

Patients Presenting with Acute Toxin Ingestion

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KEYWORDS

- Toxins • Anesthesia • Toxicity • Drug Effects
- Poisonings • Envenomations

Organ toxicity caused by poisons or drug therapy is diverse and, in many cases, not commonly encountered clinically. In general, commonly encountered conditions caused by drug/toxin pharmacology can be categorized by shared mechanisms of organ injury. The following discussion of drug/toxin-induced injury is divided into 7 categories based on shared pathophysiology of the offending toxin or therapeutic drug administration and the likelihood of being encountered by the clinician: (1) QT interval prolongation and drug-induced channelopathies; (2) acquired methemoglobinemia; (3) drugs causing hyperthermic syndromes, alcohol (ethanol)-induced injuries and herbal drug abuse injuries; (4) drug toxicity in the chronic pain patient and dextromethorphan (DMP) toxicity; (5) poisonings causing metabolic acidosis, including carbon monoxide; (6) military/terrorist poisonings, including botulism and Botox; and (7) poisonous bites and envenomations.

QT INTERVAL PROLONGATION AND DRUG-INDUCED CHANNELOPATHIES

A 34-year-old man scheduled for elective surgery is currently treated with methadone for heroine addiction. He presents the day of surgery with a serum potassium level of 3.0 mEq/L and an electrocardiograph (ECG) shows a QTc interval (corrected by the Bazett formula: $QTc = QT/\sqrt{RR}$) of 500 milliseconds with a prominent U wave. *What would you do next?*

The cardiac action potential (AP) is generated by ion flows across cell membranes through specific ion channels. Phase 0 depolarization is developed by an inward sodium current and this inward current is responsible for striking the R wave on the surface ECG (**Fig. 1**). Thus, a drug that primarily blocks the sodium channel (lidocaine) can slur or prolong the QRS complex. The T wave is struck by ventricular

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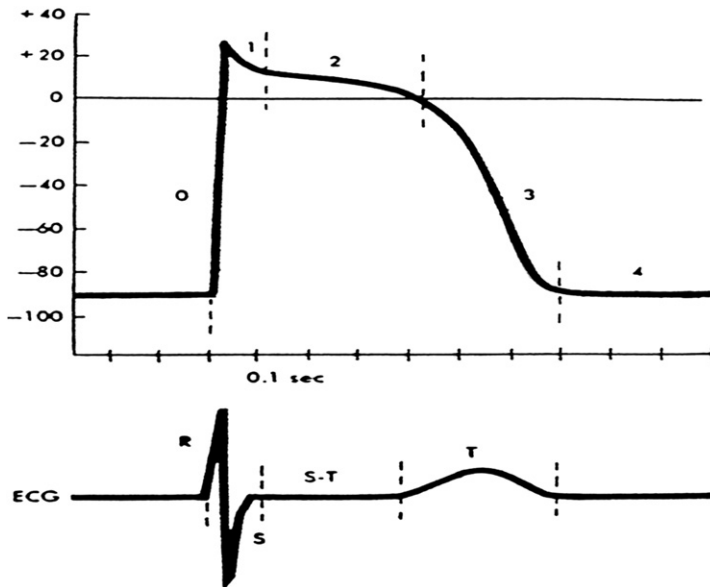


Fig. 1. The relationship of the phases of the cardiac AP with the surface ECG. Phase 0 (inward sodium current) strikes the R wave, phase 3 repolarization strikes the T wave. Sodium channel blockade will slur and prolong the QRS complex; potassium channel blockade will prolong phase 3 repolarization and lengthen the QT interval.

repolarization, which is caused by an outward potassium current (phase 3 repolarization). As **Fig. 1** shows, a major determinant of the total action potential duration (APD) (onset of phase 0 to the end of phase 3) is the duration of phase 3 repolarization.¹ The APD is determined clinically by measuring the QT interval, which, in turn, is a measure of conduction velocity. When conduction velocity slows (QT interval is prolonged) as a result of a drug effect or electrolyte effects, this can present a physiologic condition promoting the appearance of arrhythmias.

The primary potassium channels that are responsible for phase 3 repolarization are the rapid potassium current channel and the delayed rectifier current channel; the latter channel is encoded by the human ether-a-go-go (HERG) gene and is almost exclusively the channel that all of the drugs currently discussed bind to and inhibit, thereby prolonging the QTc interval. Immediately following phase 3 repolarization and before the onset of a new AP, small spontaneous inward calcium currents normally occur and are called early after depolarizations (EADs). If the conduction velocity is slowed (prolonged QTc), these EADs can summate into a positive depolarization wave at the end of phase 3, creating a U wave on the surface ECG. If the U wave achieves enough depolarization to reach threshold levels, a new R wave will be generated, creating an R on T event, thus potentially triggering a reentrant ventricular arrhythmia. This mechanism is believed to be responsible for developing the unique polymorphic ventricular tachycardia referred to as torsades de pointes (TdP).²

TdP was first described in 1964 in patients receiving the class 1A antiarrhythmic drug quinidine. A continually growing list of drugs are reported to inhibit the HERG potassium channel and cause QTc prolongation and potentially create a TdP type of arrhythmia (**Table 1**). The drugs specifically of interest to the anesthesiologist include cocaine, droperidol, sevoflurane, haloperidol, ondansetron, methadone, and all local anesthetics (with the exception of lidocaine, which does not block potassium

Table 1 Drugs known to prolong QT interval and potentially cause TdP	
Category	Drug
Antiarrhythmics	Vaughn-Williams class 1A Disopyramide, procainamide, quinidine 1C Encainide, flecainide III Amiodarone (TdP rare), dofetilide, ibutilide, sotalol
Calcium channel–blocking drugs	Diltiazem, verapamil
Psychiatric	Amitriptyline, chlorpromazine, desipramine, fluoxetine, haloperidol, imipramine, lithium, pimozide, paroxetine, sertraline, thioridazine, ziprasidone
Antihistamines	Astemizole, diphenhydramine, hydroxyzine, terfenadine
Antiinfective	Amantadine, ciprofloxacin, chloroquine, clarithromycin, erythromycin, fluconazole, grepafloxacin, itraconazole, ketoconazole, pentamidine, quinine
Antiretroviral	Amprenavir, indinavir, ritonavir
Anesthetic Drugs	Inhaled agents (sevo- and desflurane), methadone, droperidol, ondansetron, cocaine, all LAs (except lidocaine), hypokalemia especially acute onset (hyperventilation, infusions of bicarbonate, insulin, epinephrine), vasopressin, organophosphates

channels). Potassium channel blockade (prolongation of phase 3 depolarization and therefore APD) is necessary to significantly prolong the QTc interval and potentially cause TdP.³ Extracellular hypokalemia will also prolong the QTc interval by hyperpolarizing the resting membrane potential, therefore requiring a longer phase 3 repolarization period, and thus prolonging APD and QTc (Fig. 2).¹ Hypokalemia will potentiate drug-induced QTc prolongation and enhance the incidence of TdP.⁴ In addition, an estimated 1 in 10,000 individuals is a carrier of the long QT syndrome gene (congenital LQTS) and routine ECG screening may show a normal QT interval in these individuals. Congenital LQTS may be unmasked by synergism on the introduction of a drug that blocks potassium channels; for example, the onset of TdP and sudden death in

$$E = 60 \cdot \log \frac{[K]_o}{[K]_i}$$

or

$$E = -61 \cdot \log \frac{K_i}{K_o}$$

Fig. 2. The Nernst equation shows that the ratio of extracellular potassium (K_o) to intracellular potassium (K_i) is the primary determinant of the resting membrane potential (E). Chronic reduction of K_o by thiazide diuretics or acute reduction of K_o with simultaneous increase of K_i (hyperventilation, infusion of insulin, epinephrine, or bicarbonate) will hyperpolarize (make more negative) the E and require a longer phase 3 repolarization to return to baseline resting membrane potential. This process will prolong AP duration and, by definition, lengthen the QT interval.

a recreational (first-time) user of cocaine. Prolongation of the QT interval is now the most common cause of withdrawal of a drug from the market following approval by the US Food and Drug Administration (FDA). Drugs associated with QT prolongation include antipsychotics (lithium, haloperidol, and chlorpromazine), antihistamines (diphenhydramine and astemizole), and antiinfective drugs (erythromycin, clarithromycin, chloroquine). The effects of these drugs on the HERG channel are synergistic, and, along with electrolyte disturbance (hypokalemia/magnesemia), may summate into a fatal TdP type of arrhythmia. Although no absolutes are defined, a QTc interval approaching or greater than 500 milliseconds is an absolute red flag warning that TdP is an increasingly likely event.³

Cocaine

Because a large percentage of Americans 12 years of age or older (14% of the total population of the United States) have tried cocaine at least once, it is likely that the clinician will be required to give medical care to a cocaine-positive patient. Cocaine can cause coronary spasm, accelerated atherosclerosis, increased plasma catecholamines (by reuptake inhibition of norepinephrine), myocardial ischemia, and aortic dissection, so the report that 43% of cocaine users experience arrhythmia within 12 hours of cocaine ingestion⁵ is not surprising. Although more than 80% of cocaine abusers have an abnormal ECG, ECG findings specific for ischemia or infarction are infrequent (2%–6%). Increasingly frequent reports of QTc prolongation and TdP are explained by the known sodium and potassium (HERG) channel-blocking effects of cocaine. The importance of this cocaine-induced channelopathy is demonstrated by the shortening (improvement) of the QTc interval by the administration of sodium ion (sodium bicarbonate),⁶ thus antagonizing the cocaine-induced sodium channel blockade. A similar pharmacologic comparison would be giving calcium ion to a patient with an overdose of a calcium channel-blocking drug. The sodium and potassium channel blockade caused by cocaine resembles that caused by the Vaughn-Williams antiarrhythmic class 1c drug flecainide, the use of which has largely been abandoned because of TdP generation.⁷ Cocaine may unmask unrecognized and undiagnosed congenital LQTS by causing TdP and arrhythmia generation in this group of patients, explaining some of the reports of sudden death during the first-time recreational use of cocaine.

Clinical management of the cocaine-positive patient, in addition to the well-known avoidance of β -blocking drugs (including labetalol), and avoidance of drugs known to prolong APD and thus QTc (see later discussion), would be prudent. Because propofol, midazolam, synthetic opioids (fentanyl, sufentanil), neuromuscular blocking drugs, and nitrous oxide are reported to have no effect on APD, the clinician is allowed a reasonable choice of agents and a regional technique with lidocaine.

Methadone

Methadone is now the most common drug associated with TdP at Parkland Hospital in Dallas, Texas. A recent study found more than 16% of patients receiving methadone had significant QTc prolongation compared with 0% in controls, with nearly 4% of patients receiving methadone experiencing TdP. This study also showed that hypokalemia is a significant synergistic risk factor for TdP generation.⁸

Local Anesthetics (Except Lidocaine)

Bupivacaine, ropivacaine, and mepivacaine bind to and inhibit potassium channels and therefore prolong APD and the surface ECG QTc interval duration.⁹ Reports of synergism of potassium channel blockade properties between mutant potassium

channels (congenital LQTS) and local anesthetics (LAs) suggest that regional anesthesia with the LAs mentioned earlier should be approached with caution in all patients with QTc approaching 450 to 500 milliseconds. The LAs listed earlier should be used with caution in patients known to be receiving any drug known to prolong the QTc. If a regional technique with one of these LAs is pursued, continual ECG monitoring following LA injection, and continuing until the regional block is dissipated, would enhance patient safety.

Sevo- and Desflurane

These inhaled agents are known to block potassium channels and therefore prolong cardiac APD and QTc.¹⁰ Sevoflurane has been shown to synergize with the class 3 antiarrhythmic drugs sotalol and dofetilide in APD prolongation, demonstrating the necessity of the clinician to be aware of the current medication history and the effects of those drugs on QTc for those patients receiving inhaled agents.

Antiemetics

Droperidol causes a dose-dependent prolongation of the APD and QTc by blocking the HERG potassium channel.¹¹ Ondansetron is reported to have similar effects. Although arrhythmia generation is highly unlikely following small (1.25 mg or less) antiemetic doses, the usual caveat must be remembered: all drugs that block HERG channels are synergistic. Therefore, in patients currently ingesting drugs known to prolong QTc, even with a preoperative ECG showing the QTc to be less than 500 milliseconds, it may be prudent for the clinician to avoid droperidol and ondansetron and use other antiemetic drugs known to be without QTc effects (eg, dexamethasone) in those patients with a QTc greater than 450 milliseconds.

In conclusion, surgery in the case described at the start of this section should be cancelled, his hypokalemia corrected, and the dose of methadone reevaluated. A QTc approaching or greater than 500 milliseconds is a red flag for TdP and should not be ignored. If surgery is urgent, any drug already discussed that prolongs QTc should be avoided, as should hyperventilation (which causes a rapid extracellular hypokalemia, see [Fig. 2](#)); serum potassium levels should be increased with supplemental intravenous (IV) potassium. If a regional technique is chosen, lidocaine would be the LA of choice.

ACQUIRED METHEMOGLOBINEMIA

A 66-year-old man presented for emergency exploratory laparotomy for free intraabdominal air. Medication history included oral isosorbide dinitrate for ischemic heart disease. His wife also confirmed the use of Lanacane (20% benzocaine) topical spray (purchased over the counter) for recent sunburn pain and intraorally for painful mucosal ulcers caused by poorly fitting dentures. In the emergency room it was noted that his pulse oximeter read 85% to 86% despite high inhaled oxygen concentrations. Arterial blood gas (ABG) revealed an arterial P_{O_2} of 94%. *What would you do next?*

Methemoglobin (MHgb) is the oxidized (Fe^{3+}) form of iron in the hemoglobin molecule, and in this state cannot bind and transport oxygen. In addition, the oxyhemoglobin dissociation curve is left-shifted, thus reducing the peripheral unloading of O_2 .¹² The action of cytochrome b5 methemoglobin reductase normally keeps MHgb levels less than 2%. Cytochrome b5 methemoglobin reductase is also dependent on reduced nicotinic adenine dinucleotide phosphate diaphorase (methylene blue

enhances the activity of this enzyme and it is generally understood that this enzyme reduces methylene blue to leukomethylene blue; leukomethylene blue then reduces MHgb to Hgb).¹³

The most common class of drugs used clinically that cause MHgb are the LAs, which are considered indirect oxidizers; that is, in vivo metabolism of LAs produce amine metabolites that are the actual oxidizers.¹⁴ The LAs known to cause MHgb are lidocaine (rare and unlikely), mepivacaine (also unlikely), tetracaine, prilocaine (likely), and benzocaine (highly likely). Intraoral spraying of benzocaine during the inhalation phase shows rapid transmucosal airway absorption and has resulted in measured MHgb levels as high as 60%.¹⁵

Methemoglobinemia is diagnosed by MHgb levels greater than 2% or the Kronenberg test, which is a simple visual evaluation performed by dropping side by side normal blood (to serve as a visual contrast or control) and MHgb blood. The failure of the MHgb blood to change from the typical chocolate brown color following room air exposure or exposure to O₂ to a color matching that of the normal control blood drop would constitute a positive test for MHgb.¹⁶ Skin color, although certainly not diagnostic, has been described as black, gray, chocolate/brownish, purple, or pale. Blood color has been described as chocolate/brown, black, burgundy, red, cyanotic, or blue/purple. Oxygen saturation measured by standard dual (2 wave length) pulse oximetry has been reported to vary between 50% and 94%, with a median of 85%. An important finding and clue to correct diagnosis is the finding of a disconnection (of the expected SpO₂/arterial PO₂ relationship) between a simultaneously measured pulse oximetric oxygen saturation of less than 90% while the directly measured (by standard Clark electrode) arterial PaO₂ is greater than 70 mm Hg. A normal (standard) oxyhemoglobin dissociation curve would couple an SpO₂ of 90% with an arterial PO₂ of 60 mm Hg.

A common finding is the concomitant use of another oxidizing drug such as nitrate therapy, trimethoprim-sulfamethoxazole (bactrim), dapsone, phenazopyridine, and phenacetin.¹⁴ Reported complications of MHgb include myocardial infarction (in particular non-Q wave infarction with cardiac enzyme elevation), coma, seizures, respiratory failure, shock, and hypoxic cerebral injury. Most patients with MHgb greater than 8% are symptomatic. Standard (dual wave length) pulse oximeters may grossly underestimate the degree of systemic hypoxemia, whereas CO-oximeters with multiple (usually 8) light wavelengths would give a more accurate estimation of the true SpO₂ and the %MHgb.¹⁷

Prilocaine is metabolized to *ortho*-toluidine, which is responsible for Hgb oxidation to MHgb. Infants less than 6 months old are more susceptible to oxidation because of lower enzymatic levels of NADH, thus prilocaine should be avoided in this age group. Because no difference in doses of benzocaine exists between a therapeutic dose and a toxic dose and because of the difficulty in predicting which patient will develop significant MHgb with exposure, it has been suggested that the clinical use of benzocaine should be restricted or abandoned.¹⁸ In 2006 the Veterans Affairs Central Pharmacy recommended that lidocaine be used for topical anesthesia for airway procedures and that benzocaine-containing topical sprays should not be used and should be removed from hospital pharmacy inventories.

The case described at the start of this section had a measured MHgb of 18% and was successfully treated with methylene blue (1 mg/kg)¹⁹ with a prompt (within 60 minutes) improvement of the pulse oximeter (standard 2 wave length) reading to 96% to 97%. The remainder of the hospital course was uneventful following a diverting colostomy for a perforated colonic diverticulum.

DRUGS CAUSING HYPERTHERMIC SYNDROMES, ALCOHOL (ETHANOL)-INDUCED INJURIES, AND HERBAL DRUG ABUSE INJURIES

A 25-year-old woman presents to your critical care service after collapsing at a nightclub. Her past medical history includes Zoloft (sertraline) and over-the-counter St John's wort for depression. She admits to ingesting Ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] and "a couple of lines" of cocaine. She is combative, disoriented, uncooperative, has leg and arm rigidity, and her vital signs include blood pressure (BP) of 185/105, heart rate (HR) 135, and temperature 39.9°C. ECG shows sinus tachycardia with normal QTc interval and isoelectric ST segments. *What would you do next?*

Toxin-induced hyperthermic syndromes must be included in the differential diagnosis of any patient presenting with muscle rigidity and fever. It is important for the clinician to recognize the underlying cause of drug (toxin)-induced hyperthermic syndromes because proper treatment will vary depending on the cause.

Norepinephrine, dopamine, and serotonin are all neurotransmitters that effect hypothalamic control of body temperature. Drugs or toxins that alter brain concentrations of these neurotransmitters are capable of altering body temperature regulation. Cocaine, amphetamine, methamphetamine, and MDMA are known to cause the serotonin syndrome (SS), especially when combined with antidepressants.²⁰ With the common use of selective serotonin reuptake inhibitors (SSRIs) prescribed for clinical depression and the increased recreational use of the illegal drugs listed earlier (especially MDMA), a dramatic increase in the SS is being reported. The earliest case report of the SS (1955) was attributed to the combination of meperidine (Demerol) and the monoamine oxidase inhibitor (MAOI) iproniazid. The most widely reported case of the SS occurred in 1984 when 18-year-old Libby Zion died of an SS caused by the combination of meperidine and phenelzine (an MAOI).²¹ This death resulted in regulations requiring restriction of resident physician working hours, increased faculty supervision of residents, and controls for the use of patient restraints.

Most patients with the SS present with a combination of altered mental status (coma, confusion, agitation, seizures), abnormal neuromuscular activity (rigidity, myoclonus), and autonomic instability (fever, diaphoresis, tachycardia, hypertension). If the SS includes rhabdomyolysis, metabolic acidosis, coagulopathy, and marked temperature elevation (>43°C), the mortality rate is significantly increased. Many drugs, including MAOIs, amphetamines, MDMA, cocaine, tricyclic antidepressants, SSRIs, tramadol, meperidine, lithium, L-dopa, and lysergic acid diethylamide (LSD), among others, increase brain serotonin levels and thus may cause the SS.²² Increased ambient temperature (incidence of the SS peak in the summer) and motor activity (all-night dance parties) will enhance the development of the SS syndrome following the use of any drug known to increase brain serotonin levels. In addition, a significant increase in the plasma levels of catecholamines (primarily norepinephrine, with the accompanying cardiovascular effects) are reported following MDMA, amphetamine, and cocaine ingestion.²³

Therapy for the SS (as the case report at the start of this section was managed) would include external cooling, a combined α - and β -blocking drug (carvedilol) or calcium channel-blocking drugs for the sympathetic instability (hypertension and tachycardia), and benzodiazepines (midazolam) and propofol (by infusion) for control of the central nervous system (CNS) symptoms.²⁴

The neuroleptic malignant syndrome (NMS) may be difficult to distinguish clinically from the SS. The NMS is normally seen following use of high-potency neuroleptics,

such as haloperidol, but has been reported with the use of metaclopramide (Reglan),²⁵ promethazine, or following the withdrawal of antiparkinson drug therapy. Dantrolene (alone or combined with bromocriptine) is a commonly recommended therapy for NMS.

Malignant hyperthermia (MH), a well-known syndrome in the anesthesia community, is also characterized by sympathetic instability with significant elevations in plasma catecholamines. Increased survival in MH animal models has been reported following the use of α -blocking drugs.

Alcohol (Ethanol)-Induced Injuries

Alcohol abuse causes multiple injuries including stroke, cardiomyopathy, arrhythmias, intracerebral and subarachnoid hemorrhage (secondary to hypertension), accelerated atherosclerosis, aortic dissection, myocardial infarction, and hypertension, whereas light alcohol use is reported to reduce these complications. Currently alcohol abuse is considered the leading cause of nonischemic cardiomyopathy (referred to as alcoholic heart muscle disease)²⁶; 11% of total hospitalizations for heart failure are considered secondary to alcohol consumption. Up to 30% of new onset atrial fibrillation have been found to be caused by alcohol consumption.²⁷

Herbal Drug Injuries

It is estimated that 42% of the population uses alternative treatments and over-the-counter supplements. In 1994, legislation was passed that classified dietary supplements as foods, exempting them from safety standards to which prescription and over-the-counter drugs must adhere, thus increasing their availability to the general population. Although numerous herbal products are widely available, this discussion is limited to ephedra and St John's wort.

Ephedra

The availability of ephedra continues despite FDA alerts and rulings prohibiting the sale of dietary supplements containing ephedra. Although ephedra has been used for at least 5000 years in Chinese medicine, it is primarily used in the United States for weight loss or to increase energy levels. Although ephedrine was isolated from ephedra in 1887, ephedra also is known to contain pseudoephedrine, methylephedrine, norephedrine, methylpseudoephedrine, and norpseudoephedrine (all sympathomimetic alkaloids).²⁸ Ephedra is commonly combined with caffeine, forming a product that has significant agonism at the α and β adrenergic receptors and indirect agonism by augmenting norepinephrine release. Because of a large variation in the concentrations of ephedrine alkaloids present in supplements, significant cardiovascular response variation will be observed following ingestion. A common street name for ephedra in Dallas, TX, is herbal ecstasy. The euphoric and stimulant effects of ephedra are less intense but similar to the amphetamines. Anxiety, arrhythmia, palpitations, headaches, intracranial hemorrhage, hypertension, seizures, stroke, myocardial infarction, hyperthermia, and death have all been reported following ephedra use.²⁹ In fact, myocardial infarction secondary to isolated coronary artery vasospasm has been documented following ephedra ingestion in patients with normal coronary arteries.

St John's Wort

The concentration of the active constituents of St John's wort, hypericin and hyperforin, vary greatly from plant to plant, but commercial preparations are standardized to between 0.2% and 0.5% for the former constituent and 3%

for the latter. Because hypericin is known to be an MAOI, inhibiting catechol-O-methyltransferase and the reuptake of serotonin, dopamine, and norepinephrine (thus raising brain monoamine levels), this explains its popularity as a treatment of depression and anxiety.³⁰

St John's wort is an inducer of the cytochrome P450 liver enzyme systems, altering the metabolism of many drugs coadministered with the wort. There is an increased clearance of midazolam and alprazolam. Studies show a low incidence of side effects, including no effect on the QTc interval.

The problem with St John's wort is the frequent reports of interactions between herbs and prescription drugs. The SS has been reported with the concomitant use of other serotonergic drugs, as in the case described at the start of this section. In addition, decreased plasma levels of digoxin, verapamil, warfarin, methadone, cyclosporine, theophylline, amitriptyline, midazolam, alprazolam, omeprazole, and simvastatin have been reported with concomitant *Hypericum* use. Reactions from delayed emergence to cardiovascular collapse during and following general anesthesia (accomplished with fentanyl, propofol, and sevoflurane) have been reported in patients using St John's wort.

DRUG TOXICITY IN THE CHRONIC PAIN PATIENT AND DMP TOXICITY

A 60-year-old man presents to your chronic pain management clinic for control of low-back pain that was not successfully treated with 3 lumbar laminectomies, the last including bone fusion and hardware placement. He has a past history including IV drug and alcohol abuse and is hepatitis C positive. He admits to taking 6 to 9 tablets of Lorcet (Table 2) routinely during a 24-hour period. His current complaints include postprandial epigastric pain, right upper quadrant tenderness, anorexia, nausea, occasional vomiting, and weight loss. Laboratory studies report an aspartate aminotransferase (AST) plasma concentration of 324 IU/L (normal range 10–50 IU/L) and alanine aminotransferase (ALT) concentration of 190 IU/L (normal range 10–50 IU/L). *What would you do next?*

Table 2

Common drug combinations containing acetaminophen (AMP). Current recommendations limit a 24-hour AMP dose to 4 g or less

Drug Name	Hydrocodone (mg)	AMP (mg)	Codeine (mg)
Lorcet	10	650	
Lortab (Vicodin)	5	500	
Lortab 7.5	7.5	500	
Lortab 10	10	500	
Norco	5	325	
Norco	7.5	325	
Norco	10	325	
Tylenol #3	–	300	30
Tylox	5 mg (oxycodone)	500	
Percocet	5 mg (oxycodone)	325	
Percocet	10 mg (oxycodone)	650	

The 60-year-old patient described in this section was switched from Lorcet to Norco.

Acetaminophen Toxicity

Prompt recognition of acetaminophen (acetyl-*para*-aminophenol [APAP], or, for this discussion, AMP) hepatotoxicity is key to preventing morbidity and mortality. With correct dosing, 90% of AMP is conjugated with glucuronide to form nontoxic metabolites. Approximately 5% of AMP is metabolized by the hepatic cytochrome p450 oxidase enzymes to a toxic metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI). In normal dosing, NAPQI is rapidly detoxified by glutathione (GSH) to nontoxic metabolites. Chronic AMP overdoses eventually overwhelm conjugation, and increased formation of NAPQI together with GSH depletion ultimately causes hepatic necrosis. Because alcohol (ethanol) induces the p450 enzyme system, the liver has increased capability to metabolize AMP to NAPQI. Chronic alcoholics also have lower plasma GSH levels than nonalcoholics, explaining reports of a significantly greater risk of developing hepatic necrosis in the alcoholic following chronic AMP ingestion. GSH is essential for the detoxification of NAPQI and GSH stores are also reported to be depleted by malnutrition and anorexia nervosa.³¹ The Rumack-Matthew treatment (with *N*-acetylcysteine [NAC]) nomogram is useful in guiding treatment of acute AMP toxicity only, not for the subacute or chronic ingestion-induced toxicity that occurs in patients with chronic pain.

Subacute (chronic) AMP ingestions that result in hepatotoxicity occur in persons taking suprathreshold doses of AMP and who are at increased risk for AMP-induced hepatotoxicity.³² Serum concentrations of AMP, AST, and ALT should be measured in any patient at increased risk for hepatotoxicity (hepatitis, malnutrition, alcoholic, and so forth) who ingests more than 4 g of AMP per day. Patients with any AMP detected or with increased AST and ALT levels should be treated with oral NAC. Studies have shown that no patient with chronic AMP ingestion with an AST level less than 50 IU proceeded to develop hepatotoxicity, whereas 15% of those with an AST level greater than 50 IU did develop hepatotoxicity. Therefore, the patient described at the start of this section was treated with oral NAC and a change in his oral analgesic therapy (see **Table 2**).

Hepatotoxicity caused by AMP ingestion is believed to be effectively treated by NAC because NAC is a precursor for, and increases the synthesis of, GSH.³³ NAPQI will bind to the thiol groups of GSH instead of binding to hepatocytes. Once NAPQI is bound to the thiol group of GSH, it produces cysteine and mercapturic acid conjugates which are nonreactive with hepatocytes. A 72-hour oral NAC protocol is considered standard treatment of chronic AMP toxicity.³⁴

Fentanyl Patches and Lollipops

The licit and illicit use of the continuous release fentanyl transdermal patch and the fentanyl lollipop has dramatically increased in the past decade.³⁵ Transdermal fentanyl patches are designed to release 12.5, 25, 50, 75, or 100 µg/h, and result in plasma levels of fentanyl similar to those achieved with a continuous IV infusion. The manufacturer recommends that the patches be replaced after 72 hours of continual use, at which time substantial amounts of fentanyl remain in the patch (approximately 2800 µg in a 10 mg patch). Because of the continued presence of fentanyl in used patches, the used patches have been smoked, ingested, the contents extracted and injected, and steeped in hot water (creating a fentanyl tea).³⁶ Abuse of the extracted fentanyl remaining in the reservoir results in an unreliable and unpredictable dose and has resulted in several overdose fatalities.³⁷

The fentanyl lollipop (Actiq) depends on transmucosal absorption and is used primarily for cancer breakthrough pain. Abuse of either preparation of fentanyl

presents the clinician with the well-known symptoms of opioid intoxication (CNS and respiratory depression, miosis) and is treated with standard supportive care and airway management.

DMP

DMP is the dextrorotatory isomer of levorphanol, a codeine analog, and is used primarily as a cough suppressant.³⁸ Widely available in various over-the-counter cough and cold preparations, DMP is found in Robitussin and Coricidin. Despite initial classification as an opioid, DMP was believed to lack the potential for abuse or addiction. DMP does not induce the typical opioid effects of respiratory depression, miosis, or analgesia because DMP does not bind to and stimulate the κ or μ opioid receptors. Because the primary active metabolite is dextrorphan, which binds to and inhibits the *N*-methyl-D-aspartate (NMDA) receptor (as does DMP itself, a pharmacologic effect similar to that of ketamine), DMP abuse will produce the well-known phencyclidine (PCP)-like effects of visual hallucinations, euphoria, paranoia, disorientation, altered time perception, and acute psychosis.³⁹ In addition, DMP is a serotonin reuptake inhibitor and therefore is capable of causing the central serotonergic effects described earlier. Benzodiazapines, like midazolam, are effective in preventing or treating the CNS effects of the PCP-like drugs, and therefore should be a drug of choice in the treatment of the DMP-abusing patient.

POISONINGS CAUSING METABOLIC ACIDOSIS, INCLUDING CARBON MONOXIDE

A 3-year-old 16-kg boy presents to the emergency department following a mobile-home fire caused by a propane heater requiring the fire department to remove the patient through a rear bedroom window. On arrival, the patient is somnolent and, with face mask oxygen supplementation, a standard pulse oximeter reads an SpO_2 of 97%. Several minutes following admission, the patient experiences a seizure and a successful endotracheal intubation is performed. ABG analysis reveals a PO_2 of 97 mm Hg, pCO_2 of 33 mm Hg, pH 7.19, base deficit -13 mmol/L, HCO_3^- of 12 mmol/L, and lactate of 7 mmol/L. An estimated 18% body surface area burn is localized to the lower extremity. *What would you do next?*

A toxin-induced metabolic acidosis (pH $<$ 7.40, reduced HCO_3^- , and the presence of a base deficit) can arise from increased acid production or impaired acid elimination. Increased acid production may be caused by toxins that are acidic or have acidic metabolites, cause the generation of ketoacid bodies, or interfere with adenosine triphosphate (ATP) production or consumption. Laboratory evaluation of these patients becomes essential, including quantitative testing for drugs (acetaminophen, aspirin, carboxyhemoglobin [CO-Hgb], ethylene glycol, and methanol), ABG analysis, metabolic panel studies, and 12-lead ECG. In addition, the patient may have clinical symptoms suggestive of well-described toxic syndromes caused by anticholinergic or cholinergic drugs, opioids, or sympathomimetic drugs. Routine serum and urine drug screens are seldom helpful, because the presence of a particular drug only confirms exposure to that drug, whereas that drug may not be the cause of the patient's clinical condition.

A clinically useful technique in the evaluation of a toxin-induced metabolic acidosis is the calculation of the anion gap (AG).⁴⁰ Many toxins are associated with an increased AG metabolic acidosis and the presence of an increased AG acidosis may suggest poisonings caused by several toxins (Table 3) and, in addition, may have prognostic value.⁴¹ The AG is measured by the following formula: $AG = [Na^+] - [Cl^-] + [HCO_3^-]$. A normal AG is reported to be between 7 and 12 mEq/L,

Medical Conditions	Toxin or Drugs
Uremia	Ethylene glycol
Diabetic ketoacidosis, alcoholic ketoacidosis	Salicylates
Lactic acidosis states, including shock	Acetaminophen
Carbon monoxide	Amphetamines Cocaine Cyanide (including nitroprusside) Metformin/phenformin Valproic acid Propofol

depending on the reference source chosen.⁴² Thus a calculated AG greater than 12 mEq/L (± 4 mEq/L) may suggest poisoning by one of the toxins or medical conditions listed in **Table 3**.

Acidosis Caused by Toxins that are Acids or Have Acid Metabolites (Increased Acid Production)

The alcohols benzyl alcohol, ethanol, ethylene glycol, and methanol are not acidifying per se until metabolized to acidic intermediates.⁴³ Ethylene glycol is metabolized to glycolic acid, methanol to formic acid, and ethanol to acetic acid. Benzyl alcohol is a common preservative in IV medications. Salicylates are weak acids that may produce an increased AG metabolic acidosis through several mechanisms, including the uncoupling of oxidative phosphorylation, renal injury leading to renal failure and acid retention, and cause an increase in acidic ketone body formation.⁴⁴

Acidosis Caused by Toxin Interference with ATP Production or Consumption

Metabolic acidosis may result from disruption of cellular energy production or consumption. Acetaminophen is believed to inhibit (uncouple) oxidative phosphorylation that leads to an AG metabolic acidosis. Human immunodeficiency virus (HIV)-positive patients taking antiretroviral therapy may develop lactic acidosis by uncoupling oxidative phosphorylation via the inhibition of mitochondrial DNA polymerase. Increased AG metabolic acidosis is also a known result of valproic acid toxicity. The biguanide phenformin was withdrawn from clinical use because of the risk of metabolic acidosis. Another biguanide, metformin, has not to date been directly linked to metabolic acidosis, but an intentional overdose of metformin may cause AG metabolic acidosis by inhibition of the electron transport chain.⁴⁵

Several mitochondrial poisons may cause profound metabolic acidosis, including carbon monoxide, cyanide (including nitroprusside-derived cyanide ion), formic acid (formed by the metabolism of ingested methanol), and salicylates. These toxins inhibit the electron transport chain, blocking aerobic energy production that may result in an increased AG metabolic acidosis.

Acidosis Caused by Increased Acid Production

Uncontrolled diabetes, prolonged fasting and exercise, and acute alcohol consumption can induce the production of ketone bodies (acetoacetate, acetone, β -hydroxybutyrate), resulting in an AG metabolic acidosis.

The presence of lactate is primarily an indicator of (or result of) anaerobic metabolism. No net increase in H^+ ion production occurs during the anaerobic metabolism of

glucose to lactate in the production of ATP.⁴⁶ Other evidence supporting the understanding that lactate per se does not cause an AG metabolic acidosis is the observation that infusion of lactate containing fluids (Ringer lactate) results in an increase in pH because of liver metabolism of lactate to HCO_3^- and the frequent observation of increased AG metabolic acidosis in patients with normal lactate levels.⁴⁷

Treatment of Metabolic Acidosis

It is important for the clinician to correctly diagnose and treat the underlying cause of an AG metabolic acidosis. Treating metabolic acidosis with a buffer like sodium bicarbonate has been shown to be injurious because of exacerbation of acidosis. Sodium bicarbonate therapy results in an increase in the generation of carbon dioxide, which has been shown to further lower pH, thereby exacerbating acidosis.⁴⁸ Currently, sodium bicarbonate should be viewed as a sodium ion donor, useful in antagonizing drug-induced sodium channel blockade found in clinical conditions like cocaine intoxication,⁶ tricyclic antidepressant overdose, or LA toxicity; conditions characterized by a drug-induced sodium channel blockade. Patients who also may benefit from bicarbonate therapy are those poisoned with drugs whose elimination may be increased by alkalinization (salicylates).

Carbon Monoxide Poisoning

Carbon monoxide (CO) is the leading cause of poisoning deaths in the United States. A cigarette smoker is exposed to an estimated 400 to 500 ppm of CO while actively smoking. Exposure to 70 ppm may cause CO-Hgb levels to reach as high as 10% at equilibrium (4 hours). CO binds to Hgb with an affinity 200 times that of O_2 , causing a leftward shift of the oxyhemoglobin dissociation curve. CO binds to many other heme-containing proteins other than Hgb, including cytochromes (impairing oxidative metabolism), myoglobin (skeletal and cardiac muscle toxicity), and guanylyl cyclase (increased nitric oxide [NO] levels).⁴⁹ Increased brain concentrations of NO are believed to play a major role in the neurologic injury following CO poisoning.

These pharmacologic effects of CO explain the diverse consequences of CO poisoning on the CNS (headache, confusion, seizure, and coma), heart (dysrhythmia, ischemia, infarction, asystole), and skeletal muscle (rhabdomyolysis and acute renal failure).

Delayed (2–40 days postpoisoning) neurologic deterioration following apparent recovery following CO poisoning is well described. This delayed deterioration is more common in those patients initially presenting in CO-induced coma.

A nonsmoker normally has 1% to 3% CO-Hgb, whereas smokers may have up to 10%. Low CO-Hgb levels (<15%) cause mild symptoms (nausea, headache), whereas levels of 60% to 70% are usually fatal. CO-Hgb levels should be measured with a CO-oximeter, which can accurately measure CO-Hgb and other abnormal hemoglobins (MHgb). Barker and Tremper⁵⁰ showed that SpO_2 measured by standard pulse oximetry (2 wavelengths) consistently overestimated O_2 saturation in the presence of CO-Hgb. Their data show that, at 70% CO-Hgb (usually fatal in humans), a standard 2-wavelength pulse oximeter SpO_2 read 90% saturation, whereas actual oxyhemoglobin levels were 30%. Their demonstration of a linear decrease of oxyhemoglobin with increasing CO-Hgb concentrations underscores the important role of CO-oximeter (multiple wavelength) monitoring in these patients.⁵⁰

The severity of metabolic acidosis correlates with exposure duration, expression of clinical symptoms, and adverse outcomes following CO intoxication. The amount of lactate present serves as a marker for severe CO poisoning by reflecting the degree of anaerobic metabolism.

Treatment of CO poisoning begins with airway management, oxygen supplementation, and cardiovascular support. Hyperbaric oxygen therapy may have a role in preventing adverse neurologic outcomes but introduces unique problems and possible complications. Hyperbaric O₂ reduces the half-life of CO-Hgb: the half-life of CO-Hgb is 320 minutes with room air (21% O₂), 40 to 80 minutes at 100% O₂, and 20 minutes at 100% O₂ at 2.5 to 3 atmospheres.⁵¹ In addition to reducing CO-Hgb concentrations, hyperbaric O₂ also reduces CO binding at all heme-containing protein sites (cytochromes, myoglobin, and so forth). Reports of reduction in the incidence of the delayed neurologic deterioration syndrome following CO poisoning makes the use of hyperbaric oxygen compelling for those patients whose presenting symptoms include coma.

High levels of CO-Hgb (36%) have been described during desflurane anesthesia in the presence of a dehydrated CO₂ absorbant (Baralyme).⁵² Carbon dioxide absorbants containing strong alkali hydroxides (KOH, NaOH) are believed to be responsible for the degradation of inhaled anesthetic agents. The elimination of these strong alkali-containing absorbants have made CO₂ absorbent use safer, with minimal CO production with desflurane and isoflurane.⁵³ CO can also be formed during sevoflurane administration,⁵⁴ especially with Baralyme use. Because further studies are required to evaluate newer NaOH- and KOH-free absorbents, the need to avoid using dry CO₂ absorbent by frequent and routine servicing of the anesthesia machine remains, particularly in a location where patients with prior CO exposure may be anesthetized (the burn room).

The patient described at the start of this section had a measured CO-Hgb of 27%. He was treated with mechanical ventilation with high inspired oxygen concentrations and, as expected, within 12 hours the CO-Hgb concentration fell to less than 5%, allowing removal from mechanical ventilation and uneventful extubation.

MILITARY/TERRORIST POISONINGS, INCLUDING BOTULISM AND BOTOX

A 12-year-old boy is scheduled for elective surgery requiring general anesthesia. He has a history of spastic cerebral palsy and was treated for the spasticity with injections of botulinum toxin type A (Botox) on 4 occasions (the most recent 2 weeks before) in the previous 18 months. How should this patient be anesthetized? If neuromuscular blocker (NMB) use is required, which one should be used and should a normal response be expected? Is NMB monitoring important in the management of this patient? Where should the effects of the NMB be monitored: at the eye brow (orbicularis oculi) or the hand (adductor pollicis), and would it make a difference clinically? *What would you do?*

Increasing attempts by terrorist organizations to manufacture weapons causing mass injuries and fatalities requires the clinician to have some awareness of the management of these injuries. Documented use of mustard gas and the nerve agent tabun by the Iraqi military during the Iran-Iraq war and production capabilities found for *Bacillus anthracis*, rotavirus, aflatoxin, mycotoxins, and botulinum toxin found following the Gulf War demonstrate the current danger facing modern society.

Initial management of the victims of chemical and biological weapons (CBWs) includes decontamination procedures (removal or neutralization of CBWs) to limit further exposure, such as showering and the use of chemical agents (soap, hypochlorite solutions), are important measures. Medical staff training in the use of protective equipment, including full-face mask, air-purifying equipment, and chemically resistant clothing and boots is essential.

Chemical Agents

Nerve agents (sarin, tabun, soman, VX) are toxic, odorless, colorless, and tasteless, are chemically related to the organophosphate insecticides, and are irreversible inhibitors of acetylcholinesterase (AChE).⁵⁵ Organophosphate insecticide (malathion) poisonings cause several hundred thousand fatalities worldwide every year. The cholinergic crisis syndrome resulting from the systemic overdose of acetylcholine (ACH) secondary to AChE inhibition results in the well-known symptoms of salivation, bronchospasm, skeletal muscle weakness/paralysis, bradycardia, and respiratory failure. The use of succinylcholine for neuromuscular blockade will result in prolonged paralysis because of the concomitant inhibition of the plasma cholinesterases. The first phase of the cholinergic crisis is characterized by a depolarizing block at the neuromuscular junction, whereas the second phase of muscle weakness is caused by a nondepolarizing (phase 2) block, all resulting from an overdose of ACH at the neuromuscular junction. Pyridostigmine has been recommended as a pretreatment because the inhibition of AChE is competitive and reversible. Atropine and the oximes (pralidoxime, which reactivates AChE) are effective if given early following exposure. Atropine is more effective than glycopyrrolate, which has a shorter half-life and does not cross the blood-brain barrier.

Blistering agents (the mustards, such as mustard gas and nitrogen mustard, and lewisite) are liquids that cause chemical burns and blisters, resulting in respiratory failure, blindness, pancytopenia, and cancer.⁵⁶ Mustard gas smells like mustard or garlic and can be released atmospherically by explosive aerosolization. Following a latent period of 4 to 12 hours, skin erythema appears on exposed areas, with edema and first-degree burns following. With high-dose exposure, skin necrosis and sloughing occurs, requiring treatment similar to burn therapy (fluid rescue, debridement). Ocular symptoms are common (pain, blurred vision) and may lead to permanent blindness. Inhalation of mustard gas causes tracheobronchitis, cough, bronchospasm, pulmonary hemorrhage, secondary bacterial lung infections, and respiratory failure that may require intubation and mechanical ventilation.

Choking agents (chlorine, phosgene, chloropicrin) are volatile liquids that cause fulminant pulmonary edema.⁵⁷ Chlorine and phosgene are widely used in the synthesis of plastics, and therefore poisoning with these agents may be encountered following industrial accidents. Phosgene smells like freshly mown hay, is hydrolyzed to CO₂ and hydrochloric acid, explaining phosgene's ability to cause severe lung injury (pulmonary edema) following inhalation. Treatment will include corticosteroids (inhaled or IV), inhaled β₂ agonists, prophylactic antibiotics (for secondary bacterial infections), leukotriene inhibitors.

The blood agents hydrogen cyanide and cyanogen chloride inhibit the cytochrome oxidase system, causing a metabolic acidosis and tissue hypoxia resulting in seizures and respiratory and cardiac failure.⁵⁸ Hydrogen cyanide has an almond smell, is colorless, and rapidly fatal. Cyanide binds to the trivalent iron of cytochrome oxidase, interrupting the consumption of O₂. ABG analysis demonstrates an increased lactate (AG) metabolic acidosis and a reduced oxygen gradient between arterial and mixed venous blood, a characteristic finding in cyanide poisoning. Sodium thiosulfate, sodium nitrite, and hydroxycobalamin are effective treatment options.

Biologic Agents

All biologic agents have similar characteristics: release into an unprotected population with poor natural immunity will produce a high fatality and incapacitation rate. Biological weapons include viruses (variola), rickettsiae (Q fever, Rocky Mountain spotted

fever), and bacteria [*B anthracis* (anthrax), *Yersinia pestis* (plague) and *Francisella tularensis* (tularemia)]. *Y pestis* is an anaerobic gram-negative coccobacillus and is transmitted to humans primarily by rodent fleas or human-to-human droplet infection. The clinical symptoms include pneumonia, fever, hemoptysis, sepsis, and multiple organ failure requiring ventilatory and circulatory support. Streptomycin, gentamicin, and chloramphenicol are effective for *Y pestis* eradication, whereas chemoprophylaxis is provided by tetracycline or doxycycline.

B anthracis is an aerobic, gram-positive spore-forming rod that primarily infects cattle, sheep, goats, and horses. Fifty kilograms of aerosolized *B anthracis* released upwind of half a million unprotected humans would kill an estimated 20%.⁵⁹ The most common clinical presentation is cutaneous anthrax, whereas inhalation of anthrax spores can result in a highly lethal form of the disease. The recent release of anthrax spores via the US mail system resulted in the cutaneous and inhalational expression of the disease. The inhalation form begins with a cough and fever and can progress to a necrotizing mediastinitis and multiple organ failure that is refractory to treatment and is usually fatal. An enzyme-linked immunosorbent assay (ELISA) is able to rapidly detect circulating toxin, whereas Gram stains and blood cultures are aids to a correct diagnosis. Ciprofloxacin and doxycycline may be used for chemoprophylaxis.

Saxitoxin, ricin, and botulinum toxin are the most toxic chemicals currently known, and they injure by a variety of mechanisms. *Clostridium botulinum* strains produce several neurotoxins that are the most toxic chemicals known. Neurotoxin A (Botox) binds to presynaptic ACH receptors, permanently inhibiting ACH release,⁶⁰ and requires the generation of new end-plate boutons to reestablish normal neuromuscular function.⁶¹ Following botulinum toxin exposure, bulbar palsy (dysarthria, dysphagia, diplopia, ptosis) followed by progressive descending weakness ending in respiratory failure occurs, requiring prolonged mechanical ventilation for survival.

Ricin is derived from castor bean seeds and is a waste product of castor oil production. Inhalation of high doses is rapidly fatal, with no definitive treatment available. Saxitoxin is produced by a flagellate sea organism that produces the red tide. It can become concentrated in shellfish and is responsible for paralytic shellfish poisoning. Saxitoxin is a potent blocker of sodium channels, thereby resulting in a generalized failure of the cardiorespiratory system.

Humans who have received recent Botox therapy (such as the case described at the start of this section) may have an atypical response to NMBs. Fiacchino and colleagues⁶² described resistance to a nondepolarizing NMB (vecuronium) in humans treated chronically with Botox and the mechanism is believed to be caused by a Botox-induced ACH receptor upregulation, similar to that seen following burn injury. There is a report describing the unmasking of occult myasthenia gravis shortly (first few days) following Botox injection. This report suggests a biphasic effect of Botox; that is, an early partial systemic neuromuscular blockade following the injection, implying an increased sensitivity to nondepolarizing NMBs could be expected to occur following recent (within a few days) Botox treatment.⁶³ The location of NMB monitoring may be particularly important in the patient treated with Botox because recovery studies evaluating respiratory (diaphragm) mechanics show that adequate recovery of airway protection and ventilatory adequacy may not occur until nearly complete neuromuscular recovery occurs, as demonstrated by adductor pollicis train-of-four ratio recovery of 0.80 or more.⁶⁴ Thus, monitoring the effect of NMBs at the adductor pollicis more accurately demonstrates complete diaphragm recovery and is therefore a more reliable margin of safety indicator-monitoring site compared with monitoring at the orbicularis oculi muscle.

POISONOUS BITES AND ENVENOMATIONS

An 8-year-old boy weighing 30 kg presents to the emergency room after sustaining a bite (confirmed by fang marks) to the right lower leg by the southern copperhead (*Agkistrodon contortrix*). The leg is currently swollen and edematous, indicating severe envenomation. Antivenin therapy was started (following negative skin tests), but the patient did not receive the full calculated dose because of urticaria, bronchospasm, and wheezing. Following treatment with histamine blockers and epinephrine, the patient developed what appeared to be an anterior compartment syndrome, confirmed by measured compartment pressures greater than 40 mm Hg. The patient is now scheduled for an emergency fasciotomy. What further laboratory tests, including tests for a possible coagulation disorder, should be ordered before proceeding with anesthesia? Does this history influence the choice for NMBs? Would an altered response to NMBs be expected? Would regional anesthesia (spinal or epidural) have a place in the anesthetic management of this patient? *How would you proceed?*

Marine Envenomations

Invertebrate envenomations include jellyfish (schyphozoa), anemones, and fire coral (hydrozoa). The most dangerous of the hydrozoas is the Portuguese man-of-war which can be found in the Atlantic Ocean and Gulf of Mexico and can cause fatal envenomations. In Australia, the jellyfish species *Carukia barnesi* can cause severe and sometimes fatal envenomations.⁶⁵ The symptoms of envenomations include muscle cramps and headache, which may progress to hypertension, pulmonary and cerebral edema, and cardiac failure. Jellyfish venoms are antigenic, causing a variety of reactions, including rash, skin necrosis, neural and cardiac toxicity, and hemolysis. Death has resulted from anaphylaxis, but other symptoms include nausea, vomiting, headache, confusion, seizures, muscle spasm, angioedema with airway loss, and severe bronchospasm. Treatment includes flooding the envenomation site with 5% acetic acid (household vinegar), whereas isopropyl alcohol will cause further discharge of unfired nematocysts and is not recommended.⁶⁶ IV magnesium sulfate reduces pain⁶⁷ and the sympathetic response to envenomation; hot water (43–45°C) immersion, including total body shower with hot water following widespread envenomation, will inactivate the venom.

The echinoderm most commonly involved in envenomation is the sea urchin. The usual presentation is envenomation following a human stepping on the sea urchin, breaking off venom-containing spines into the skin. Treatment is similar to that of jellyfish envenomation.

Vertebrate envenomations include stingrays, lionfish, and stonefish. Stingray envenomation is the most common.⁶⁸ Although potentially serious cardiac dysrhythmias, seizures, and coma have been reported, the more likely life-threatening injuries are puncture wounds of the abdomen or chest. Wound irrigation followed by hot water immersion (causing venom degradation) is usually adequate treatment. Lionfish envenomation is characterized by severe localized pain and swelling. Treatment is the same as for stingray envenomation.⁶⁹ Antivenom is only available for stonefish envenomations.

Snake Envenomations

Two families of poisonous snakes are found in North America: the crotalids and elapids.

The crotalid (rattlesnake, cottonmouth, copperhead) are responsible for most envenomations.⁷⁰ The spectrum of clinical presentations from crotalid bites range from

asymptomatic to cardiovascular collapse and death. Tissue damage at the bite site is the most common complication following envenomation. Hemorrhagic toxins cause damage to capillary endothelium, allowing red blood cell extravasation that causes edema and hemorrhagic blebs. Venom metalloproteinases cleave protumor necrosis factor (pro-TNF), releasing active TNF, which initiates an aggressive inflammatory response.⁷¹ This aggressive inflammatory response makes an accurate diagnosis of compartment syndrome difficult, requiring objective measurement of compartment pressures a requirement for correct diagnosis. A clinical coagulopathy is found in up to 50% of bite victims.⁷² Venom may cause lysis of fibrinogen and fibrin leading to complete defibrination and platelet aggregation leading to widespread thrombosis and thrombocytopenia. Therefore, regional anesthesia should be approached with extreme caution in the bite victim. Neuromuscular blockade secondary to calcium channel blockade that inhibits ACH release is known to occur, especially with the Mojave rattlesnake (*Crotalus scutulatus*, commonly found in the American southwest),⁷³ and potentially synergize with NMBs.

Treatment depends on the severity of the envenomation. With extremity swelling, compartment syndrome must be documented with pressure measurement (>30 mm Hg) before fasciotomy.⁷⁴ Antivenom is the treatment of choice for crotalid bite-induced coagulopathy. Two antivenom products are available: a polyvalent antivenom of equine origin, and an ovine (sheep) polyvalent Fab immunoglobulin fragment product. Hypersensitivity to the equine product makes the sheep-derived product the preferred antivenom. Padda and Bowen⁷⁵ published a case report on rapid onset and prolonged duration of a nondepolarizing neuromuscular blocking agent (vecuronium) following human envenomation by a northern copperhead. Thus, for a recent envenomation victim, the administration of NMBs should be carefully titrated and adequate reversal documented by continuous neuromuscular monitoring by nerve stimulation.

SUMMARY

Drug- or toxin-induced pathology that the clinician may encounter and therapeutic approaches to these syndromes are discussed in this review. Although these syndromes have diverse causes and mechanisms of injury, they are organized by shared or similar mechanisms of injury and pathophysiology to present a more cohesive and understandable discussion.

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