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## Toxicology in the ICU : Part 2: Specific Toxins

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## Toxicology in the ICU

### Part 2: Specific Toxins

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**This is the second of a three-part series that reviews the generalized care of poisoned patients in the ICU. This article focuses on specific agents grouped into categories, including analgesics, anticoagulants, cardiovascular drugs, dissociative agents, carbon monoxide, cyanide, methemoglobinemia, cholinergic agents, psychoactive medications, sedative-hypnotics, amphetamine-like drugs, toxic alcohols, and withdrawal states. The first article discussed the general approach to the toxicology patient, including laboratory testing; the third article will cover natural toxins.**

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**Abbreviations:** AChE = acetylcholinesterase; ADH = alcohol dehydrogenase; APAP = acetaminophen; ATP = adenosine triphosphate; BB =  $\beta$ -blocker; CCB = calcium channel blocker; CO = carbon monoxide; DDI = drug-drug interaction; EG = ethylene glycol; FHF = fulminant hepatic failure; GABA =  $\gamma$  aminobutyric acid; HBO = hyperbaric oxygen; HCN = hydrogen cyanide; HD = hemodialysis; INR = international normalized ratio; IPA = isopropanol; LMWH = low-molecular-weight heparin; MeOH = methanol; MetHgb = methemoglobin; MR = modified release; NAC = N-acetylcysteine; NAPQI = N-acetyl-para-benzoquinoneimine; OP = organophosphate; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

This is the second of a three-part series that reviews the generalized care of poisoned patients in the ICU. This article focuses on specific agents likely to be encountered in the ICU.

#### ACETAMINOPHEN

Acetaminophen (APAP) toxicity occurs when nontoxic metabolic pathways are overwhelmed, causing enhanced production of N-acetyl-para-benzoquinoneimine (NAPQI).<sup>1</sup> This increased NAPQI depletes glutathione stores and results in hepatotoxicity.<sup>2,3</sup>

Acetaminophen toxicity typically leads to vomiting within 24 h of ingestion. Subsequently, marked hepatic dysfunction, including elevation of prothrombin time,

may develop. Peak hepatic injury with centrilobular necrosis typically occurs 4 days postingestion. Metabolic acidosis, coagulopathy, renal failure, and encephalopathy occur following massive ingestions. Significant renal injury may develop in the absence of hepatic failure.<sup>4</sup>

The Rumack-Matthew nomogram is used following an acute, one-time ingestion of APAP to determine if treatment with N-acetylcysteine (NAC) is necessary (Fig 1).<sup>5–8</sup> N-acetylcysteine acts as a free radical scavenger and cysteine donor to facilitate glutathione regeneration.<sup>9</sup> If therapy is begun within 8 h of ingestion, the risk of fulminant hepatic failure (FHF) approaches zero.<sup>1</sup> However, patients who present in a delayed manner ( $> 24$  h postingestion) still benefit from therapy with NAC.<sup>9</sup> The oral regimen involves 72 h of treatment, although a shorter course in selected patients may be appropriate.<sup>10</sup> The IV regimen involves a loading dose administered over 1 h, followed by a continuous infusion for 20 h. IV NAC can subsequently be discontinued if the patient is asymptomatic and prothrombin time and transaminases are improving. In cases with rising transaminases, NAC should be continued at 6.25 mg/kg/h until the patient is asymptomatic with improving hepatic function tests.

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Criteria for considering liver transplantation for APAP-induced FHF is an arterial pH < 7.3 despite resuscitation, or the combination of grade III/IV hepatic encephalopathy, prothrombin time > 100 s, and serum creatinine level > 3.4 mg/dL.<sup>11</sup> The early recognition of these abnormalities and consideration for transfer to a transplant center are paramount. A neuroprotective protocol has been suggested for APAP-induced FHF.<sup>12</sup>

Acetaminophen can cross the placenta, but NAPQI cannot. It is not until the second trimester that the fetus is able to produce NAPQI.<sup>2,13</sup> The indications for use and dosing of NAC are the same in pregnancy.<sup>14</sup>

### SALICYLATE

Acute salicylate toxicity produces tinnitus, hyperventilation, abdominal pain, and vomiting.<sup>15</sup> Tachycardia, diaphoresis, delirium, and seizures are observed in severe toxicity. Serum salicylate concentrations may not peak for > 24 h following overdose, especially with enteric-coated formulations.<sup>16</sup>

Brainstem stimulation causes a respiratory alkalosis.<sup>17</sup> Severe toxicity leads to uncoupling of oxidative phosphorylation, decreased adenosine triphosphate (ATP) production, increased acidosis, and hyperthermia.<sup>18</sup>

The primary treatment goal is to minimize distribution into the brain.<sup>19</sup> Aggressive fluid resuscitation and alkalinization with IV sodium bicarbonate will reduce CNS penetration and enhance elimination. Normokalemia should be maintained to assist with urine alkalinization. If sedation and/or endotracheal intubation are performed it is crucial to maintain respiratory alkalemia.<sup>20</sup> Blood glucose should be followed and hypoglycemia immediately corrected. Hypoglycorrachia (low cerebrospinal fluid glucose) in animals occurs even with normal serum concentrations.<sup>21</sup>

Because acidemia increases the volume of distribution of salicylate, serum concentrations may decrease despite worsening toxicity. In symptomatic patients, fluid resuscitation and alkalinization should be started immediately, prior to diagnostic confirmation. Salicylate is efficiently removed by hemodialysis (HD); indications include severe acidosis and/or rising salicylate concentrations refractory to medical management, encephalopathy, cardiopulmonary dysfunction, or renal failure. Mortality is related to not recognizing the need for immediate treatment (alkalinization and HD) in patients with encephalopathy.

### ANTICOAGULANT AND ANTIPLATELET MEDICATIONS

Warfarin toxicity frequently results from dose adjustments or drug-drug interactions (DDIs).<sup>22</sup> The urgency of warfarin reversal depends on the interna-

tional normalized ratio (INR) and clinical scenario (Table 1).<sup>23,24</sup> The risk of bleeding correlates with the INR and often results from trauma or unknown conditions.<sup>23,25</sup> Following warfarin overdose, the INR may not peak for several days, and multiple doses of vitamin K may be needed to control coagulopathy. Ingestion of superwarfarins (eg, brodifacoum-containing rodenticides) may require large daily doses of vitamin K for weeks.

The adenosine 5'diphosphate receptor antagonists include ticlopidine, clopidogrel, and prasugrel. Bleeding time can be used to indirectly measure adenosine 5'diphosphate-receptor antagonism, but platelet aggregometry is a superior method for monitoring effects.<sup>26</sup> Significant bleeding should be treated with platelet transfusion; desmopressin administration can be considered.<sup>27</sup>

There are currently three low-molecular-weight heparins (LMWHs) approved for use in the United States; enoxaparin, dalteparin, and tinzaparin. Although both unfractionated heparin and LMWHs bind to antithrombin III, LMWHs result in more profound inhibition of factor Xa.

The two main potential complications with heparin are bleeding and heparin-induced thrombocytopenia. Although heparin-induced thrombocytopenia can occur with any heparin-containing agent,<sup>28</sup> it is less common with the LMWHs. If bleeding develops while on unfractionated heparin, protamine sulfate can be used to reverse the effects of heparin. Each 1 mg of protamine reverses 100 units of heparin. The LMWHs, however, are only partially reversible with protamine. Although there are no studies concerning treatment of LMWH toxicity, bleeding resistant to protamine should be treated with blood products and/or recombinant factor VIIa.<sup>27</sup> Laboratory monitoring is generally unnecessary when using LMWHs as the risk of bleeding has not been shown to correlate with the severity of factor inhibition, even in overdose.

### CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) antagonize L-type calcium channels resulting in vasodilation and decreased inotropy, dromotropy, and chronotropy. Verapamil or diltiazem toxicity produces myocardial depression and vasodilation, whereas dihydropyridine (eg, amlodipine) overdose causes more vasodilation in those without baseline cardiac disease or  $\beta$ -blocker (BB) use and occasionally results in reflex tachycardia. Although a massive ingestion of any CCB can be life-threatening, verapamil is the most lethal.<sup>29</sup>

Cardiac effects include bradycardia, atrioventricular blocks, and junctional rhythms. Hypotension and

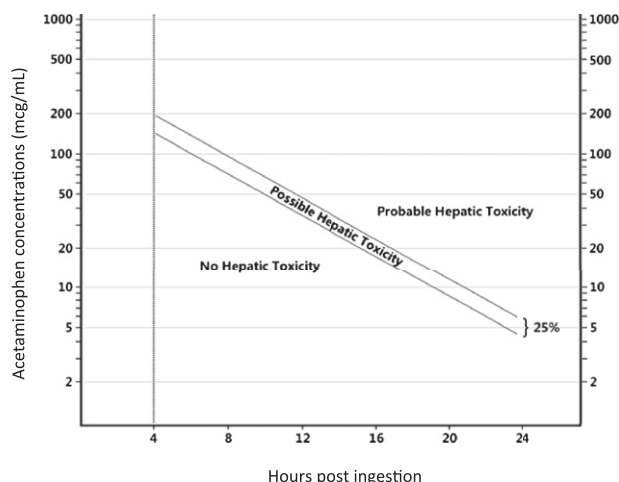


FIGURE 1. Rumack Mathew nomogram.

hyperglycemia are common.<sup>30</sup> Warm, dry skin from vasodilation sometimes provides a false impression of adequate cardiac output. The presence of new renal insufficiency or metabolic acidosis despite warm, dry skin and apparently adequate blood pressure requires additional assessment of cardiac function, such as echocardiography or a pulmonary artery catheter.

Onset of clinical effects following ingestion of immediate-release formulations typically occurs within 6 h. Modified-release (MR) formulations may result in delayed and prolonged toxicity; a minimum of 18 h of observation is required.<sup>31</sup>

Treatment starts with hemodynamic support via careful volume resuscitation and early use of direct-acting vasopressors. Calcium infusion may improve BP and can be tried, but effects are variable and may result in hypercalcemia. Temporary pacing can be used for refractory, clinically significant bradyarrhythmias. Hyperinsulinemic euglycemia therapy can be considered.<sup>32</sup> The use of cardiopulmonary bypass, extracorporeal membrane oxygenation, and

intraaortic balloon pumps are described for refractory shock.<sup>33-36</sup>

## β-BLOCKERS

Blockade of  $\beta$  receptors results in a decrease in cyclic adenosine monophosphate concentrations.<sup>37</sup> Bradycardia, hypotension, variable degrees of conduction blocks, heart failure, and occasional hypoglycemia are seen. Membrane-stabilizing BBs, such as propranolol, inhibit sodium channels, producing QRS prolongation and negative inotropy.<sup>38,39</sup> Propranolol also crosses the blood-brain barrier and can produce seizures or coma.<sup>40</sup> Sotalol blocks potassium efflux to lengthen the QTc interval.<sup>41</sup>

Patients who remain asymptomatic can be medically cleared following a 6-h observation for immediate-release products and 8 h for MR products.<sup>42</sup> Sotalol toxicity, however, can have a delayed onset and requires at least 12 h of observation.<sup>41,42</sup>

Management of BB toxicity includes the early use of glucagon because of its activation of adenylate cyclase independent of  $\beta$  receptors.<sup>43-45</sup> Initial doses should be 2- to 5-mg IV push in adults followed by a continuous infusion at the response dose (in milligrams per hour). Up to 10 mg glucagon IV may be required initially in some patients. Emesis, hyperglycemia, and tachyphylaxis may complicate glucagon therapy.<sup>46,47</sup> Use of direct-acting vasopressors may be necessary.

## DIGOXIN

Cardiac glycosides inhibit the sodium-potassium ATPase pump, increasing intracellular sodium and extracellular potassium. A rise in intracellular sodium concentration is accompanied by a rise in intracellular calcium and increased contractility. Digoxin toxicity also produces increased automaticity and vagally-mediated bradycardia and conduction blocks.<sup>48</sup>

Table 1—Guidelines for Warfarin Reversal

INR	CHEST Guidelines	Australasian Society of Thrombosis and Haemostasis
2-5; No bleeding	Lower or omit dose	Lower or omit dose
5-9; No bleeding	Hold 1-2 doses or 1-2.5 mg po vitamin K	Hold warfarin. If bleeding risk high, 1-2 mg po or 0.5-1 mg IV vitamin K
$\geq 9$ ; No bleeding	Hold warfarin; give 5 mg po vitamin K	Hold warfarin. If bleeding risk low, give 2.5-5 mg po vitamin K or 1 mg IV vitamin K
Serious bleeding	Hold warfarin. Give 10 mg IV vitamin K, supplemented by FFP, PCC, or rVIIa	If high risk, give 1 mg IV vitamin K, consider PCC, FFP
Life-threatening bleeding	Hold warfarin. Give FFP, PCC, or rVIIa, supplemented by 10 mg IV vitamin K	Hold warfarin. Give 5-10 mg IV vitamin K, PCC and FFP

Data from Baker et al<sup>23</sup> and Ansell et al.<sup>24</sup> FFP = fresh frozen plasma; INR = international normalized ratio; PCC = pooled complex concentrate; rVIIa = recombinant factor VIIa.

Clinical manifestations depend on chronicity. Acute toxicity is characterized by nausea and vomiting followed by bradycardia and/or conduction abnormalities. Weakness and altered mentation may occur but are more common with chronic poisonings. Chronic toxicity can occur in the setting of renal dysfunction, inappropriate dosing, or DDIs and is more commonly associated with GI, neuropsychiatric (eg, delirium), and visual (eg, xanthopsia) manifestations. Cardiac manifestations include virtually any dysrhythmia, with the exception of rapidly conducted atrial tachydysrhythmias.<sup>49</sup> Bidirectional ventricular tachycardia, although uncommon, is relatively specific.

Digoxin concentrations, renal function, electrolytes, urine output, and cardiac status should be closely monitored. It is important to note that total digoxin concentrations may be uninterpretable if drawn within 6 h of the last dose, being elevated because of delayed tissue distribution. Hyperkalemia is a marker of acute toxicity and is associated with increased mortality.<sup>50</sup> Hypokalemia and/or hypomagnesemia may predispose to clinical effects with chronic toxicity.<sup>51</sup>

Indications for digoxin-specific Fab fragments include hyperkalemia ( $\geq 5.5$  mEq/L) following acute overdose and life-threatening dysrhythmias (Table 2).<sup>52</sup> In patients with severe baseline cardiac dysfunction, reduced Fab fragment dosing should be considered, if nonmoribund, to avoid reversing therapeutic digoxin effects. Renal failure impairs the excretion of both digoxin and digoxin-Fab complexes; recrudescence of symptoms is possible due to dissociation of the digoxin-Fab complex.<sup>53,54</sup> After treatment with Fab fragments, total digoxin concentrations are elevated and misleading. Consequently, only free digoxin levels should be followed clinically. However, free digoxin concentrations are not available in many laboratories.

### DISSOCIATIVE AGENTS

Ketamine, phencyclidine, and dextromethorphan (through its metabolite, dextrophan) are dissociative agents that produce intoxication by antagonism of N-methyl-D-aspartate glutamate receptors.<sup>55,56</sup> Clinical effects include delirium, hypertension, tachycardia,

nystagmus, diaphoresis, hyperthermia, and rhabdomyolysis.<sup>57-61</sup> Adrenergic or cholinergic effects may predominate in ketamine or phencyclidine poisoning.<sup>62</sup> Dextromethorphan preparations commonly contain antihistamines, which produce anticholinergic toxicity after overdose. In combination with other serotonergic drugs, dextromethorphan can initiate serotonin syndrome.

Toxicity is best managed with supportive care, including limiting stimuli to minimize agitation. Active cooling for hyperthermia, fluid resuscitation, and use of benzodiazepines for agitation or seizure are recommended.<sup>61,63</sup>

### CARBON MONOXIDE

Carbon monoxide (CO) is an odorless, colorless, and nonirritating gas with rapid systemic absorption. The amount of CO absorbed depends on ambient CO concentration, length of exposure, and physiologic parameters (eg, minute ventilation, cardiac output). After absorption, carboxyhemoglobin is formed and is incapable of transporting oxygen to tissue, which shifts the oxyhemoglobin dissociation curve to the left. CO poisoning produces headache, dizziness, nausea, confusion, coma, and death.

Cardiovascular effects are possible with significant CO toxicity, even in asymptomatic patients or those without coronary artery disease.<sup>64-66</sup> An ECG should be done on all patients with neurologic or cardiovascular effects. Cardiac enzymes levels should be assessed in patients with severe clinical toxicity, abnormal ECG, or history of cardiovascular disease. Management of individual patients should focus on clinical findings rather than the degree of elevation of carboxyhemoglobin concentrations. Two-wavelength pulse oximeters are incapable of detecting decreased oxygen saturations from CO poisoning. The diagnosis is made with multiwavelength co-oximetry.

All patients should receive 100% normobaric oxygen until symptoms have resolved. Although hyperbaric oxygen (HBO) is known to decrease the half-life of carboxyhemoglobin, there is controversy over the indications for its use and its effectiveness.<sup>67-72</sup> The use of HBO should be considered in patients with a significantly elevated carboxyhemoglobin

**Table 2—Indications and Dosing for Digoxin-Specific Fab Fragments**

Indications	Dosing, No. of Vials
Life-threatening dysrhythmias	Known serum digoxin concentration: No. vials = digoxin concentration (ng/mL) $\times$ patient weight (kg)/100
Severe end-organ dysfunction	Known amount of digoxin ingested: No. vials = amount ingested $\times$ 0.8/0.5
Hyperkalemia ( $> 5.5$ mEq/L)	Empirical dosing (unknown amount/concentration): Acute ingestion = 10 vials Chronic ingestion = 6 vials

Data from Reference 52.



concentration and syncope, seizures, cardiac ischemia, or continued altered sensorium despite receiving 100% normobaric oxygen. Fetal hemoglobin appears to have a higher affinity for CO, which might place the fetus at greater risk of CO toxicity. There is controversy over HBO recommendations for pregnant patients.<sup>67,73-76</sup> Acute CO poisoning may lead to delayed neuropsychiatric changes, but there are no established criteria to identify which subgroup(s) of patients benefit from HBO.<sup>76,77</sup>

## CYANIDE

In vivo, cyanide exists as hydrogen cyanide (HCN) and inhibits cytochrome  $a_3$  in mitochondrial cytochrome oxidase, thereby halting electron transport, oxygen consumption, and ATP formation.<sup>78</sup> Cyanide toxicity may develop after exposure to cyanide salts, HCN (including smoke inhalation), and cyanogens, which include plant or herbal cyanogenic glycosides, nitriles, and nitroprusside. Rapid onset of coma, seizure, metabolic acidosis, tachycardia, and hypotension suggest cyanide toxicity. However, toxicity can be delayed after ingestion of cyanogenic glycosides or exposure to nitriles.

A bitter-almond odor or bright red skin/blood is rarely noted. A percent saturation gap, the difference between measured and calculated oxyhemoglobin percentage, is not produced in cyanide toxicity.<sup>79</sup> Cyanide poisoning can shorten the QT interval to the point of "T on R" phenomenon.<sup>80</sup>

Two antidotal strategies are available: (1) IV sodium nitrite and sodium thiosulfate, or (2) IV hydroxocobalamin with or without sodium thiosulfate. Nitrite raises methemoglobin (MetHgb) concentrations, removing HCN from tissues. Thiosulfate enhances transsulfuration of HCN to thiocyanate, which is renally excreted.<sup>81</sup> Hydroxocobalamin acts by combining with HCN to form cyanocobalamin, which is also renally eliminated. A more in-depth discussion of hydroxocobalamin can be found in part one of this series.<sup>32</sup>

Hydrogen cyanide is commonly found in smoke, although no randomized trials have demonstrated that any cyanide antidotes change survival from smoke inhalation. However, neither sodium thiosulfate nor hydroxocobalamin decrease oxygen carrying capacity through MetHgb formation, which could be advantageous when significant carboxyhemoglobinemia is also present.

## METHEMOGLOBINEMIA

Acquired methemoglobinemia usually results from exposure to a xenobiotic that oxidizes hemoglobin's

ferrous iron to ferric iron. Common causes of methemoglobinemia include local anesthetics (eg, benzocaine), nitrites, phenazopyridine, and dapsone. Nonmedicinal causes include aniline and nitrobenzene.<sup>82</sup> Infants are at risk for methemoglobinemia from infections.<sup>83</sup> Persons with partial cytochrome  $b_5$  reductase deficiency are predisposed to develop methemoglobinemia; patients with glucose-6-phosphate dehydrogenase deficiency are not.<sup>84</sup>

Oxidation of one to three irons of the heme tetramers impairs the remaining ferrous heme from unloading oxygen, shifting the oxygen-hemoglobin dissociation curve to the left. In the absence of anemia, visible cyanosis is appreciated when MetHgb concentrations exceed 1.5 g/dL and usually occurs before significant impairment of oxygen delivery. Other signs and symptoms of impaired oxygen delivery include dyspnea, tachycardia, hypertension, and tachypnea followed by coma, lactic acidosis, seizures, bradycardia, and terminal arrhythmias.<sup>85</sup>

Diagnosis is confirmed with multiwavelength co-oximetry. Standard pulse oximetry readings are falsely elevated as MetHgb fractions begin to rise, and eventually fall to about 85% (still falsely elevated) where they remain even as MetHgb concentrations increase.<sup>86</sup> Arterial  $PO_2$  is normal in the absence of coexistent causes of hypoxemia. Arterial and venous blood may appear abnormally dark. Agents responsible for MetHgb formation may produce an accompanying oxidant stress-induced hemolysis.

Treatment consists of removing the offending agent and administering oxygen to optimize remaining oxygen carrying capacity. Patients with significant signs or symptoms of impaired oxygen delivery can be treated with IV methylene blue, which activates a normally inactive pathway for MetHgb reduction. Patients with glucose-6-phosphate dehydrogenase deficiency may not respond to methylene blue and may be at increased risk for hemolysis.<sup>87</sup> Total oxygen carrying capacity, rather than only MetHgb fractions, should be followed. Transfusion may be required in severe toxicity. Sulfhemoglobinemia can accompany, or be mistaken for, methemoglobinemia and will not respond to methylene blue.

## ORGANOPHOSPHATES

Organophosphate (OP) compounds include insecticides, medicinals, and nerve agents. The onset and severity of poisoning depend on the specific compound, amount and route of exposure, and rate of metabolic degradation.<sup>88</sup> Organophosphates inhibit neuronal acetylcholinesterase (AChE), resulting in acetylcholine accumulation and overstimulation of muscarinic and nicotinic receptors (Table 3).<sup>89</sup>

**Table 3—Clinical Effects of Organophosphate Toxicity**

Muscarinic Effects Predominate, Responsible For Morbidity/Mortality		Nicotinic Effects	CNS Effects
S - salivation	D - diaphoresis/diarrhea	Muscle fasciculation	Confusion
L - lacrimation	U - urination	Weakness	Ataxia
U - urination	M - miosis	Respiratory failure (diaphragmatic fatigue)	Seizures
D - defecation	B - bronchorrhea/bradycardia		Coma
			Neuropsychiatric changes (unproven)
G - GI upset	E - emesis	Hypertension	
E - emesis	L - lacrimation	Tachycardia	
		Hyperglycemia	
		Acidemia	
	S - salivation	Ketosis	
		Hypokalemia	

An intermediate syndrome, consisting of proximal muscle weakness occurring several days after resolution of acute symptoms, has been described and may reflect inadequate initial treatment. A delayed polyneuropathy has also been reported, typically occurring several weeks after a large exposure, and is believed to involve the inhibition of neuropathy target esterase, leading to weakness.<sup>90,91</sup>

Acute OP toxicity is diagnosed based on clinical presentation; however, plasma and erythrocytic AChE activities serve as surrogates for neuronal AChE activity. Unfortunately, results are not typically available in a timely manner at many centers.

Most OP-induced morbidity and mortality are due to respiratory failure from bronchospasm, bronchorrhea, and weakness/paralysis. Endotracheal intubation may be required. Pharmacologic interventions involve the use of atropine, pralidoxime, and benzodiazepines (Table 4). Initial management may require extraordinary doses of atropine.<sup>92</sup> IV glycopyrrolate may provide an alternative if atropine is unavailable.<sup>93</sup> Succinylcholine is degraded by AChE; its use may result in prolonged paralysis.<sup>94</sup> Atropine, a muscarinic receptor antagonist, will do nothing to prevent weakness and paralysis.

The exact role of pralidoxime is controversial. Atropine may be as effective as atropine plus pralidoxime in the treatment of acute OP poisoning.<sup>95</sup> Improved survival has been shown in moderately severe OP-poisoned patients who received early, continuous pralidoxime infusion compared with those who received intermittent boluses.<sup>96</sup> Supportive care along with appropriate, early use of atropine, and pralidoxime in moderately to severely OP-poisoned patients, remain the foundation of treatment.<sup>97</sup>

#### ANTIDEPRESSANTS

The selective serotonin reuptake inhibitors (SSRIs) prevent reuptake of serotonin, thereby increasing synaptic serotonin concentrations.<sup>98</sup> Mild sedation and vomiting are the most common manifestations

of acute toxicity.<sup>99</sup> Serotonin-norepinephrine reuptake inhibitors (SNRIs) antagonize the reuptake of serotonin and norepinephrine at therapeutic doses and after overdose. In general, SSRIs and SNRIs are well tolerated in overdose; unique features are listed in Table 5.<sup>100-105</sup> Care is symptomatic and supportive, and seizure activity responds to benzodiazepines.

Tricyclic antidepressants are much more toxic than SSRIs and SNRIs. Mechanisms of action and clinical effects are outlined in Table 6.<sup>106-108</sup> Following acute overdose, clinical effects of toxicity typically occur within 2 h of ingestion,<sup>109</sup> although significant toxicity can be delayed for up to 6 h. Hypotension is due to vasodilation ( $\alpha$  blockade) and myocardial depression (sodium channel blockade). Management includes fluid resuscitation, sodium bicarbonate, and the use of direct-acting vasopressors.<sup>110</sup> Rises in blood pH and serum sodium concentration attenuate sodium channel blockade, and IV hypertonic sodium bicarbonate is used to treat intraventricular conduction delays, refractory hypotension, and ventricular dysrhythmias. Although QRS prolongation typically responds to IV sodium bicarbonate, no trials provide guidance for when to initiate bicarbonate treatment in normotensive patients. Sodium bicarbonate should be given in the face of QRS prolongation when there is accompanying hypotension or ventricular dysrhythmias. If ventricular dysrhythmias persist despite maximal alkalinization (pH > 7.55), hypertonic saline (eg, 200 mL 3% NaCl in an adult) and/or lidocaine should be used. Seizures are treated with benzodiazepines. Use of lipid emulsion has been anecdotally reported in cases of refractory shock unresponsive to standard therapy.<sup>111</sup>

#### LITHIUM

Lithium exhibits a narrow therapeutic index and toxic effects occur frequently.<sup>112,113</sup> Lithium poisoning occurs in three scenarios; acute, acute-on-chronic therapy, and chronic. Acute ingestions are often associated with limited toxicity because of low baseline

**Table 4—Management of OP Toxicity**

Agent	Indication	Dosing	Comments
Atropine	Cholinergic toxicity	1-2 mg (0.05 mg/kg for pediatrics) IV push as an initial dose. Observe for effect or worsening. Subsequent doses should be doubled, every 2-3 min, as needed.	Dose based on controlling cholinergic symptoms. No maximal dose. Do not withhold because of tachycardia. Will not reverse nicotinic effects. Can consider an infusion. Other potential agents include; glycopyrrolate, diphenhydramine.
Pralidoxime	Severe OP toxicity	1-2 g (25-50 mg/kg) IV over 30 min, then 500 mg/h (10-20 mg/kg/h) infusion.	Continuous infusions are better than intermittent boluses.
Benzodiazepine	Seizure, anxiety, fasciculations	Diazepam 10-20 mg IV; repeat/titrate doses as needed.	If used for seizure; consider longer-acting agents (eg, phenobarbital) for recurrent seizures.

OP = organophosphate.

tissue concentrations and a prolonged distribution phase, although absorption is delayed with MR formulations. Acute-on-chronic ingestions occur following acute lithium ingestion in patients with therapeutic concentrations. Although usually well tolerated, acute-on-chronic ingestions are more likely to result in toxicity than ingestions by naive patients. Chronic toxicity typically develops during lithium therapy when decreased elimination occurs from DDIs, dehydration, or acute kidney injury. Chronic toxicity can present with pronounced effects because of the established tissue concentrations and may occur with minimal increase in total body lithium burden. Diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nondihydropyridine CCBs, and nonsteroidal antiinflammatories impair lithium clearance.<sup>114-116</sup>

Mild toxicity commonly comprises only diarrhea and vomiting, which can reduce renal lithium elimination. More severe findings include tremor, hyperreflexia, clonus, and cogwheel rigidity (but can also occur at therapeutic concentrations). Choreoathetoid movement, dysarthria, and ataxia are also possible. As toxicity worsens, drowsiness, confusion, seizures, and coma ensue.<sup>106,117</sup> Cardiac effects are common but typically of limited consequence and include nonspecific ST/T wave changes, varying AV blocks, QT prolongation, and sinus bradycardia.<sup>118-124</sup>

Chronic therapeutic dosing or overdose may produce nephrogenic diabetes insipidus from decreased

incorporation of type-2 aquaporin channels into renal tubule cells.<sup>125</sup> Other endocrine disturbances seen with chronic lithium therapy include hypothyroidism and hyperparathyroidism.<sup>126,127</sup>

In general, lithium concentrations correlate poorly with toxicity.<sup>128-130</sup> Concentrations checked soon after ingestion may be elevated due to prolonged tissue distribution. Treatment of toxicity involves correcting hypovolemia, ensuring sodium repletion, and maintaining adequate urine output. Ideally, 0.9% normal saline should be used for initial hydration, as sodium depletion enhances renal lithium reabsorption.

Although lithium is highly dialyzable, evidence of improved outcomes with HD is lacking. The decision to perform HD must be based on clinical findings (eg, encephalopathy), renal function, and serial lithium concentrations. If used, dialysis should be continued until the serum lithium concentration is near zero because of anticipated rebound as lithium redistributes from tissue into the vascular compartment.<sup>131</sup>

#### SELECTED MUSCLE RELAXANTS AND SEDATIVE-HYPNOTICS

Sedative-hypnotics, carisoprodol, and baclofen produce drowsiness, ataxia, coma, and respiratory depression. Isolated benzodiazepine overdoses, however, rarely cause enough respiratory depression to be fatal. Mixed overdoses, in which multiple drugs are ingested that can independently

**Table 5—Unique Features Associated With Selected SSRIs and SNRIs**

Drug	Unique Feature	Reference
Bupropion	Delayed seizures	100
Citalopram/escitalopram	Seizures, QT prolongation	101, 102
Venlafaxine	QRS prolongation, ventricular tachycardia, seizures	103-105

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.



**Table 6—Toxicity Associated With Tricyclic Antidepressants Ingestions Based on Mechanism of Action**

Mechanism of Action	Toxicity
Blocking reuptake of biogenic amines	Therapeutic effect, tachycardia
Sodium channel antagonism	QRS prolongation, seizures
Muscarinic receptor antagonism	Anticholinergic toxicity
Histamine receptor antagonism	Sedation
Inhibition of potassium efflux	QT prolongation
$\alpha_1$ Receptor antagonism	Vasodilatation, hypotension, reflex tachycardia
GABA-A receptor antagonism	Seizures

Data from Bosse et al,<sup>105</sup> Desarkar et al,<sup>106</sup> and Buckley and McManus.<sup>107</sup> GABA =  $\gamma$  aminobutyric acid.

cause respiratory depression, can be fatal, however. Large ingestions sometimes cause bradycardia and hypotension. Most of these agents or metabolites activate GABA-A receptors, whereas baclofen is a GABA-B receptor agonist.

Although unique features of several of these agents are found in Table 7, a few of these drugs merit specific mention. Baclofen overdose produces hypothermia, hypotension, bradycardia, coma, and seizures.<sup>132</sup> Chloral hydrate can cause GI hemorrhage, hypotension, long QT, and other tachydysrhythmias. Non-torsade ventricular dysrhythmias are believed to involve enhanced catecholamine effects and may respond to BBs.<sup>133-141</sup>  $\gamma$ -Hydroxybutyrate and related compounds cause CNS depression and respiratory failure with higher doses.<sup>142,143</sup> In overdose, carisoprodol can lead to coma and myoclonus.

Treatment is supportive. Any patient chronically taking a sedative-hypnotic, baclofen, or carisoprodol is at risk for withdrawal and should be restarted on their medication when awake.

### TOXIC ALCOHOLS

Toxic alcohols refer to methanol (MeOH), ethylene glycol (EG), and isopropanol (IPA). All three parent compounds are osmotically active and begin metabo-

lism via alcohol dehydrogenase (ADH). MeOH is metabolized to formic acid and EG is converted to glycolic and oxalic acids. Clinical toxicity is caused by the metabolites.<sup>144</sup> Isopropanol undergoes metabolism to acetone; both compounds are CNS depressing.

Since IPA is converted to acetone, but not to acetoacetate or  $\beta$  hydroxybutyrate, a metabolic acidosis does not occur following ingestion. Clinical findings associated with IPA are typically limited to CNS depression and, occasionally, hemorrhagic gastritis. Because of acetone-induced interference, a falsely elevated serum creatinine may be seen.<sup>145</sup> Treatment is supportive as in ethanol intoxication; there is no role for ADH inhibition.

Both EG and MeOH initially produce an increased osmol gap, which is followed by an elevated anion gap metabolic acidosis and coma in severe cases. EG toxicity is distinguished by calcium oxalate crystalluria and acute renal failure.<sup>146,147</sup> Methanol sometimes produces impaired vision and blindness with retinal hemorrhages<sup>148</sup>; intracerebral hemorrhages have been described.<sup>149,150</sup>

Serum EG, MeOH, and IPA concentrations are not routinely available at most centers but are useful if results are obtainable within several hours. Initial treatment decisions are typically based on history, examination, and laboratory results (eg, anion gap

**Table 7—GABA-Agonist Sedative-Hypnotic Agents With Selected Features**

Drug/Drug Class (examples)	Unique Features in Overdose
Barbiturates (phenobarbital)	Phenobarbital's renal excretion can be enhanced with urinary alkalization. Multidose activated charcoal may reduce the area under the curve for phenobarbital.
Benzodiazepines	GABA-agonist withdrawal can be life threatening. Use of flumazenil can precipitate acute benzodiazepine withdrawal and is not recommended.
Baclofen	Seizures can occur in overdose and withdrawal. Manifest effects at GABA-B receptors.
Nonbenzodiazepine sleep aids (zolpidem, zaleplon, eszopiclone)	Can also lead to tolerance and withdrawal.
Carisoprodol	Myoclonus and seizure possible. Rapid, intense withdrawal possible.
Chloral hydrate	Ventricular dysrhythmias, torsades de pointes.
GHB	Hypothermia, bradycardia, and myoclonus possible; rapid onset and recovery.

GHB =  $\gamma$ -hydroxybutyrate. See Table 6 legend for expansion of other abbreviation.

metabolic acidosis with or without an osmol gap). A detailed discussion of these laboratory studies was covered in part one of this series.<sup>32</sup>

Management of EG or MeOH poisoning involves inhibition of ADH via ethanol or fomepizole to prevent formation of toxic metabolites. Fomepizole, however, is easier to dose and produces fewer side effects.<sup>151</sup> Sodium bicarbonate is recommended based on animal data and a human case report suggesting effectiveness.<sup>152-154</sup> Although some guidelines recommend HD based on serum concentrations,<sup>155,156</sup> data suggest that dialysis may not be required without evidence of refractory acidosis or end-organ dysfunction.<sup>157-159</sup> Following large ingestions, HD may be of benefit due to fomepizole-induced prolongation of methanol's elimination half-life<sup>144</sup> or by correcting fluid status and preventing osmotic diuresis.<sup>160</sup> Leucovorin and folic acid are effective in animal models of MeOH poisoning and form the basis for use in humans.<sup>144,156</sup> Use of thiamine and pyridoxine in EG toxicity to increase metabolism via nontoxic pathways has been suggested and given their benign side effect profile, they are recommended.<sup>156,161</sup>

WITHDRAWAL STATES

Early identification of ICU patients at risk for withdrawal is important in avoiding associated complications, yet can be difficult because of altered sensorium, comorbidities, or limited and inaccurate histories. Common withdrawal syndromes are summarized in Table 8.

Although recommendations vary for the optimal management of sedative-hypnotic withdrawal, including ethanol, data support initially treating with benzodiazepines or phenobarbital.<sup>162-165</sup> Cited dosing regimens include scheduled, as needed (based on signs and symptoms), and front loading. The use of a front-loading technique is associated with rapid resolution of symptoms and involves gaining initial control with bedside titration of GABA-A-agonists, based on clinical response, followed by either scheduled or as-needed doses. Close monitoring for inadequate control of symptoms as well as iatrogenic-induced oversedation must be maintained. In patients with hepatic dysfunction there are no data that support increased complication rates when using hepatically metabolized agents (eg, diazepam). Currently, there are no randomized trials involving dexmedetomidine for the treatment of alcohol withdrawal.

Withdrawal from baclofen can be difficult to manage, especially if the withdrawal is due to a malfunctioning intrathecal pump. In such cases, the ideal management includes replacement of intrathecal baclofen as soon as possible.<sup>166,167</sup>

Opiate withdrawal is typically not life threatening. Altered sensorium generally does not occur. An exception to this is acute precipitation of agitated delirium following administration of large doses of naloxone. Treatment of opiate withdrawal involves a slow taper of a long-acting opioid.<sup>168,169</sup> Acute pain should be treated separately with shorter-acting agents. Stimulants, such as cocaine or amphetamines, do not produce a characteristic physiologic withdrawal syndrome.

Table 8—Xenobiotics With the Potential for Withdrawal

Withdrawal	Examples (Partial Lists)	Sign and Symptoms	Treatment Options
GABA-agonist (any agent that increases CNS $\gamma$ -aminobutyric acid activity)	Ethanol	Altered mental status (delirium, anxiety)	Restart medication. If not possible, initiate GABA-agonist agent with long half-life (eg, diazepam, phenobarbital). Prophylactic, standing orders for patients at high risk.
	Benzodiazepines	Abnormal neuromuscular activity (tremor, clonus, seizure)	
	Barbiturates	Tachycardia, hypertension,	
	Hypnotics/sleep aids (eg, zolpidem)	hyperthermia, respiratory alkalosis	
	Carisoprodol (Soma)		
Opiates	GHB		Restart medication. Initiate opiate with long half-life (eg, methadone, controlled release oxycodone). Buprenorphine. Symptom control with antiemetics, clonidine, sedative.
	Heroin	Anxiety	
	Morphine	Restlessness	
	Oxycodone	Nausea	
	Fentanyl	Diarrhea	
		Rhinorrhea	
		Yawning	
		Piloerection	
Antidepressants, psychotropic agents		Myalgias/arthralgias	Restart medication. Use agent from same drug class with long half-life (eg, fluoxetine for SSRI withdrawal).
		Craving	
	SSRIs	Anxiety	
	Venlafaxine	Paresthesias	
		Headache	
		Worsening of baseline psychiatric symptoms	

See Tables 5-7 legends for expansion of abbreviations.

## CONCLUSIONS

Poisoned patients frequently require tailored care based on their exposure, clinical condition, and comorbidities. Supportive care and the prevention of secondary sequelae are paramount. Optimal care involves discussing individual patients with a regional poison control center (in the United States, call 800-222-1222) or medical toxicologist.

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