Each year, new agents are added to the pharmacopoeia, expanding the list of possible toxicologic reactions. In response, new antidotes are introduced, uses of more established antidotes evolve, and new therapeutic approaches to well-established toxicologic syndromes are developed. This brief update on critical care toxicology focuses on a few of the most important new developments. The recognition and management of the serotonin syndrome are discussed as an example of a toxicologic syndrome that is occurring more frequently as a consequence of the introduction of new pharmacotherapies. New developments in the therapy of well-known toxicologic reactions are next considered in relation to acetaminophen overingestion. Examples of evolving uses of older antidotes include octreotide to treat sulfonamide overdose and glucose and insulin to treat calcium channel blocker overdose. Finally, we examine new antidotes including fomepizole to inhibit alcohol dehydrogenase, and snake antivenom antibodies to treat envenomations. Critical care specialists must keep abreast of these trends to most effectively care for patients with toxicologic exposures.

**GENERAL APPROACH TO TOXICOLOGIC SYNDROMES**

The approach to therapy of acute toxicologic syndromes has gradually evolved. The need to obtain a complete history and to seek clues on physical examination remains essential (Table 1). The prehospital care record is important because this represents the patient’s status before institution of therapy. On arrival at the hospital, pharmacologic intervention can confound the clinical findings and make it difficult to recognize a specific toxicologic syndrome. The use of emetics is now discouraged, but gastric lavage is still performed routinely in many centers for the prompt removal of pills and fragments. However, even this practice is becoming more selective because of controlled trials indicating that outcomes are not improved by performing gastric evacuation in all patients (1, 2). Gavage should still be performed in patients arriving within an hour of a potentially significant ingestion or after ingestion of toxins that do not adsorb to charcoal, such as heavy metals or lithium (3, 4). Prompt administration of activated charcoal of sufficient dose is suspected helps to assure that clinicians are providing optimal therapy in a timely fashion.

**SEROTONIN SYNDROME**

The medical therapy of psychiatric disorders such as depression and bipolar affective disorders includes agents that increase central nervous system (CNS) serotonin transmission and activity. The serotonin syndrome is a complication of the use or misuse of such medications and is characterized by confusion, autonomic instability, and neuromuscular abnormalities (Table 2). This constellation of symptoms was first seen in the 1950s in patients receiving iproniazid and pethidine (meperidine) and in the 1960s in patients receiving L-tryptophan (5–8). The pathophysiology of the serotonin syndrome is not entirely clear, but animal studies have confirmed the role of serotonin and the identity of the responsible receptors. In rats, serotonin syndrome is blocked by the nonspecific 5-hydroxytryptamine antagonists methysergide and metergoline, but not by specific 5-hydroxytryptamine2 receptor antagonists such as ketanserin and pipamperone (9). This implicates 5-hydroxytryptamine1A receptor activation in the brainstem and spinal cord as playing an important role in the genesis of the syndrome.

The serotonin syndrome is most often seen in patients who are taking two or more medications at therapeutic doses that increase CNS serotonergic activity by different mechanisms (Table 3). The most commonly reported combinations are monoamine oxidase inhibitors with meperidine, tryptophan, selective serotonin reuptake inhibitors, or tricyclic antidepressants (5, 8). Single agents can also precipitate the syndrome, sometimes at therapeutic doses, but mainly in association with overingestion. A prospective study observed the development of signs and symptoms of serotonin syndrome in 16 of 38 patients taking clomipramine, a tricyclic antidepressant that increases CNS serotonergic activity (10). 3,4-Methylenedioxymethamphetamine (Ecstasy) has also been reported to cause the syndrome as a single agent (11). An inadequate washout period between the cessation of one serotonergic agent and the start of another can also precipitate the syndrome.

The most important step in managing the serotonin syndrome is to recognize the symptoms in a patient taking serotonergic medications. After reviewing 12 reports in the literature that included 38 cases of serotonin syndrome, Sternbach developed a set of criteria for diagnosing the serotonin syndrome (8) (see Table 2). Symptoms typically start minutes to hours after drug ingestion and usually resolve within 12 to 24 hours. Mild cases present with limited symptoms, whereas more severe cases have an altered sensorium and muscular hyperactivity as evidenced by myoclonus, shivering, rigidity, and hyperthermia. Untreated patients are at risk of developing rhabdomyolysis, renal failure, hepatic dysfunction, disseminated intravascular coagulation, and in massive overingestion, cardiovascular collapse and death. Treatment is directed at
Avoiding all serotonergic medications, such as meperidine or dextromethorphan, and decreasing the muscular hyperactivity with benzodiazepines and associated hyperthermia with rapid external cooling. Cyproheptadine or neuromuscular blockade may be necessary if benzodiazepines fail (12). With good supportive care applied promptly, most patients recover quickly (5, 8).

**N-ACETYLCYSTEINE FOR FULMINANT HEPATIC FAILURE FROM ACETAMINOPHEN TOXICITY**

Acetaminophen is one of the most commonly used pharmaceutical agents, and it is found in multiple over-the-counter and prescription medications. Not surprisingly, it is also the most common cause of drug overdose reported to the American Association of Poison Control Centers. Management of acetaminophen overdose consists of appropriate gastric decontamination, supportive care, and administration of N-acetylcysteine therapy, based on an adaptation of the Rumack–Matthew nomogram (13). At therapeutic doses, acetaminophen is metabolized primarily by glucuronidation and sulfation in the liver, with a minor proportion of drug undergoing P-450 metabolism to the toxic metabolite N-acetylbenzoquinonimine, which is detoxified by hepatic glutathione. When excessive quantities of acetaminophen are ingested (i.e., acute ingestions of greater than 7.5 g in an adult or 150 mg/kg in a child) (14), endogenous glutathione stores are depleted, allowing N-acetylbenzoquinonimine to accumulate and react with cellular proteins, causing hepatic and renal dysfunction.

**N-acetylcysteine serves as an antidote by repleting glutathione reserves and acting as a glutathione substitute intracellularly.** If given within 8 hours of acetaminophen ingestion, N-acetylcysteine prevents hepatotoxicity (15). Patients who begin N-acetylcysteine therapy later than 8 hours postingestion or have ingested large doses of acetaminophen chronically are at risk of hepatotoxicity despite therapy. A small subset of hepatotoxics will develop fulminant hepatic failure. Previously, patients developing fulminant hepatic failure had high morbidity and mortality rates. However, advances in orthotopic liver transplantation and the increasingly liberal use of prolonged intravenous as opposed to limited courses of oral N-acetylcysteine have decreased the mortality of these patients and have led to the development of a set of prognostic criteria to identify those at risk of mortality (16). Patients with the single criterion of a systemic pH less than 7.30 after fluid and hemodynamic resuscitation have a 95% mortality.

Although it was long thought that initiation of N-acetylcysteine beyond the first 16 hours after ingestion was probably futile, evidence supporting the idea that late administration might be effective was provided in 1990, when a retrospective analysis showed a significant reduction in mortality of patients with fulminant acetaminophen-induced hepatic failure treated with late intravenous N-acetylcysteine (37% in the treatment group compared with 58% in the untreated group) (17). Among survivors, the mean time from ingestion to the beginning of therapy was 15.5 hours, with a delay of up to 36 hours in one patient (17). Subsequently, a prospective trial randomized 50 patients with fulminant acetaminophen-induced hepatic failure to receive late intravenous N-acetylcysteine versus vehicle control (18). Experimental therapy was continued until each patient either recovered, died, or underwent liver transplantation. The treatment group had a median time from overdose to N-acetylcysteine therapy of 53 hours (range, 36 to 80 hours). Compared with the untreated group, those treated with N-acetylcysteine had reduced mortality (52 versus 80%), a lower incidence of cerebral edema (40 versus 68%), and required less inotropic medication for blood pressure support (all p < 0.05).

The beneficial effect of N-acetylcysteine in these patients may be from improved oxygen transport and consumption at the tissue level, as suggested by the increase in the oxygen-extraction ratio following local anesthesia. Patients who develop fulminant hepatic failure after acetaminophen ingestion, regardless of how much time has passed since the ingestion, should be treated with N-acetylcysteine, preferably via the intravenous route. However, practical constraints or product unavailability may necessitate initiation of therapy by the oral or enteral route. We recommend a loading dose of 140 mg/kg, followed by a maintenance dose of 70 mg/kg every 4 hours. This is continued until the biochemical indicators of hepatotoxicity have improved substantially. If the enteral route is not functioning and intravenous medication is unavailable, it is possible to create an intravenous solution from the oral preparation (20). However, it is important to have an experienced pharmacist prepare the solution because

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**Table 1. Clinical Findings of Toxicologic Syndromes Commonly Encountered in the Critical Care Setting**

<table>
<thead>
<tr>
<th>Toxicologic Syndrome</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>CNS effects: Hallucinations, confusion, sedation, seizures</td>
</tr>
<tr>
<td></td>
<td>Peripheral effects: Decreased GI motility, dry mucosa and skin, hyperthermia, mydriasis, tachycardia, urinary retention</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>CNS effects: Confusion, lethargy, seizures</td>
</tr>
<tr>
<td></td>
<td>Peripheral effects: “SLUDGE,” N-acetylbenezol oxidate</td>
</tr>
<tr>
<td>Opioid</td>
<td>Bradycardia, CNS depression, decreased GI motility, hypotension, miosis, respiratory depression</td>
</tr>
<tr>
<td>Sedative–hypnotic</td>
<td>Bradycardia, CNS depression, hypotension, respiratory depression</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>CNS depression, normal vital signs, no respiratory depression in oral overdose without concomitant CNS depressants</td>
</tr>
<tr>
<td>Sympathomimetic</td>
<td>Agitation, diaphoresis, hypertension, hyperthermia, tachycardia, severe cases: cardiac dysrhythmias, seizures</td>
</tr>
</tbody>
</table>

**Table 2. Suggested Diagnostic Criteria for Serotonin Syndrome**

Coincident with the addition of or increase in a known serotonergic agent to an established medical regimen, at least three of the following clinical features should be present:

- Mental status changes (confusion, hypomania)
- Agitation
- Myoclonus
- Hyperreflexia
- Diaphoresis

Other etiologies (e.g., infectious, metabolic, substance abuse, or withdrawal) must be excluded

A neuroleptic must not have been started or increased in dosage before the onset of the signs and symptoms listed above

* Adapted from Sternbach (8).
TABLE 3. PHARMACOLOGIC AGENTS THAT ENHANCE CNS SEROTONIN ACTIVITY: LISTED BY MECHANISMS OF ENHANCEMENT

<table>
<thead>
<tr>
<th>Serotonin agonists</th>
<th>Inhibit serotonin reuptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspirone</td>
<td>Amphetamines</td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Lithium</td>
<td>Meperidine</td>
</tr>
<tr>
<td>mCPP</td>
<td>Nefazodone, trazadone</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Triptans</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Increase serotonin release</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
</tr>
<tr>
<td>Codeine and derivatives</td>
<td></td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>Enhance serotonin synthesis</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>i-Tryptophan</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td></td>
</tr>
<tr>
<td>MDMA</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: CNS = central nervous system; LSD = lysergic acid diethylamide; mCPP = meta-chlorophenylpiperazine; MDMA = methylenedioxymethamphetamine.

adverse reactions occur frequently, including cutaneous reactions in 10% and bronchospasm in 5%, with a 2.8-fold increased risk in patients with asthma (21). Preparation of a dilute solution with a 0.2-µm pore size filter, slow infusion of the bolus (over 30–60 minutes), and pretreatment of asthma patients with antihistamines are recommended.

OCTREOTIDE FOR SULFONYLUREA OVERDOSE

The number of different medications to treat diabetes mellitus has increased dramatically, but sulfonylureas remain a mainstay of therapy and overdoses are common. Sulfonylureas inhibit potassium ion efflux in vitro and increase pancreatic β cell sensitivity to glucose in vivo (22), potentiating the secretion of insulin. Thus, sulfonylurea overdose leads to a hyperinsulinemic state that causes hypoglycemia, the severity and duration of which is related to the potency and half-life of the specific drug ingested. In past studies, the overall mortality of patients experiencing severe hypoglycemia from sulfonylureas was approximately 10% (23). Treatment of sulfonylurea-induced hypoglycemia starts with glucose therapy, oral or intravenous or both, and gastrointestinal decontamination. Other commonly used therapies include glucagon, dextrose, corticosteroids, and urinary alkalization to enhance urinary elimination for chlorpropamide overdose. In the past, hypokalemia, hypophosphatemia, and rebound hypoglycemia have been problematic, particularly after overdoses of sulfonylureas with prolonged half-lives.

Octreotide is a synthetic analog of somatostatin that has greater potency and a longer duration of action. Besides their inhibitory action on insulin release, somatostatin and octreotide both inhibit CNS release of growth hormone and thyrotropin and secretion of gastrointestinal tract hormones such as gastrin, secretin, and motilin (24). In addition to its emerging role as a therapy for sulfonylurea overdose, octreotide is currently used in the treatment of growth hormone- and thyrotropin-secreting pituitary adenomas, metastatic pancreatic islet cell and carcinoid tumors, bleeding esophageal varices, and secretory diarrhea (25).

Studies examining the effects of somatostatin and octreotide on sulfonylurea-induced hypoglycemia have included animal and volunteer human studies. These have demonstrated the short-term inhibitory effect of somatostatin on insulin release during glucose infusions or tolbutamide administration.
was based on the observations that although myocytes normally utilize free fatty acids as substrates for energy metabolism, stressed myocardium shifts to glucose as the preferred substrate (33). More recently, however, experimental studies have shown improved myocardial inotropy and survival in experimental animals with verapamil treated with insulin infusions as compared with controls (34, 35). In one study, all dogs treated with insulin for their verapamil-induced myocardial toxicity survived, whereas mortality was 100 and 67% among those treated with glucagon and epinephrine, respectively (p < 0.05) (34). These favorable effects may be attributable to counteraction by exogenous insulin of the diabetogenic effect of acute verapamil poisoning, including blockade of pancreatic insulin release and increased systemic insulin resistance (36). In these experimental models, insulin also improved lactate oxidation and reversed the diminished fatty acid uptake of verapamil-toxic myocardium (37).

Although clinical data on the use of insulin and glucose for calcium channel blocker toxicity are scanty, a study of calcium channel blocker toxicity in patients who failed traditional treatments suggests that the beneficial actions that were observed in animals also occur in humans (38). In this case series, the mean insulin infusion rate was 0.5 IU/kg per hour (range, 0.1–10 IU/kg per hour), with systemic blood pressure improving within 60 to 90 minutes. The duration of the insulin infusion depended on the patient’s clinical condition and response to therapy, but ranged from 9 to 49 hours with a mean of 27 hours. The major adverse effects were hypoglycemia and hypokalemia (as low as 2.2 mEq/L). Although glucose was infused throughout the insulin infusion, serum glucose concentration fell to less than 60 mg/dl in four of five patients, with the lowest being 29 mg/dl, underscoring the need for close glucose monitoring. The glucose infusion was adjusted accordingly, with peak glucose infusion rates ranging from 10 to 75 g/hour (38).

Based on the current evidence, patients experiencing bradycardia or hypotension after ingesting calcium channel blockers should be initially resuscitated with traditional therapies such as intravenous crystalloid fluids, calcium salts, and glucagon. Those who have persistent hypotension, bradyarrhythmias, or conduction disturbances should be infused with insulin and glucose. Severely bradycardic and hypotensive patients may require vasopressor agents, cardiac pacing, or temporary intraaortic balloon counterpulsion until they can metabolize the calcium channel blocker.

### 4-METHYLPYRAZOLE (FOMEPIZOLE) FOR METHANOL OR ETHYLENE GLYCOL INGESTIONS

The traditional management of toxic alcohol ingestions uses ethanol infusions and hemodialysis if serum levels exceed certain thresholds. The two most commonly ingested toxic alcohols, methanol and ethylene glycol (found mostly in windshield washer fluid and automobile antifreeze, respectively), are not themselves highly toxic; however, they produce toxic metabolites when metabolized by alcohol dehydrogenase (see Figure 1). Therefore, initial therapy is directed at decreasing the production of the toxic metabolites. Ethanol is an effective inhibitor of toxic metabolite production from the toxic alcohols because it has a higher affinity as a substrate for alcohol dehydrogenase. However, to achieve effective inhibition of toxic alcohol metabolism by alcohol dehydrogenase, ethanol levels must be high (at least 100 mg/dl or 25% of the serum toxic alcohol concentration, whichever is higher).

Adverse effects of ethanol infusions include phlebitis and fluid overload, whereas the oral route causes gastrointestinal distress. Central nervous system intoxication and fatty infiltration of the liver occur with both routes. Although ethanol is inexpensive, administration is complicated by the need for frequent monitoring of serum ethanol levels and repeated dosage adjustments because ethanol enhances its own metabolism (39). Because of these problems associated with chronic ethanol administration, alternative inhibitors of alcohol dehydrogenase have been sought. Early studies showed that pyrazole is an effective inhibitor of alcohol dehydrogenase in animals poisoned with ethylene glycol (40), but it caused bone marrow, liver, and renal toxicity. 4-Methylpyrazole (or fomepizole) was developed as a less toxic alternative. In multiple animal models, it has proven to be an effective inhibitor of alcohol dehydrogenase, without the toxicities associated with pyrazole (41). Also, multiple clinical reports have documented its utility in both methanol and ethylene glycol poisoning.

Two prospective, observational multicenter trials have evaluated the effectiveness of fomepizole in toxic alcohol poisoning. In the first (42), 19 patients with ethylene glycol poisoning had substantial improvements of their metabolic acidoses within hours of initiation of fomepizole therapy. In addition, the mean serum glycolate level fell from 89.7 mg/dl (range, 0–264 mg/dl) to 0 mg/dl over 24 hours. Seventeen patients underwent concomitant hemodialysis, and nine, who presented later after ingestion and had higher plasma glycolate concentrations (>97 mg/dl), had impaired kidney function. Eighteen of the 19 patients survived, one succumbing to complications of an acute

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**Figure 1.** Schematic of pathways for methanol and ethylene glycol metabolism. Ethanol saturates and fomepizole inhibits alcohol dehydrogenase (ADH), and both thereby block the formation of toxic intermediates such as formic and glycolic acids. If unmetabolized, methanol and ethylene are slowly excreted intact in the urine, but hemodialysis is often used to speed clearance. Several metabolic intermediates have been omitted for clarity of presentation.
myocardial infarction that occurred before the initiation of therapy. Fomepizole therapy was administered intravenously, using a loading dose of 15 mg/kg, followed by maintenance bolus doses of 10 mg/kg every 12 hours for 48 hours. The bolus doses were then increased to 15 mg/kg every 12 hours because of autoinduction of fomepizole hepatic metabolism. Therapy was continued until the serum ethylene glycol concentration was less than 20 mg/dL, requiring a mean of 3.5 doses of fomepizole per patient (range, 1–7 doses) (42).

The second study was another prospective observational trial of 11 patients poisoned with methanol (43). Fomepizole treatment was associated with a decrease in serum formic acid concentration, normalization of blood pH from the initial acidemia, and return of visual acuity abnormalities to baseline status by the time of hospital discharge. Seven patients underwent hemodialysis and nine patients survived, with two succumbing to anoxic brain injury that was present at the time of enrollment. The fomepizole dosing regimen was the same as for ethylene glycol described here previously, with patients in the methanol study receiving a median of four doses per patient (range, 1–10 doses). Fomepizole was well tolerated in both studies. Adverse side effects included headache, rash, tachycardia, anxiety, and seizures, but these were deemed more likely to be related to the alcohol ingestion than to the fomepizole.

These studies support the clinical safety and efficacy of fomepizole as an alcohol dehydrogenase inhibitor. It effectively inhibits the formation of toxic metabolites, rapidly improves metabolic imbalances, and prevents end-organ damage (e.g., renal failure or blindness). As shown in Table 4, fomepizole markedly prolongs the elimination half-lives of ethylene glycol and methanol, even more on average than ethanol (44–46), thus effectively preventing the generation of toxic metabolites. Concomitant hemodialysis is still usually required in patients with high alcohol levels or high anion gap acidoses, however, to accelerate the removal of the alcohols and toxic metabolites (44, 46). Although the studies have been uncontrolled and provide no direct comparison to traditional therapy with ethanol, they demonstrate that fomepizole has several advantages over ethanol therapy, including easier administration and monitoring and the avoidance of mental status changes, hypoglycemia, and hepatotoxicity. For these reasons, fomepizole is preferred to ethanol infusion for the therapy of methanol poisoning. The recommended dosing regimen is the same as that used in the study protocols (42, 43). Patients receiving hemodialysis require an additional bolus dose of 15 mg/kg at the end of each dialysis session, and therapy is continued until the serum ethylene glycol or methanol concentration is less than 20 mg/dL.

However, fomepizole is unlikely to reduce mortality below that of a carefully monitored ethanol infusion, and considering that the cost to treat an adult with fomepizole for 48 hours is approximately $5,000 for the drug alone, therapy should be reserved for serious intoxications. The U.S. Food and Drug Administration has approved fomepizole for individuals > 12 years old with ethylene glycol or methanol poisoning. On the basis of the above-described studies, the authors recommend reserving the use of fomepizole for intoxications with toxic alcohol levels greater than 20 mg/dL, metabolic acidosis (bicarbonate level less than 20 mEq/L), or a urine-to-serum osmolar gap greater than 10 mOsm/L. Fomepizole therapy is also advisable when there is a lack of experience with ethanol therapy or the inability to provide frequent laboratory monitoring in confirmed poisonings.

### SNAKE Fab ANTIVENOM

Most of the roughly 10,000 venomous snake bites reported annually in the United States are caused by members of the subfamily Crotalinae (pit vipers). Pit vipers are divided into three genera: *Crotalus* (rattlesnakes), *Sistrurus* (pygmy rattlesnakes and massasauga), and *Agkistrodon* (copperheads and water moccasins). Crotaline venom is complex and composed of proteolytic enzymes, neurotoxins, cardiotoxins, direct lytic factors, hemolysins, and coagulation and anticoagulation factors (47, 48). Standard treatment for envenomations includes generalized wound care and antivenom therapy. For years, the only antivenin available in the United States has been an equine-derived serum IgG (Antivenin Crotalidae Polyvalent [ACP]; Wyeth, Paoli, PA). Although this antivenin has been effective, its use is associated with a high occurrence (23%) of acute hypersensitivity reactions, including urticaria, anaphylactoid reactions, and anaphylaxis (49). In addition, the incidence of serum sickness can be as high as 80% when more than five vials of ACP are administered (50, 51). Consequently, physicians have hesitated to use antivenin unless patients show moderate to severe signs of envenomation or progression of envenomation (see Table 5).

More recently, ovine-derived serum monovalent Fab antivenom (Crofab) (Savage Laboratories, Melville, NY) was developed for crotaline poisoning and has been used in two human trials. Venoms used in the production of the ACP and Fab antivenoms are listed in Table 6. By eliminating the Fc fragment, the Fab preparation greatly reduces the risk of allergic reactions. The first trial was a prospective series of 11 patients who were each initially treated with 4 vials of Fab antivenom and an additional 4 vials if clinical signs or laboratory values worsened. All patients were observed in the hospital for at least 48 hours and followed up at 7 and 14 days (52). Three patients had worsening of symptoms after initiation of therapy, and six received the full eight vials of antivenom. After 7 days, one patient still had a prolonged prothrombin time and three had hypofibrinogenemia.

The second trial prospectively monitored 38 patients with moderate pit viper envenomations, initially treated with 4 to 12 vials of the Fab antivenom (53). Local symptoms were stabilized within 24 hours in all treated patients. Twenty patients (53%) had late, persistent, or recurrent thrombocytopenia and hypofibrinogenemia, persisting up to 2 weeks in a few patients. During follow-up, 28 patients received additional Fab antivenom for an average total dose of 10.9 vials per patient. Six patients (16%) had mild to moderate hypersensitivity reactions, another six (16%) developed serum sickness, and none developed anaphylaxis. No patient in either trial had clinically significant bleeding. The occurrence of immunologic reactions reported for the Fab antivenom is much lower than for the ACP antivenom. The incidence of recurrent coagulopathy in patients treated with the ACP antivenom is approximately 45%, which is slightly less than the Fab antivenom (54).

### TABLE 4. MEAN HALF-LIVES OF ELIMINATION* OF ETHYLENE GLYCOL AND METHANOL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ethanol</th>
<th>Fomepizole</th>
<th>With Ethanol and Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethylene glycol</strong></td>
<td>2.5–4.5 (44)†</td>
<td>17 (46)</td>
<td>19.7 (42)</td>
</tr>
<tr>
<td><strong>Methanol</strong></td>
<td>3.01 (46)‡</td>
<td>43 (46)</td>
<td>54 (43)</td>
</tr>
</tbody>
</table>

*In hours.
† Numbers in parentheses indicate reference source. These were not direct comparisons from controlled trials, and values should serve as approximations only.
‡ Derived from low-level infusions in normal subjects. Half-life is longer at toxic levels.
The treatment regimen for the Fab antivenom is an initial intravenous dose of four to six vials, which can be repeated within 1 hour if the manifestations (e.g., local swelling, coagulopathy) are not controlled after the first dose. An additional two vials are administered every 6 hours for 18 hours to prevent the recurrence of manifestations. Retreatment with two more vials of Fab antivenom is recommended if any of the following occur: fibrinogen less than 50, platelet count less than 25,000/mm³, international normalized ratio (INR) greater than 3.0, activated partial thromboplastin time (aPTT) greater than 50 seconds, or if the coagulopathy worsens (54).

All patients treated with Fab antivenom require hospitalization for close monitoring of symptoms and the need for further therapy, and monitoring up to 2 weeks after envenomation may be necessary.

The more favorable side effect profile of the Fab antivenom has established it as the antivenin of first choice for Crotalinae envenomations and, from a risk–benefit perspective, favors earlier initiation of therapy and treatment of milder envenomations. In addition, the manufacturer has stopped production of ACP, so the Fab antivenom has become the only antivenin available for Crotalinae envenomations. However, the Fab antivenom has some disadvantages, including a high rate of coagulopathy and considerable expense. Each two-vial kit costs approximately $1,700 (U.S.), and therefore the drug cost for a complete course of Fab antivenin therapy can be as much as $14,000. Therefore, from a cost–effectiveness perspective, therapy should still be reserved for patients with moderate to severe envenomations.

CONCLUSION

As is the case with most fields in medicine, clinical toxicology has rapidly evolved as the number of toxicologic syndromes and antidotes has increased in response to the ever-expanding pharmacopoeia. In the current update, we have focused on several areas in which significant changes have occurred. In the case of serotonin syndrome, the rapidly increasing use of serotonin reuptake inhibitors in the therapy of depression necessitates that clinicians recognize the manifestations of the syndrome and be aware of potential drug interactions that are likely to produce it. The use of late N-acetylcysteine for fulminant liver injury from acetaminophen overdose is a change in the approach, reflecting new evidence that some amelioration of injury and improved survival may occur, even when used in cases that previously would have been considered irreversible. Octreotide for sulfonylurea overdoses and insulin and glucose for calcium channel blocker over ingestions represent newer, inexpensive applications of older therapies. Fomepizole for toxic alcohol ingestions is a new antidote that is becoming a standard of care because of its efficacy and safety in comparison with ethanol infusions, despite its greater expense. Finally, with regard to pit viper envenomations, the older polyvalent antivenom has been replaced with a newer Fab antivenom that is associated with a much lower risk of allergic reactions. The topics covered in this update were selected to highlight developments in the field of clinical toxicology that impact on critical care medicine, but the list is far from exhaustive. Approaches to the management of toxicologic syndromes will undoubtedly continue to expand and evolve, and critical care clinicians are encouraged to keep abreast of new developments.

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