 12 hours for four doses (48 hours) then 15 mg/kg every 12 hours thereafter [8,82]; all doses should be administered as a slow intravenous infusion over 30 minutes. During hemodialysis, the frequency of dosing should be increased to every 4 hours. Therapy should be continued until ethylene glycol or methanol concentrations are less than 20 mg/dL and the patient is asymptomatic.

Hydroxocobalamin

Hydroxocobalamin is a safe and effective treatment of cyanide toxicity that has recently been approved in the United States. The reaction of hydroxocobalamin with cyanide results in the displacement of a hydroxyl group by a cyano group to form cyanocobalamin (vitamin B_{12}), which is then excreted in the urine [83]. The usual adult dose of hydroxocobalamin is 5 g, which may be repeated in cases of massive cyanide poisoning [84,85]. The pediatric dose is 70 mg/kg up to 5 g [86]. Virtually every patient

receiving this antidote develops orange-red discoloration of the skin, mucous membranes, and urine. This resolves within 24 to 48 hours [87].

N-Acetylcysteine

Significant acetaminophen overdoses may need to be treated with *N*-acetylcysteine if the patient has a toxic serum acetaminophen concentration or has indicators of hepatocellular damage [88]. *N*-acetylcysteine increases glutathione levels and serves as a glutathione surrogate. An acetaminophen overdose may deplete glutathione, permitting the toxic metabolite to destroy hepatocytes. *N*-acetylcysteine is most effective if administered within 8 hours of the acetaminophen ingestion; however, it can still be effective days after the ingestion when patients are already in hepatic failure and acetaminophen levels are no longer detectable [88].

N-acetylcysteine can be given by both oral and intravenous administration [88]. Oral is 140 mg/kg loading dose followed by 70 mg/kg every 4 hours for 17 doses. Intravenous is 150 mg/kg loading dose followed by 50 mg/kg over 4 hours followed by 100 mg/kg infused over 16 hours.

Parenteral administration of *N*-acetylcysteine eliminates compliance problems associated with oral therapy (adverse taste and odor caused by the sulfhydryl groups) and circumvents the problems associated with acetaminophen-induced vomiting.

Naloxone

Opioid poisoning from the abuse of morphine derivatives or synthetic narcotic agents may be reversed with the opioid antagonist naloxone [89]. Naloxone is commonly used in comatose patients as a therapeutic and diagnostic agent. The standard dosage regimen is to administer from 0.4 to 2 mg slowly, preferably intravenously. The intravenous dose should be readministered at 5-minute intervals until the desired end point is achieved: restoration of respiratory function, ability to protect the airway, and an improved level of consciousness [90]. If the intravenous route of administration is not viable, alternative routes include intramuscular and intraosseous [90]. A patient may not respond to naloxone administration for a variety of reasons: insufficient dose of naloxone, the absence of an opioid exposure, a mixed overdose with other central nervous and respiratory system depressants, or medical or traumatic reasons.

Naloxone can precipitate profound withdrawal symptoms in opioid-dependant patients. Symptoms of withdrawal include agitation, vomiting, diarrhea, piloerection, diaphoresis, and yawning [90]. Care should be taken to administer this agent as necessary only to restore adequate respiration and airway protection. Naloxone's clinical efficacy can last for as little as 45 minutes [89]. Patients are at risk for recurrence of narcotic effect. This is particularly true for patients exposed to methadone or sustained-release

opioid products. In addition, renal insufficiency increases naloxone's elimination half-life, placing the patient at risk for resedation hours after the initial dose. Patients should be observed in a monitored setting for resedation for at least 4 hours after reversal with naloxone. If a patient does resedate, it is reasonable to administer naloxone as an infusion. An infusion of two thirds the effective initial bolus per hour is usually effective [90].

Pralidoxime chloride

Pralidoxime chloride reactivates acetylcholinesterase by exerting a nucleophilic attack on the phosphorus resulting in an oxime-phosphate bond that splits from the acetylcholinesterase leaving the regenerated enzyme. This reactivation is clinically most apparent at skeletal neuromuscular junctions, with less activity at muscarinic sites [91]. Pralidoxime must be administered concurrently with adequate atropine doses. The process of aging prevents pralidoxime from regenerating the acetylcholinesterase-active site, and is ineffective after aging has occurred. The sooner pralidoxime is administered, the greater the clinical effect. The recommended dose of pralidoxime is 1 to 2 g for adults or 20 to 50 mg/kg for children by intravenous route. Slow administration over 15 to 30 minutes has been advocated to minimize side effects [68,92]. These side effects include hypertension, headache, blurred vision, epigastric discomfort, nausea, and vomiting. Rapid administration can result in laryngospasm, muscle rigidity, and transient impairment of respiration [91].

Pralidoxime is rapidly excreted by the kidney with a half-life of approximately 90 minutes [93]. A continuous infusion is often recommended after the loading dose to maintain therapeutic levels [94–97]. Currently, the World Health Organization recommends a bolus of greater than 30 mg/kg followed by an infusion of greater than 8 mg/kg/h [98].

Pyridoxine

Isoniazid, hydrazine, and the *Gyrometria* species of mushrooms can decrease the brain concentrations of γ-aminobutyric acid by inhibiting pyridoxal-5-phosphate activity, resulting in the development of severe seizure activity [99,100]. The administration of pyridoxine (vitamin B_6) can prevent or actively treat the central nervous system toxicity associated with these toxins [101]. Pyridoxine is administered on a gram-for-gram basis with isoniazid (ie, the amount of pyridoxine should equal the amount of isoniazid). If the ingested amount of agent is unknown, the dose of pyridoxine should be 5 g administered intravenously [101]. This dose can be repeated.

Summary

The emergency physician often is required to care for critically poisoned patients. Prompt action must be taken for patients who present with serious

toxic effects or after potentially fatal ingestions. Because many poisons have no true antidote and the poison involved may initially be unknown, the first step is simply focused on supportive care. Identifying the causative poison, through a detailed history, recognizing a toxidrome, or laboratory analysis may help direct care. There are several antidotes available that can be life saving, and the clinician should promptly identify those patients who may benefit from these agents.

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