Toxidromes

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KEYWORDS

• Toxidrome • Syndrome • Poisoning • Toxicology

KEY POINTS

- A toxidrome is a constellation of findings, either from the physical examination or from ancillary testing, which may result from any given poison. It serves to clue the clinician into the correct diagnosis.
- Common toxidromes include: anticholinergic toxidrome, cholinergic toxidrome, opioid toxidrome, sympathomimetic toxidrome.
- Even though these toxidromes can aid the clinician in narrowing the differential diagnosis, care must be exercised to realize the exceptions and limitations associated with each.

Poisonings are commonly encountered in critical care medicine.[1] Patients can be exposed to potential toxins either accidentally (eg, drug interactions or occupational exposures) or intentionally (eg, substance abuse or suicide attempt). The outcome following a poisoning depends on numerous factors, such as the dose taken, the characteristics of the substance, the time to presentation to the health system, and the preexisting health status of the patient. If a poisoning is recognized early and appropriate supportive care is initiated quickly, most outcomes will be favorable.

This article introduces the basic concepts for the initial approach to the poisoned patient and the initial steps in stabilization. Next, it introduces some key concepts in diagnosing the poisoning with focus on the various classic toxidromes, including those based on physical examination, laboratory analysis, and the ECG.

INITIAL CLINICAL EVALUATION

All patients presenting with toxicity or potential toxicity should be managed supportively regardless of the perceived toxidrome encountered.[2,3] The patient's airway

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should be patent and adequate ventilation assured. If necessary, endotracheal intubation should be performed with assisted ventilation initiated. Too often, physicians are lulled into a false sense of security when a poisoned patient's oxygen saturations are adequate on high-flow oxygen. If the patient has either inadequate ventilation (eg, from profound sedation) or a poor gag reflex, the patient may be at risk for subsequent carbon dioxide narcosis with worsening acidosis or aspiration.

The initial treatment of hypotension consists simply of adequate administration of intravenous (IV) fluids. Close monitoring of the patient's pulmonary status should be performed to assure that pulmonary edema does not develop as fluids are infused. The health care providers should place all potentially unstable overdose patients on continuous cardiac monitoring and pulse oximetry, and perform frequent neurologic reassessments. In all patients with altered mental status, the patient's blood glucose level should be checked. Poisoned patients should receive a large-bore peripheral IV line and all symptomatic patients should have a second line placed in either the peripheral or central venous system. Placement of a urinary catheter should be considered early in the care of hemodynamically unstable poisoned patients to monitor urinary output as an indicator of adequate perfusion.

Identification of the constellation of signs, symptoms, laboratory findings, and ECG changes that define a specific toxicologic syndrome, or toxidrome, may narrow a differential diagnosis to a specific class of poisons and guide subsequent management.[4,5] Select toxidromes that may be diagnosed via the physical examination may be found in **Table 1**. Many toxidromes have several overlapping features. For example, anticholinergic findings are highly similar to sympathomimetic findings, with an exception being the effects on sweat glands: anticholinergic agents produce warm, flushed dry skin, whereas sympathomimetic agents produce diaphoresis. Toxidrome findings may also be affected by individual variability, comorbid conditions, and coingestants. For example, tachycardia associated with sympathomimetic or anticholinergic toxidromes may be absent in a patient who is concurrently taking beta-adrenergic receptor antagonist medications. Additionally, although toxidromes may be applied to classes of drugs, some individual agents within these classes may have one or more toxidrome findings absent.[6] For instance, meperidine is an opioid analgesic but does not induce miosis, which helps define the classic opioid toxidrome. When accurately identified, the toxidrome may provide invaluable information for diagnosis and subsequent treatment, although the many limitations impeding acute toxidrome diagnosis must be carefully considered.[7]

Table 1
Selected physical examination toxidromes

Toxidrome	Signs and Symptoms
Anticholinergic	Mydriasis, tachycardia, anhidrosis, dry mucous membranes, hypoactive bowel sounds, altered mental status, delirium, hallucinations, urinary retention
Cholinergic	Diarrhea, diaphoresis, involuntary urination, miosis, bradycardia, bronchospasm, bronchorrhea, emesis, lacrimation, salivation
Opioid	Sedation, miosis, decreased bowel sounds, decreased respirations, bradycardia
Sympathomimetic	Agitation, mydriasis, tachycardia, hypertension, hyperthermia, diaphoresis

PHYSICAL EXAMINATION TOXIDROMES

Anticholinergic Toxidrome

Anticholinergic agents act by inhibiting muscarinic receptors.[8] Muscarinic receptors primarily are associated with the parasympathetic nervous system, which innervates numerous organ systems, including the eye, heart, respiratory system, skin, gastrointestinal tract, and bladder. Sweat glands, innervated by the sympathetic nervous system, also are modulated by muscarinic receptors.

Following exposure to a muscarinic antagonist, findings consistent with anticholinergic syndrome develop on physical examination. Characteristic manifestations of the anticholinergic syndrome have long been taught using the old medical adage "dry as a bone, blind as a bat, red as a beet, hot as a hare, and mad as a hatter," which correspond with anhidrosis, mydriasis, flushing, hyperthermia, and delirium, respectively.

Depending on the dose and time postexposure, several of central nervous system (CNS) effects may manifest.[9] Restlessness, apprehension, abnormal speech, confusion, agitation, tremor, picking movements, ataxia, stupor, and coma have all been described following exposure to various anticholinergic agents. When manifesting delirium, the individual often stares into space, mutters, and fluctuates between occasional lucid intervals with appropriate responses and periods of vivid hallucinations. Phantom behaviors, such as plucking or picking in the air or at garments, are characteristic. Hallucinations are prominent and may be benign, entertaining, or terrifying to the patient experiencing them. Exposed patients may have conversations with hallucinated figures or they may misidentify persons they typically know well. Simple tasks typically performed well by the exposed person may become difficult. Motor coordination, perception, cognition, and new memory formation are altered.

Mydriasis causes photophobia. Impairment of near vision occurs because of loss of accommodation and reduced depth of field secondary to ciliary muscle paralysis and pupillary enlargement. Tachycardia may occur. Exacerbated heart rate responses to exertion are also expected. Systolic and diastolic blood pressure may show moderate elevation. A decrease in precapillary tone may cause skin flushing. Intestinal motility slows and secretions from the stomach, pancreas, and gallbladder decrease resulting in decreased bowel sounds. Nausea and vomiting may occur. All glandular cells become inhibited, and dry mucus membranes of the mouth and throat are noted. Inhibition of sweating results in dry skin, which is best examined in the axilla or groin due to the high concentration of muscarinic sweat glands in these areas. Urination may be difficult and urinary retention may occur. Urinary retention may contribute to an anticholinergic patient's agitation and early urinary catheter placement is recommended. The exposed patient's temperature may become elevated from the inability to sweat and dissipate heat. In warm climates this may result in marked hyperthermia.

Cholinergic Toxidrome

A true cholinergic toxidrome is the opposite of the anticholinergic toxidrome depicted previously. Cholinergic agents activate muscarinic acetylcholine receptors. However, the clinical syndrome encountered by many cholinergic agents may vary considerably because many muscarinic agonists are also agonists of other receptors. For example, organophosphates, considered classic cholinergic agents, do not only cause muscarinic activation, but also activate the sympathetic system.[10]

Acetylcholine is a neurotransmitter found throughout the nervous system, including the CNS, the autonomic ganglia (sympathetic and parasympathetic), the postganglionic parasympathetic nervous system, and at the skeletal muscle motor end plate.[11] Acetylcholine binds to and activates muscarinic and nicotinic receptors. The enzyme,

acetylcholinesterase (AChE), regulates acetylcholine activity within the synaptic cleft. Acetylcholine binds to the active site of AChE where the enzyme rapidly hydrolyzes acetylcholine to choline and acetic acid. These hydrolyzed products rapidly dissociate from AChE so that the enzyme is free to act on another molecule. Organophosphates and carbamate insecticides act as AChE inhibitors by binding at the enzyme's active site. The inhibited enzyme is unable to inactivate acetylcholine. As a result, excessive acetylcholine stimulation occurs. Subsequently, not only are the muscarinic receptors activated but also are the nicotinic receptors leading to both activation of the sympathomimetic system and stimulation of the neuromuscular junction. Nicotine poisoning is clinically similar to an organophosphate or carbamate poisoning. Nicotine directly stimulates the nicotinic receptors and, therefore, stimulates the sympathetic and parasympathetic ganglia.

A pure cholinergic toxidrome affects nearly every organ system.[12] The respiratory system effects of cholinergic agents tend to be dramatic and are considered to be the major factor leading to the death of the victim.[13] Profuse watery nasal discharge, nasal hyperemia, marked salivation, and bronchorrhea have all been described. Prolonged expiratory phase, cough, and wheezing may manifest as a consequence of lower respiratory tract bronchorrhea and bronchoconstriction. Bradydysrhythmias and hypotension may be seen. Lacrimation, blurred vision, and miosis can occur. The sweat glands are innervated by sympathetic muscarinic receptors and profuse diaphoresis can occur. Cholinergic innervation causes an increase in gastric and intestinal motility and a relaxation of reflex anal sphincter tone. As a result, profuse watery salivation and gastrointestinal hyperactivity with resultant nausea, vomiting, abdominal cramps, tenesmus, and uncontrolled defecation are characteristic features of a cholinergic toxidrome. Cholinergic stimulation of the detrusor muscle causes contraction of the urinary bladder and relaxation of the trigone and sphincter muscles resulting in involuntary urination. Mnemonics that have been used to describe the cholinergic toxidrome include DUMBBELS (defecation, urination, miosis, bronchorrhea, bronchoconstriction, emesis, lacrimation, and salivation) or SLUDGE (salivation, lacrimation, urination, defecation, gastrointestinal dysfunction, and emesis).

Seizures are frequently seen in severe cholinergic poisoning, due to the CNS effects of excess acetylcholine.[14] Stimulation of the nicotinic receptors at the motor end plate can initially result in fasiculations but can rapidly progress to a flaccid paralysis (similar to the depolarizing paralytic agent succinylcholine). The propensity to cause seizures as well as paralysis puts cholinergic patients at risk for nonconvulsive status epilepticus.

Atropine is the initial drug of choice in symptomatic cholinergic patients.[15] Atropine acts as a muscarinic receptor antagonist and blocks neuroeffector sites on smooth muscle, cardiac muscle, secretory gland cells, peripheral ganglia, and in the CNS. Atropine is, therefore, useful in alleviating bronchoconstriction and bronchorrhea, tenesmus, abdominal cramps, nausea and vomiting, bradydysrythmias, and seizure activity. Atropine can be administered by either the IV, intramuscular, or endotracheal route. The dose varies with the type of exposure, but generally is higher than doses used in Advanced Cardiac Life Support protocols for symptomatic bradycardia. For the mildly and moderately symptomatic adult, 2 mg is administered every 5 minutes to desired clinical effect. In the severely poisoned patient, dosages will need to be increased and given more rapidly. Tachycardia is not a contraindication to atropine administration in these patients and may be due to sympathetic system stimulation. Drying of the respiratory secretions and resolution of bronchoconstriction are the therapeutic end points used to determine the appropriate dose of atropine. This will be clinically apparent because the patient will have ease of respiration, improved ventilator mechanics, and decreased airway pressures if receiving positive pressure

ventilation. Atropine has no effect on the nicotinic receptors and, therefore, has no effect on the autonomic ganglia and neuromuscular junction. Therefore, muscle weakness, fasciculations, tremors, and paralysis associated with organophosphate, carbamate, and nicotine poisoning are not indications for further atropine dosing. It does have a partial effect on the CNS and is helpful in resolving or preventing seizures.

Pralidoxime chloride is used to treat organophosphate poisoned patients only and does not have a role for carbamate or nicotine poisoning. It reactivates AChE by exerting a nucleophilic attack on the phosphorus resulting in an oxime–phosphate bond that splits from the AChE, leaving the regenerated enzyme. This reactivation is clinically most apparent at skeletal neuromuscular junctions, with less activity at muscarinic sites. Pralidoxime must, therefore, be administered concurrently with adequate atropine doses. The recommended dose of pralidoxime is 1 to 2 g, for adults, by the IV route. Slow administration over 15 to 30 minutes has been advocated to minimize side effects. 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. Pralidoxime is rapidly excreted by the kidney with a half-life of approximately 90 minutes. Therefore, a continuous infusion is often recommended after the loading dose to maintain therapeutic levels.[16] Currently, the World Health Organization recommends a bolus of greater than 30 mg/kg followed by an infusion of greater than 8 mg/kg per hour. Due to the high risk of seizures in symptomatic cholinergic-poisoned patients, empiric treatment with benzodiazepines is also recommended.

Opioid Toxidrome

Opioid syndrome is commonly encountered in medicine. Opiates are the naturally derived narcotics, such as morphine and codeine, found in opium. Opium is isolated from the poppy plant, *Papaver somniferum*. Opioids are a broader class that include opiates and include all substances that bind to opioid receptors. Opioids include the semisynthetic and synthetic compounds such as hydrocodone, hydromorphone, oxycodone, methadone, and fentanyl. These drugs all have potent analgesic and sedative properties but different pharmacokinetic properties.

Opioids exert their clinical effects by binding to three major classes of opioid receptors: mu (μ), kappa (κ), and delta (δ); or OP_3, OP_2, and OP_1, respectively. Various opioids have different affinity profiles with respect to opioid receptors, which explains the differences in the clinical effects. For example, mu receptors are primarily responsible for the sensation of euphoria, and specific opioids are preferred for abuse due to their potent mu-receptor agonism.

Opioid poisoning can have widespread clinical manifestations depending on the agent used, dose, method of delivery, and the presence of coingestants. The classic toxidrome consists of miosis plus respiratory and CNS depression. Although pinpoint pupils are often associated with opioid poisoning, one should not rely on them exclusively in making the diagnosis. Gastrointestinal motility is decreased, resulting in decreased or absent bowel sounds on physical examination. CNS and respiratory depression can lead to several potentially serious secondary effects, including anoxic brain injury, aspiration pneumonia, and rhabdomyolysis.

Several opioids cause additional nonclassic signs and symptoms that may confound the clinical diagnosis. For example, tramadol, propoxyphene, and meperidine may cause seizures.[17,18] Propoxyphene causes cardiac conduction abnormalities (eg, prolongation of the QRS interval) and dysrhythmias.[19] Methadone is known to cause QT interval prolongation. Movement disorders may also be seen with drugs such as fentanyl, including life-threatening chest wall rigidity. Certain opioids, such

as meperidine, fentanyl, and tramadol, have serotonergic properties and may lead to a serotonin syndrome when combined with other serotonin agonists.[20] Adulterants or contaminants may confound the clinical presentation of a patient presenting with opioid toxicity. For example, clenbuterol-contaminated heroin produced an outbreak of an atypical clinical illness consisting of tachycardia, palpitations, hypokalemia, and hyperglycemia.[21] The opioid toxidrome may be mimicked by nonopioid agents such as clonidine, oxymetazoline, and antipsychotic drugs.

Opioid poisoning may be reversed with several opioid antagonists (eg, naloxone or naltrexone). 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 IV dose should be readministered at 5 minute intervals until the desired endpoint is achieved: restoration of respiratory function, ability to protect the airway, and an improved level of consciousness. If the IV route of administration is not viable, alternative routes include intramuscular, intraosseous, intranasal, or inhalational (ie, via nebulization). 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 CNS and respiratory depressants, or for medical or traumatic reasons.

Naloxone can precipitate profound withdrawal symptoms in opioid-dependant patients. Symptoms include agitation, vomiting, diarrhea, piloerection, diaphoresis, and yawning. Caution should be exercised in administration of naloxone and only the amount necessary to restore adequate respiration and airway protection should be used. Naloxone's clinical efficacy can last for as little as 45 minutes. Therefore, patients are at risk for recurrence of sedation, particularly for patients exposed to methadone or sustained-release opioid products. Patients should be observed for resedation for at least 4 hours after reversal with naloxone. Naloxone is renally eliminated and the elimination kinetics are not easily predicted in patients with renal failure; therefore, patients with renal impairment should be observed for resedation for a longer period of time. 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 with patients monitored closely for the potential development of withdrawal symptoms or worsening sedation as the drug is either metabolized or absorbed, respectively.

Sympathomimetic Toxidrome

Norepinephrine is the neurotransmitter for postganglionic sympathetic (adrenergic) fibers that innervate skin, eyes, heart, lungs, gastrointestinal tract, exocrine glands, and some neuronal tracts in the CNS. Physiologic responses to activation of the adrenergic system are complex and depend on the type of receptor (α1, α2, β1, β2), some of which are excitatory and others that have opposing inhibitory responses. Stimulation of the sympathetic nervous system produces CNS excitation (agitation, anxiety, tremors, delusions, and paranoia), tachycardia, seizures, hypertension, mydriasis, hyperpyrexia, and diaphoresis. In severe cases, cardiac arrhythmias and coma may occur.

Hyperthermic Toxidromes

Toxin-induced hyperthermia syndromes include sympathomimetic hyperthermia, uncoupling syndrome, serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia, and anticholinergic poisoning.[22] Sympathomimetics, such as amphetamines and cocaine, may produce hyperthermia due to excess serotonin and dopamine resulting in thermal deregulation.[23] Treatment is primarily supportive

and may include active cooling and administration of benzodiazepine agents. Uncoupling syndrome occurs when the process of oxidative phosphorylation is disrupted, leading to heat generation and a reduced ability to aerobically generate adenosine-5′-triphosphate. Severe salicylate poisoning is a characteristic intoxication that has been associated with uncoupling.[24] Serotonin syndrome occurs when there is a relative excess of serotonin at both peripheral and central serotonergic receptors.[25] Patients may present with hyperthermia, alterations in mental status, and neuromuscular abnormalities (rigidity, hyperreflexia, and clonus) although there may be individual variability in these findings. It is associated with drug interactions, such as the combination of monoamine oxidase inhibitors and meperidine, but may also occur with single-agent therapeutic dosing or overdose of serotonergic agents. The serotonin antagonist cyproheptadine has been advocated to treat serotonin syndrome in conjunction with benzodiazepines and other supportive treatments, such as active cooling. However, cyproheptadine may only be administered orally and its true efficacy is not well known, which limits its overall utility. Neuroleptic malignant syndrome is a condition caused by relative deficiency of dopamine within the CNS.[26] It has been associated with dopamine receptor antagonists and the sudden withdrawal of dopamine agonists such as levodopa-carbidopa products. Clinically it may be difficult to distinguish from serotonin syndrome and other hyperthermic emergencies. Clinically, patients develop hyperthermia, rigidity, autonomic instability, and mental status changes. Elevations in creatine kinase activity and white blood cell count can be seen. Bromocriptine, amantadine, and dantrolene have been used for treatment in some reports, but true efficacy has not been fully delineated. Malignant hyperthermia occurs when genetically susceptible individuals are exposed to depolarizing neuromuscular blocking agents or volatile general anesthetics.[27] Treatment consists of removing the inciting agent, supportive care, and dantrolene administration. Finally, anticholinergic poisoning may result in hyperthermia through impairment of normal cooling mechanisms such as sweating. Supportive care, including active cooling and benzodiazepines, is the primary treatment of this condition. Overall, differentiating between the various hyperthermic toxidromes may be challenging and additional causes of hyperthermia, such as heat stroke and/or exhaustion and infection, should also be explored. In most toxin-induced hyperthermic syndromes, treatment includes benzodiazepine administration, active cooling, and general supportive care.

LABORATORY TOXIDROMES

When used appropriately, diagnostic tests may be of help in the management of the intoxicated patient. When a specific toxin, or even a class of toxins, is suspected, requesting qualitative or quantitative levels may be appropriate. 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 about to the cause of a poisoning by responsible diagnostic testing.

Toxins Inducing an 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 (eg, ethylene glycol, methanol, or isopropanol) intoxication. Though this test may have utility in such situations, it has many pitfalls and limitations that limit its effectiveness.

Osmotic concentrations may be expressed in terms of either osmolality (milliosmoles per kilogram of solvent [mOsm/kg]) or osmolarity (milliosmoles per liter of

solution [mOsm/L]).[28] Osmolality can be measured (Osm_m) by use of an osmometer, a tool that most often uses the technique of freezing point depression.[29] Serum osmolarity (Osm_C) may be estimated clinically by any of several equations,[30] involving the patient's serum glucose, sodium, and urea nitrogen, which normally account for almost all of the measured osmolality.[31] One of the most commonly used of these calculations is expressed as:

$$Osm_C = 2(\text{sodium}) + (\text{urea nitrogen})/2.8 + (\text{glucose})/18$$

The numerical factor in the sodium term (which is expressed in millimoles per liter) accounts for corresponding anions that contribute to osmolarity; whereas, the numerical factors in the other two terms convert their concentrations units from milligrams per deciliter to millimoles per liter.[32] Finding the osmolar contribution of any other osmotically active substances that is reported in milligrams per deciliter (eg, urea nitrogen and glucose) is accomplished by dividing by one-tenth of the substance's molecular weight in daltons.[32] For urea nitrogen this conversion factor is 2.8 and for glucose it is 18. Similarly, additional terms, along with corresponding conversion factors, may be added to this equation to account for ethanol and the various toxic alcohols (assuming they have been measured and their results are expressed in milligrams per deciliter) as:

$$Osm_C = 2(\text{sodium}) + (\text{urea nitrogen})/2.8 + (\text{glucose})/18 + (\text{ethanol})/4.6 + (\text{methanol})/3.2 + (\text{ethylene glycol})/6.2 + (\text{isopropanol})/6.0$$

The difference between the measured (Osm_M) and calculated (Osm_C) osmotic concentrations is the osmole gap[32]:

$$\text{Osmole gap} = Osm_M - Osm_C$$

One problem with this equation is that the units are different because the measured form is in units of osmolality (milliosmoles per kilogram) and the calculated form is in units of osmolarity (milliosmoles per liter). This unit difference is generally not considered significant for clinical purposes and the gap may be expressed in either units.[30]

If a significant elevation of the osmole gap is discovered, the difference in the two values may represent presence of foreign substances in the blood.[30] A list of possible causes of an elevated osmole gap is listed in **Box 1**. Unfortunately, what constitutes a normal osmole gap is widely debated. Conventionally, a normal gap has been defined as less than or equal to10 mOsm/kg. The original source of this value is an article from Smithline and Gardner,[33] which declared this number as pure convention. Further clinical study has not shown this assumption to be correct. Glasser and colleagues[34] studied 56 healthy adults and reported that the normal osmole gap ranges 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.[35] Another study, by Aabakken and colleagues,[36] looked at the osmole gaps of 177 patients admitted to their emergency department and reported their range (mean ± 2SD) to be from −10 to 20 mOsm/kg. A vital point brought forth by the authors of this study, however, is that the day-to-day coefficient of variation for their laboratory in regard to sodium was 1%. They concluded that this level of imprecision translates to an analytical standard deviation of 9.1 mOsm/kg in regard to the osmole gap. This analytical imprecision alone may account for the variation found in osmole gaps of many patients. This concern that even small errors in sodium, urea nitrogen, glucose, and osmolality assays can result in large variations of the osmole gap has been voiced by other

Box 1
Causes of an elevated osmole gap

- Toxic alcohols
  - Ethanol
  - Isopropanol
  - Methanol
  - Ethylene glycol
- Drugs and excipients
  - Mannitol
  - Propylene glycol
  - Glycerol
  - Osmotic contrast dyes
- Other chemicals
  - Ethyl ether
  - Acetone
  - Trichloroethane
- Disease or illness
  - Chronic renal failure
  - Lactic acidosis
  - Diabetic ketoacidosis
  - Alcoholic ketoacidosis
  - Starvation ketoacidosis
  - Circulatory shock
  - Hyperlipidemia
  - Hyperproteinemia

researchers.[37] 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/kg—a value considered normal by the traditionally accepted upper normal limit of 10 mOsm/kg. If, however, this patient had an osmole gap of −5 mOsm/kg just before ingestion of a toxic alcohol, the patient's osmole gap must have increased by 14 mOsm/kg to reach the new gap of 9 mOsm/kg. If this increase was due to ethylene glycol, it would correspond to a toxic level of 86.8 mg/dL.[38] 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 will have been metabolized to the acidifying metabolites. These metabolites do not influence the osmole gap because they are anions that displace bicarbonate and are accounted for by the doubled-sodium term in the equation; hence no osmole gap elevation will be detected.[30,39] Therefore, 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[40] reported a patient with ethylene glycol toxicity who presented with an osmole gap of 7.2 mOsm/L due to a delay in presentation. Darchy and colleagues[37] presented two other cases of significant ethylene glycol toxicity with osmole gaps of 4 and 7 mOsm/L, respectively. The lack of an abnormal osmole gap in these cases was speculated to be due to either 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 **Box 1** may be present. A "normal" osmole gap should be interpreted with caution; a negative study may, in fact, not rule out the presence of such an ingestion—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) while confirmation from serum levels of the suspected toxin are pending.

Toxins Inducing an Anion Gap Metabolic Acidosis

Obtaining a basic metabolic panel in all poisoned patients is generally recommended. When low serum bicarbonate is discovered on a metabolic panel, the clinician should determine if an elevated anion gap exists. The equation most commonly used for the serum anion gap calculation is[41]:

$$\text{Anion gap} = Na^+ - (Cl^- + HCO3^-)$$

The primary cation (sodium) and primary anions (chloride and bicarbonate) are represented in the equation.[42] Other serum cations are not commonly included in this calculation, because either their concentrations are relatively low (eg, potassium), or they may not have been assayed (eg, magnesium), or assigning a number to represent their respective contribution is difficult (eg, cationic serum proteins).[43] Similarly, there are a multitude of other serum anions (eg, sulfate, phosphate, or organic anions) that are also difficult to measure or to quantify in terms of charge-concentration units (milliequivalents per liter).[42,43] The anion gap represents these "unmeasured" ions. The normal range for the anion gap has conventionally been accepted to be 8 to 16 mEq/L,[43] but more recent changes in the technique for measuring chloride have resulted in a lowered range, closer to 6 to 14 mEq/L.[42] Practically speaking, an increase in the anion gap beyond an accepted normal range, accompanied by metabolic acidosis, represents an increase in unmeasured endogenous (eg, lactate) or exogenous (eg, salicylate) anions.[41] A list of the more common causes of this phenomenon is organized in the classic MUDPILES mnemonic (methanol, uremia, diabetic ketoacidosis [may also include alcoholic or starvation ketoacidosis], paraldehyde, isoniazid and iron, lactic acidosis, ethylene glycol, and salicylates). The P has been removed from the classic acronym because the drug paraldehyde is no longer available (**Box 2**).

It is imperative that clinicians who care for poisoned patients initially presenting with an increased anion gap metabolic acidosis investigate the cause of that acidosis. Many symptomatic poisoned patients may have an initial mild metabolic acidosis on presentation due to elevation of serum lactate. This can occur for a variety of reasons, including acidosis related to tissue hypoperfusion or a recent seizure. However, with adequate supportive care including hydration and oxygenation, the anion gap acidosis should improve. If, despite adequate supportive care, an anion gap metabolic acidosis worsens in a poisoned patient, the clinician should consider

Box 2
Potential toxic causes of increased anion gap metabolic acidosis

Methanol

Uremia

Diabetic ketoacidosis

Iron, inhalants (ie, carbon monoxide, cyanide, toluene), isoniazid, ibuprofen

Lactic acidosis

Ethylene glycol, ethanol (alcoholic) ketoacidosis

Salicylates, starvation ketoacidosis, sympathomimetics

either toxins that form acidic metabolites (eg, ethylene glycol, methanol, or ibuprofen) or toxins which cause lactic acidosis by interfering with aerobic energy production (eg, cyanide or iron).[44]

ELECTROCARDIOGRAPHIC TOXIDROMES

Interpretation of the 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.[45] Despite the fact that drugs have widely varying indications for therapeutic use, many unrelated drugs share common ECG effects if taken in overdose. Potential toxins can be placed into broad classes based on their cardiac effects. Two such classes, also known as ECG toxidromes, include agents that block the cardiac potassium efflux channels (resulting in QT interval prolongation) and agents that block cardiac fast sodium channels (resulting in QRS interval prolongation). The recognition of specific ECG changes associated with other clinical data (toxidromes) potentially can be life saving.

QT Prolongation

Studies suggest that approximately 3% of all noncardiac prescriptions are associated with the potential for QT prolongation. Myocardial repolarization is driven predominantly by outward movement of potassium ions. Blockade of the outward potassium currents by drugs prolongs the action potential.[46] This subsequently results in QT interval prolongation and the potential emergence of T or U wave abnormalities on the ECG.[47] 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 after-depolarization) and promote triggered activity. These changes may lead to reentry and subsequent ventricular tachycardia, most often as the torsades de pointes variant of polymorphic ventricular tachycardia.[48] 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.[49] 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 ($QTc = QT/\sqrt{RR}$) 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. The potential for an arrhythmia for a given QT interval will vary from drug to drug and patient to patient.[50] Bradycardia in the setting of drug-induced QT prolongation is more likely to degrade into torsades de pointes than in a patient with the same numerical QT with a tachycardic rate. Drugs associated with QT prolongation are listed in **Box 3**.[51] Other causes 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.[52]

QRS Prolongation

The ability of drugs to induce cardiac Na^+ channel blockade and thereby prolong the QRS complex has been well described in numerous literature reports.[53] 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.[54] In some cases, the QRS complex may take the pattern of recognized bundle branch blocks.[55,56] In the most severe cases, the QRS prolongation becomes so profound that it is difficult to distinguish between ventricular and supraventricular rhythms.[57,58] Continued prolongation of the QRS may result in a sine wave pattern and eventual asystole. It has been theorized that the Na^+ channel blockers can cause slowed intraventricular conduction, unidirectional block, the development of a reentrant circuit, and resulting ventricular tachycardia.[59] This can then degenerate into ventricular fibrillation. Differentiating a prolongation of the QRS complex due to Na^+ channel blockade in the poisoned patient versus other nontoxic causes can be difficult. Rightward axis deviation of the terminal 40 milliseconds of the QRS axis has been associated with tricyclic antidepressant poisoning.[60,61] However, the occurrence of this finding in other Na^+ channel blocking agents is unknown. Myocardial Na^+ channel blocking drugs comprise a diverse group of pharmaceutical agents (**Box 4**). Patients poisoned with these agents will have a variety of clinical presentations. For example, sodium channel blocking medications such as diphenhydramine, propoxyphene, and cocaine may also produce anticholinergic, opioid, and sympathomimetic syndromes, respectively.[19,62,63] In addition, specific drugs may affect not only the myocardial Na^+ channels but also calcium influx and potassium efflux channels.[64,65] 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 4**, however, are similar in that they may induce myocardial Na^+ channel blockade and may respond to therapy with hypertonic saline or sodium bicarbonate.[19,58,63] It is, therefore, reasonable to treat poisoned patients that have 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. Also, it can improve inotropy and help prevent arrhythmias.[53]

There are other drug-induced ECG changes that may be seen, depending on the agent ingested. For example, lithium may result in nonspecific T-wave inversions or flattening, and beta-blockers may cause bradycardia and heart blocks. Physicians managing patients who have taken overdoses of medications should be aware of the various ECG changes that potentially can occur in the overdose setting.

Box 3
Potassium efflux channel blocking drugs

- Antihistamines
  - Astemizole
  - Clarithromycin
  - Diphenhydramine
  - Loratidine
  - Terfenadine
- Antipsychotics
  - Chlorpromazine
  - Droperidol
  - Haloperidol
  - Mesoridazine
  - Pimozide
  - Quetiapine
  - Risperidone
  - Thioridazine
  - Ziprasidone
- Arsenic trioxide
- Bepridil
- Chloroquine
- 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

Halofantrine

Hydroxychloroquine

Levomethadyl

Methadone

Pentamidine

Quinine

Tacrolimus

Venlafaxine

WORD OF CAUTION: URINE DRUG SCREENING

Many clinicians regularly obtain urine drug screening on patients with an altered sensorium or on those suspected of a drug overdose. Such routine urine drug testing, however, is of questionable benefit. Kellermann and colleagues[66] found little impact of urine drug screening on patient management. Similarly, Mahoney and colleagues[67] concluded that toxic screening added little to treatment or disposition of overdose patients. In a study of over 200 overdose patients, Brett[68] 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[69] noted that a positive drug screen had minimal impact on patient treatment.

Some investigators do argue in favor of routine testing. Fabbri and colleagues[70] countered that comprehensive screening may aid decisions on patient disposition, resulting in fewer admissions to the hospital and less demand on critical care units. However, the screen used in their retrospective study tested for over 900 drugs and is not available to most clinicians. Milzman and colleagues[71] argued in favor of screening trauma victims, stating that the prognosis of intoxicated patients is unduly poor secondary to low Glasgow coma scale scores, although patient treatment and disposition did not seem to be affected.[71]

The effect of such routine screening in management changes is low because most of the therapy is supportive and directed at the clinical scenario (ie, mental status, cardiovascular function, and respiratory condition). Interpretation of the results can be difficult even when the objective for ordering a comprehensive urine screen is

Box 4
Sodium 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
- Phenothiazine
  - Mesoridazine
  - Thioridazine
- Propranolol
- Propoxyphene
- Quinine
- Verapamil

adequately defined. Most assays rely on antibody identification of drug metabolites, with some drugs remaining positive days after use and thus potentially not 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[72] 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 (GHB), fentanyl, and ketamine. The recent increase in Internet-acquirable drugs, such as synthetic cannabinoids (eg, "spice" and "K2") and synthetic amphetamines, such as mephedrone and methylenedioxypyrovalerone ("bath salts"), are not detected on typical health system drug screens.

Interpretation is further confounded by false positive and false negative results. George and Braithwaite[73] 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 via cross-reactivity with the anti-phencyclidine ("PCP") antibodies used in the urine RapidTest d.a.u. assay (Siemens Health care Diagnostics, Tarrytown, NY, USA).[74] False-positive benzodiazepine results were found in patients receiving the nonsteroidal antiinflammatory drug oxaprozin who were screened using the EMIT (DuPont Medical Products, Wilmington, DE, USA) and TDx (Abbott Laboratories, North Chicago, IL, USA) urine immunoassays.[75] Conversely, antibodies used in the immunoassays may not detect all drugs classified within a specific drug class. For example, the EMIT II Plus Opiate (Dade Behring, Deerfield, IL, USA) urine immunoassay will not detect physiologic doses of methadone. This assay detects codeine and its metabolites, morphine and morphine-3-glucuronide. It can also detect hydrocodone, which is structurally related to morphine; but also meperidine (in high doses), even though it is structurally unrelated to morphine. Additionally, cross-reactivity of certain prescription and certain over-the-counter medications used in therapeutic amounts for true illness may elicit positive screens. Diphenhydramine has been documented to interfere with the EMIT II urine immunoassay for propoxyphene.[76] Additionally, codeine will give positive opioid screen, which may be incorrectly attributed to morphine or heroin use.

The utility 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 rarely guides patient treatment or disposition.

SUMMARY

Critical care physicians often care for poisoned patients. Many of these patients will do well with simple observation and never develop significant toxicity. However, for patients who present with serious toxic effects or after potentially fatal ingestions, prompt action must be taken. As many poisons have no true antidote and the poison involved may initially be unknown, the first step is competent supportive care. Attention to supportive care, vital signs, and prevention of complications are the most important steps. Taking care of these issues will often be all that is necessary to assure recovery.

Identifying the poison, either through history, identifying a toxidrome, or laboratory analysis may help direct care or patient disposition and should be attempted. There are several antidotes available that can be life saving and prompt identification of patients who may benefit from these should be attempted.

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