Toxicology in the Critical Care Unit*

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Toxicologic conditions are encountered in critically ill patients due to intentional or unintentional misuse of or exposure to therapeutic or illicit drugs. Additionally, toxicities related to medical interventions may develop in hospitalized patients. This review focuses on recent developments in the field of critical care toxicology. Early interventions to decrease absorption or enhance elimination of toxins have limited value. Specific interventions to manage toxicities due to analgesics, sedative-hypnotics, antidepressants, antipsychotics, cardiovascular agents, alcohols, carbon monoxide, and cholinergic agents are reviewed. Hospital-acquired toxicities due to methemoglobinemia, propylene glycol, and propofol should be recognized and treated. The clinician is continually required to incorporate clinical judgment along with available scientific data and clinical evidence to determine the best therapy for toxicologic conditions.
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Toxicologic conditions in patients admitted to the ICU usually result from intentional or unintentional misuse of or exposure to therapeutic or illicit drugs. Additionally, significant toxicities can develop in hospitalized patients being treated for other illnesses. While evidence-based management is ideal, the characteristics of this patient population limit the feasibility of high-quality interventional trials. Recommendations for care of these patients are usually based on pharmacologic knowledge, animal studies, human volunteer studies, case reports, and consensus opinions. This review focuses on relevant updates on toxicities commonly encountered in adult critical care medicine. More exhaustive information can be found in reviews.[1–4]

Early Management Issues

Critical care management of the patient with a toxicologic condition requires rapid diagnosis and appropriate specific treatment while providing supportive care. Diagnosis requires a thorough history and physical examination combined with several laboratory tests.[3] The clinical evaluation may reveal the presence of characteristic clinical syndromes, called toxidromes, that suggest particular offending agents. However, many overdose patients treated in the ICU have used more than one agent, and toxidromes may overlap. Laboratory tests that may be of value include calculation of the anion, osmolal, and oxygen saturation gap, ECG, and quantitative toxicology assays for specific drugs. If the specific agent is unclear or multiple drugs have been ingested, an acetaminophen level should be obtained because of the lack of specific signs or symptoms and the potential benefit afforded by early, appropriate therapy. Quantitative testing for other drugs or toxins should be guided by clinical and laboratory findings. Qualitative toxicology assays performed on urine detect a limited number of drugs and have little impact on patient management.[5,6]

Several interventions have been routinely performed in patients with suspected oral overdose to decrease GI absorption or enhance elimination with little evidence of effectiveness (Table 1). Of these interventions, single-dose activated charcoal (SDAC) is the most utilized. The benefit of SDAC decreases when comparing administration at 60 to 120 min after ingestion in volunteer studies with a single-agent ingestion.[7] There is a theoretical benefit to administering charcoal at later times if there is a suspicion of delayed GI absorption.

ANALGESICS

Analgesics are the most common agents that result in toxicity necessitating hospitalization throughout the world. Acetaminophen (paracetamol) accounts for the majority of toxicity and accounts for the highest number of deaths from poisoning in the United States.[16] The utility of N-acetylcysteine (NAC) as an antidote in preventing acetaminophen-induced hepatotoxicity has been demonstrated since 1977. The Rumack-Matthew nomogram uses acetaminophen levels to determine the need for NAC administration in single acute ingestions of immediate-release acetaminophen.[4,17] Unfortunately, many patients have a history of long-term use, repeated ingestions, or use of extended-release formulations that limit the utility of the nomogram.[18] In patients who ingest extended-release acetaminophen, assessment of a second acetaminophen level 4 to 6 h after the first level is recommended if the initial level was in the nontoxic range.[19] Regardless of the time after ingestion, therapy with NAC provides significant benefit to those patients with acetaminophen-induced hepatic enzyme elevation.[1]

NAC can be administered orally or IV with equivalent effects[18,20]; Table 2 provides dosing. The IV formulation was approved in the United States in 2004; however, significant experience with compounding an IV formulation from the oral preparation has developed, and the compounded product appears to be safe.[21] The use of compounded medications is governed by local pharmacy boards; thus, clinicians need to obtain input from pharmacists regarding the legality of using compounded NAC. Either form of NAC should be administered within the first 8 h after ingestion to prevent hepatotoxicity.[22] Oral administration of NAC may cause vomiting due to the odor, and higher doses of antiemetics may be necessary. IV administration of NAC is associated with anaphylactoid reactions that are usually easily managed. Another therapeutic consideration when treating a single acute ingestion is the shorter dosing schedule of IV NAC compared to the oral form (20 h vs 72 h).

Definitive treatment guidelines are not established for patients who present with chronic or repeated ingestions of acetaminophen. Transaminase elevation (> 50 IU/L) and an acetaminophen level > 10 mg/L on presentation have been suggested as indications for treating with NAC.[24] Generally, treatment with NAC, whether oral or IV, is continued in these patients until serum acetaminophen levels are undetectable and liver function has normalized or is normalizing. SDAC may reduce the need for NAC treatment if used within 2 h of acute acetaminophen ingestion.[25] A recent review[26] suggests that the concomitant use of activated charcoal and NAC therapy improves patient outcomes. The oral NAC dose does not need to be increased if administered after activated charcoal, nor does there need to be a time lag between the two therapies.[27]

Table 1—Interventions To Limit Absorption or Enhance Elimination of Toxins

Interventions	Recommendations
Cathartics	Not recommended; no clinical benefit[8]
Ipecac	Not recommended; no clinical benefit[9]
Gastric lavage	Not routinely recommended; no known clinical benefit[10]
Whole-bowel irrigation	Not recommended for routine use; may be of benefit in ingestions of sustained-release or enteric-coated drugs[11]
Urine alkalinization (pH > 7.5)	Recommended in salicylate ingestions[12]
SDAC	Beneficial if administered within 1 h of ingestion; benefit beyond 1 h after ingestion cannot be excluded[7]
Multiple-dose activated charcoal	Not recommended for routine use; increases drug elimination of carbamazepine, dapsone, phenobarbital, quinine, and theophylline; no known clinical benefit[13]
Renal replacement therapy	Beneficial in lithium, toxic alcohol, salicylate, valproate, and theophylline toxicities; other toxicities may also benefit, but require patient specific consideration[14]; continuous renal replacement therapy not recommended for routine use; however, specific patients unable to tolerate conventional hemodialysis may benefit[15]

Table 2—Dosing of IV and Oral NAC Following Toxic Acetaminophen Ingestion*

Dosage	Special Considerations
Oral: 140 mg/kg loading dose followed by 70 mg/kg q4h for 17 doses	Any NAC vomited within 1 h of administration should be repeated
IV: 150 mg/kg loading dose over 15 min followed by 50 mg/kg infusion over 4 h, followed by 100 mg/kg over 16 h (total 300 mg/kg)	Use with caution in asthmatics and patients in whom an anaphylactoid reaction is a concern

*From Flomenbaum et al.[23]

Acetaminophen-induced hepatitis may progress to fulminant hepatic failure, and appropriate referral for liver transplantation may be necessary. The King's College criteria (KCC) for prognosis in acetaminophen-induced hepatoxicity (Table 3) are often used, but other indicators include lactate and amylase levels.[28] Patients who fit the KCC have a predictably high mortality, but the sensitivity is not ideal; thus, liver transplant may be of benefit to some patients who do not fit the KCC.

Ingestion of opioid analgesics is increasing, and misuse may result in significant respiratory, CNS, or hemodynamic depression. Critical care management of these complications is usually based on providing supportive care. The opioid antagonist naloxone is used to reverse significant respiratory depression associated with opioids. Typically, patients respond to IV doses of 0.04 to 0.4 mg; however, synthetic opioids such as fentanyl or buprenorphine may require doses as high as $\geq$ 10 mg.[1,30] Counteracting the respiratory depressant effect of longer-acting opioids may require a continuous infusion of naloxone. In these cases, the naloxone infusion is initiated at an hourly rate of two thirds of the IV bolus dose needed to reverse the respiratory depression and titrated to effect. Tramadol, an opioid considered to be a safer alternative to conventional opioids, should be recognized as a drug with abuse potential. Rare but significant toxicity, including death, has been associated with this drug especially when combined with other CNS depressants.[31] Seizures are a common manifestation of tramadol intoxication and usually occur within 24 h of ingestion.[32] The misuse of fentanyl as a street drug that is often combined with heroin is increasingly recognized. Urine toxicology assays will not detect fentanyl as an opiate.[33,34]

Sedative-Hypnotics and Muscle Relaxants

Sedative-hypnotics and muscles relaxants are agents that may lead to the need for respiratory support in the ICU. Recently, alprazolam and carisoprodol have been noted to cause significant harm to patients in overdoses.[35,36] Alprazolam was specifically associated with an increased ICU length of stay when compared to other benzodiazepines. Flumazenil as a diagnostic agent in benzodiazepine overdose should be used cautiously, especially in those patients with chronic benzodiazepine use, epilepsy, or coingestion with medications that may increase the risk for seizures such as tricyclic antidepressants.[37] Flumazenil is not indicated as a substitute for airway protection because its half-life is shorter than ingested benzodiazepines.[38]

Antidepressants

Overdoses with cyclic antidepressants (CAs) are less common due to greater usage of selective serotonin reuptake inhibitors (SSRIs).[39] Although there is insufficient evidence to support a particular therapy in CA overdose, the use of sodium bicarbonate to alkalinize blood to a pH of 7.45 to 7.55 is still considered the primary therapy to prevent and treat cardiac arrhythmias associated with CAs.[40] Proposed criteria for initiating sodium bicarbonate have been variable (Table 4), but in general we recommend blood alkalinization with QRS $>$ 120 ms. Hypertonic saline solution may be a therapeutic option in refractory cases based on animal studies and limited clinical experience. The cardiotoxicity associated with CAs is due to sodium-channel blockade in the His-Purkinje and myocardial cells, and sodium helps to overcome this blockade. Additionally, CAs have α-adrenergic blocking properties that may cause marked hypotension and α-agonists such as norepinephrine are indicated to improve hypotension refractory to volume replacement.[41,42]

SSRI overdose is unlikely to cause significant harm unless large quantities are ingested acutely ($>$ 75 times the usual daily dose). Fatalities associated with SSRI overdose are almost always associated with co-ingestion of other substances.[43] Serotonin syndrome (SS), which is a condition resulting from an excess of intrasynaptic serotonin, may occur with overdose or therapeutic use of SSRIs. This syndrome may also be associated with the use of serotonergic agents, including CAs, monoamine oxidase inhibi-

Table 3—KCC for Liver Transplantation in Acetaminophen-Induced Acute Liver Failure*

List for transplantation if:
  Arterial pH $<$ 7.3 after adequate fluid resuscitation
List for transplantation if all three of the following occur within a
  24-h period:
    Creatinine $>$ 3.4 mg/dL
    Prothrombin time $>$ 100 s (international normalized ratio $>$ 6.5)
    Grade III or worse encephalopathy

*From Bernal et al.[29]

Table 4—Potential Criteria for Use of Sodium Bicarbonate in Antidepressant Overdose

Cardiac conduction delay, QRS $>$ 100 to 160 ms
Wide complex tachyarrhythmia
Cardiac arrest
Right-bundle-branch block
R in AVR $\geq$ 3 mm
Refractory hypotension

tors, and triptans, or co-administration of multiple serotonergic agents.[44] Medications with monoamine oxidase inhibitor activity such as linezolid may precipitate the syndrome when administered concurrently with a serotonergic agent.[45] Diagnosis requires recognition of symptoms that include mental status changes, autonomic instability (hyperthermia, heart rate and BP fluctuation, arrhythmias and diaphoresis), and neuromuscular abnormalities such as tremor, myoclonus, or hypertonicity. Symptoms of SS are usually noted to improve within 24 h after withdrawal of the offending agent(s). Severe manifestations of this syndrome may include hyperthermia and cardiorespiratory dysfunction necessitating aggressive interventions such as neuromuscular blockade and mechanical ventilatory support. Cyproheptadine, a drug with serotonin antagonist properties, has been advocated to treat SS in doses of 12 to 32 mg daily; however, this recommendation is based on a few case reports.[46–48]

Antipsychotics

Patients presenting with antipsychotic overdose usually only require supportive care until clinical abnormalities including mental status changes, myotoxicity, and ECG abnormalities improve. The use of atypical antipsychotics, especially olanzapine, has been associated with the development of diabetes mellitus and diabetic ketoacidosis. The exact mechanism behind this relationship is unclear. Therapy requires addressing the metabolic abnormalities and consideration of a different antipsychotic such as risperidone, which is not significantly associated with the development of diabetes.[49] The most significant complication associated with antipsychotic drugs is neuroleptic malignant syndrome (NMS). Although most commonly associated with haloperidol exposure, NMS is also reported with newer antipsychotic agents such as clozapine, olanzapine, and risperidone. Symptoms suggestive of this syndrome are very similar to the aforementioned SS and include mental status changes, autonomic instability, and skeletal muscle rigidity. Differentiating between the two syndromes is often difficult, and a thorough medication history is often necessary to delineate the specific etiology.[50] As with SS, therapy requires cessation of the causal medication. Other medical therapies, including benzodiazepines, dopaminergic agents, and dantrolene, may be of benefit; however, the relative rarity of this syndrome precludes systematic evaluation of these interventions. Benzodiazepines appear to hasten recovery in milder cases and those with significant muscle rigidity. Use of amantadine and bromocriptine is associated with a de-

crease in morbidity and mortality.[51] Dantrolene has been recommended as a therapy for NMS, especially when significant hyperpyrexia and muscular rigidity are present, but a recent review[52] did not reveal universal efficacy. Morbidity and mortality are often associated with autonomic instability and airway compromise, so appropriate monitoring and supportive care are essential.

The treatment of choice for significant lithium toxicity continues to be hemodialysis. The decision to institute hemodialysis therapy requires consideration of several factors, including risks of the procedure, duration of lithium exposure, severity of clinical manifestations, and serum lithium concentration (levels > 2.5 mmol/L in chronic exposure and > 4 mmol/L in acute exposure are potentially life threatening). Conventional hemodialysis is effective in rapidly reducing circulating lithium concentrations; however, intracellular lithium is less affected and subsequent transcellular equilibration leads to a rebound increase in lithium levels after hemodialysis. Thus, extended and repeated courses of hemodialysis may be necessary. The rapidly declining lithium levels during hemodialysis may be associated with adverse neurologic effects. The use of continuous renal replacement techniques avoids the rebound increase in lithium levels.[53]

Cardiovascular Medications

Significant overdoses with cardiovascular medications often require critical care support. All antihypertensives may cause harm, but overdoses with calcium-channel blockers (CCBs) and β-blockers result in the most severe hemodynamic abnormalities. As most β-blockers and CCBs used in clinical practice are long-acting formulations, delayed and continuous absorption can lead to prolonged clinical presentations. Whole-bowel irrigation may be considered in patients with delayed presentations.[54] The dihidropyridine class of CCBs (*eg*, amlodipine and nimodipine) usually leads to significant hypotension without bradycardia, whereas the nondihidropyridine class of CCBs (*eg*, diltiazem and verapamil) leads most commonly to bradycardia and, in the most severe overdoses, cardiogenic shock and sinus arrest. Therapies for CCB overdose usually require volume resuscitation and vasopressors to maintain BP and heart rate. Vasopressors such as dopamine and norepinephrine are first-line agents, but hypotension unresponsive to these agents may respond to vasopressin.[55] IV calcium salts are also often used in supraphysiologic doses, and care must be taken to avoid extravasation during IV administration. Ionized calcium levels should be monitored when using high doses of calcium. IV glucagon is not as widely

accepted for CCB toxicity as it is for β-blocker toxicity, but a review[56] of animal studies suggests a possible beneficial effect in both toxicities. A hyper-insulinemic euglycemia protocol requiring insulin infusion while maintaining acceptable serum glucose levels by exogenous glucose administration is another therapeutic choice in severe CCB overdose.[57,58] To date, evidence supporting this therapy is based on case reports and one case series that demonstrates improvement in BP and metabolic acidosis.[59] The benefit afforded by insulin appears to be due to increased cardiac carbohydrate metabolism efficiency and direct inotropic effects of insulin.[54,60] Insulin infusion rates of 0.5 to 1 U/kg/h or higher have been reported, and close monitoring for prevention of hypoglycemia and hypokalemia is imperative. Severe CCB toxicity unresponsive to therapies mentioned above may require cardiac pacing and other advanced therapies such as intra-aortic balloon pump or extracorporeal membrane oxygenation.[61]

β-Blocker toxicity is still most commonly treated by administering high-dose glucagon therapy. A glucagon bolus of 5 to 10 mg (150 μg/kg) over 1 to 2 min is frequently used in this setting. Clinical effect (increased heart rate or BP) is usually noted within a few minutes; however, as glucagon has a short duration of action, a continuous infusion of 2 to 10 mg/h is usually necessary.[58] Nausea and vomiting can be noted as a side effect of high-dose glucagon therapy.[62] The hyperinsulinemic euglycemia protocol, as discussed above, may also have some benefit in β-blocker toxicity.[54,59]

ALCOHOLS

Toxicity due to ethylene glycol and methanol is still encountered in the ICU. Early diagnosis by history and appropriate laboratory evaluation is imperative, as is early therapy with alcohol dehydrogenase inhibitors such as fomepizole and ethanol. Fomepizole is easier to administer, does not require monitoring of levels, and does not produce sedation; however, fomepizole is significantly more expensive than ethanol. Ethanol can be administered orally or IV but requires monitoring of blood levels, and patients often require intubation due to sedative effects. Both therapies require adjustments of increased dosages with dialysis. The presence of an osmolar gap without an anion-gap metabolic acidosis suggests an early presentation after ingestion, before metabolism of the alcohol to acids or the concomitant presence of significant ethanol. In these cases, therapy with fomepizole alone may be considered, and hemodialysis may be avoided. However, close monitoring of acid-base and renal status is paramount to ensure appropriate response to therapy.[63] If an anion-gap metabolic acidosis is present without a significant osmolar gap, the alcohol has likely been metabolized to acids, and hemodialysis is necessary to remove the toxic metabolites. The utility of urine fluorescence to aid in the diagnosis of suspected ethylene glycol ingestion has been questioned.[64]

Another alcohol toxicity that may be encountered in ICU patients is propylene glycol toxicity. This agent is usually associated with prolonged, high-dose IV infusions of lorazepam or diazepam as propylene glycol is the medication solvent. Significant lactic acidosis, hypotension, and multisystem organ dysfunction have been reported that responds rapidly to cessation of the offending medication.[65] Changing the benzodiazepine to a similar agent such as midazolam is usually required to minimize the risk of benzodiazepine withdrawal. Propylene glycol can also be found in commercially available antifreeze and de-icing solutions, and at least one case has been reported of ingestion leading to propylene glycol toxicity.[66]

Recently reported cases[67,68] of hand sanitizer ingestion in a prison and a hospital may herald a new trend, as hand sanitizer use has become ubiquitous. Most hand sanitizers dispense ethanol or isopropanol-based solutions. Health-care providers need to consider the possibility of misuse of these agents resulting in toxicity.

ILLICIT DRUGS

Toxicity associated with illicit drugs, such as cocaine, amphetamines, phencyclidine, heroin, and γ-hydroxybutyrate, is commonly encountered in critical care units. Treatment is largely supportive, and recognition of toxicity allows focused care aimed at treating and preventing complications. Unfortunately, there have been no significant advances in treatment of illicit drug toxicity in critical care. A recently published review[69] of this topic summarizes relevant information.

CARBON MONOXIDE

Carbon monoxide poisoning is likely the most common cause of fatal poisoning worldwide.[70] Therapy for carbon monoxide poisoning centers on providing supplemental 100% oxygen and considering use of hyperbaric oxygen. The indications for use of hyperbaric oxygen continue to be debated, but therapy may be considered for patients with significant carbon monoxide poisoning. Consultation with a hyperbaric oxygen specialist should be performed to assess the need for and specifics associated with the therapy.[71–73]

Methemoglobinemia

Topical anesthetics such as lidocaine and benzocaine are well recognized to cause methemoglobinemia, especially when skin or mucosal integrity is compromised leading to greater systemic absorption. Methemoglobinemia associated with topical anesthetic use is most commonly associated with transesophageal echocardiography, endoscopy, and bronchoscopy.[74,75] Clinicians performing such procedures should be aware of this complication and be prepared to administer appropriate therapy.[76] Diagnosis is usually suggested by a significant drop in oxygen saturation or the presence of cyanosis. Additionally, arterial blood may be a characteristic chocolate-brown color owing to oxidation of iron in hemoglobin. Confirmation of the diagnosis requires co-oximetry measurement of elevated methemoglobin levels. Significantly elevated levels of methemoglobin, usually $> 30\%$, may lead to stupor, seizures, circulatory failure, and coma. Thus, early recognition and treatment is paramount. Therapy for symptomatic methemoglobinemia requires cessation of the suspected offending agent(s) and IV administration of methylene blue at 1 to 2 mg/kg IV over 5 min. The dose may be repeated if no improvement is noted after 30 min.[1]

Propofol Infusion Syndrome

Exposure to propofol has been associated with a syndrome that includes lactic acidosis, rhabdomyolysis, and renal, cardiac, and circulatory failure. This constellation of findings was previously reported in the pediatric population and labeled as *propofol infusion syndrome*. Cases in the adult critically ill population have also been reported.[77] The syndrome is usually associated with high doses of continuous propofol administration for prolonged periods (> 5 mg/kg/h for > 48 h), but some reports[77–79] suggest much shorter exposures. Due to the common use of propofol as a sedative and the nonspecificity of findings associated with this syndrome in the critically ill population, a definite causal relationship has yet to be established. A generally accepted recommendation is to monitor patients closely for the development of unexplained lactic acidosis, rhabdomyolysis, and cardiac and/or renal failure while infusing propofol.[79] Any such unexplained abnormality should lead to immediate cessation of propofol administration.

Cholinergic Toxicity

Cholinergic toxicity caused by organophosphates is encountered commonly in developing countries but occurs infrequently in the United States. The use of supportive care, including early mechanical ventilation and pharmacotherapy with atropine, is well established.[1] Oximes such as pralidoxime and obidoxime are frequently utilized to reverse muscle weakness, but significant clinical evidence to support use of oximes in organophosphate toxicity is lacking.[80,81] Fresh frozen plasma may also be of benefit in treatment, possibly by increasing plasma cholinesterase levels.[82] A study[83] found Glasgow coma scale score < 6 and corrected QT > 610 ms to be good predictors of respiratory failure in patients presenting with organophosphate poisoning. This data are of value to medical support systems in developing countries with limited resources.

Summary

The management of toxicity in critical care requires significant effort by the clinician to recognize and rapidly evaluate patients in order that focused therapies may be instituted. Incorporation of available scientific data and evidence along with clinical judgment is necessary to determine the best possible therapeutic course. As new agents are introduced into clinical practice or illicit use, it is vitally important that clinicians maintain knowledge of toxic effects and their management. Resources such as toxicology specialists and Poison Control Centers should be consulted for needed assistance. In the United States, the nationwide Poison Control Center phone number is 1-800-222-1222. An additional resource available by subscription is the Web-based POISINDEX® system.[84]

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