4 General Management of the Poisoned Patient

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Introduction

Accidental death was the fourth leading cause of mortality in the United States in 2014. Within causes of accidental deaths, unintentional poisoning has been at the top since 2011 [1]. This does not include deaths from intentional self-poisoning and thus underestimates the total number of deaths related to poisoning. This information underscores the importance of developing adequate treatment strategies for the poisoned patient.

A systematic approach to the management of various medical situations is now commonplace. One such example is that of Advanced Trauma Life Support (ATLS). Studies of ATLS have shown an improvement in knowledge, clinical skills, and decision-making among participants compared to non-ATLS trained individuals [2]. While reviews on the benefit of ATLS on mortality are mixed, we believe that an organized approach to the management of various medical conditions is, nonetheless, of great benefit [2]. Such a systematic approach can readily be applied to the poisoned patient. Like other systematic approaches, management of the poisoned patient can be guided by the ABCs: airway, breathing, and circulation. Toxicologists frequently include D and E in this mnemonic, which stands for decontamination and elimination, respectively. This chapter will cover the initial management of the suspected poisoned patient, followed by workup and diagnosis, and finally, definitive treatment and antidote administration where appropriate.

Initial Management of the Poisoned Patient: The ABCs

As mentioned above, a conventional mantra in the initial management of acutely ill patients is the ABCs. This means assessing and intervening where necessary to stabilize the airway, breathing, and circulation. Not only is the assessment of the ABCs critical in the initial stabilization of patients, but it can also provide clues as to the specific poison involved. Intravenous access (IV), supplemental oxygen, cardiac monitoring, and blood sugar assessment are often piggybacked onto the ABCs, making the full mantra ABCs, IV, O2, monitor, and "fingerstick" to measure the blood glucose. These interventions will be mentioned peripherally in the discussion of the ABCs below, but their importance in assessment and stabilization of the patient cannot be overstated.

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Initially, the airway should be assessed for patency. Local trauma and thermal or caustic injury may lead to edema and loss of the airway. Cholinergic toxicity, as occurs with organophosphate poisoning, causes significant oropharyngeal secretions which may compromise the airway. Patients with severe central nervous system (CNS) depression may be unable to maintain their airway, and a decreased or absent gag reflex increases the risk for aspiration. Jaw thrust, suction, and nasopharyngeal and oropharyngeal airways can be used to improve airway patency temporarily. These interventions may not be possible in the setting of trauma, do not address lower airway edema from thermal or caustic injury, and do not protect against aspiration. In these settings, the establishment of a secure airway (i.e., intubation) should be considered and performed as the clinical context dictates.

Once a stable airway has been identified or secured, attention should be moved to the patient's breathing. First, is the patient breathing at all? If not, this necessitates immediate intervention, at least initially, with bag valve mask (BVM) ventilation if not already addressed during the assessment of the airway. If the patient is breathing, is he or she hypoxic and in need of supplemental oxygen? Does the hypoxia improve with supplemental oxygen? A persistently low oxygen saturation despite intervention might be a clue that the patient is suffering from methemoglobinemia. In addition to the above, assessment of the quality of breathing is essential as well. Is the patient's breathing fast or slow, deep or shallow? Slow and shallow respirations may be a clue that the patient has ingested an opioid or other sedative-hypnotic drug. Rapid breathing may be compensatory in the setting of metabolic acidosis or the result of direct respiratory stimulation in the brainstem, as occurs with salicylates. Real-time end-tidal carbon dioxide monitoring is particularly helpful in determining the adequacy of rate and depth of breathing and thus, ventilation.

Finally, circulation should be assessed. Of note, some now advocate for the assessment of circulation before airway or breathing (a CAB approach). Regardless of the order, the following holds true. Assessment of a pulse is the priority, as its absence necessitates chest compressions and initiation of cardiopulmonary resuscitation. If a pulse is present, a blood pressure reading should be obtained and hypotension addressed (usually initially with IV fluids). The patient should also be placed on a cardiac monitor, as this will aid in the assessment of rate and rhythm. Significant rate disturbances (bradycardia and tachycardia) can be a cause of hypotension and should be addressed. Also, these rate disturbances can give clues as to the etiology of the poisoning, such as with opioids and other sedative-hypnotics causing bradycardia, and sympathomimetics and anti-muscarinic drugs causing tachycardia. Rhythm is also essential, as it can give clues to the etiology of rate disturbances (examples being heart block in bradycardia or atrial fibrillation with a rapid ventricular response in tachycardia). Any significant rate or rhythm disturbances should be addressed as per advanced cardiovascular life support (ACLS) guidelines.

Diagnosis and Workup

After the initial stabilization of the patient, the focus should be turned to workup and diagnosis. As with much of medicine, a thorough history and physical exam are essential for accurate diagnosis. Unfortunately, the specific substance ingested is often unknown, or the patient may be unwilling or unable to give history. In these cases, assessment for the presence of a toxidrome may help at least identify an etiologic class of drug or toxin. A toxidrome is a specific grouping of signs and symptoms that indicate a type of or a particular poison [3–7]. Please see Table 4.1 for a list of particular toxidromes and their findings. Not all signs or symptoms delineated in the table are necessarily present at any one time. This is particularly true when the patient has ingested multiple drugs or toxins, which may make it difficult to identify a particular toxidrome.

Laboratory testing, imaging, and other ancillary testing are also helpful in the management and diagnosis of the poisoned patient. A complete metabolic panel (CMP) is useful in assessing electrolytes, the presence of an acidosis (gap or otherwise), kidney function, and transaminase levels. Many toxins cause acidosis, and arterial

Table 4.1 Toxidromes

Toxidrome (associated drug class)	Signs and Symptoms
Anti-muscarinic (antihistamines, tricyclic antidepressants, atropine)	Tachycardia, dry mucous membranes, decreased sweating, delirium, mydriasis, hyperthermia, urinary retention, decreased bowel sounds
Cholinergic (organophosphate insecticides, nerve agents)	Miosis, bronchorrhea, bronchospasm, urination, defecation, diaphoresis, emesis, lacrimation, bradycardia (theoretically, in practice often tachycardic)
Opioid	Miosis, sedation, bradypnea, decreased bowel sounds, bradycardia/hypotension/ hypothermia (severe)
Sedative-hypnotic	Sedation, bradypnea, bradycardia/hypotension/ hypothermia (severe)
Sympathomimetic	Mydriasis, agitation, tachycardia, hypertension, diaphoresis, hyperthermia

References: [5–8]

blood gas (ABG) or venous blood gas (VBG) can quantitate this derangement. An ABG or VBG can also identify the primary acid/base disorder, as well as the presence of mixed disorders. A lactate level should be considered, as many toxins cause lactic acidosis. Other toxins may cause renal injury (ethylene glycol, NSAIDs, methotrexate) or are primarily renally excreted (digoxin, lithium), and reduced kidney function may alter management. Electrolyte derangements may be a direct result of a toxin (hypokalemia and theophylline) or secondary to vomiting and diarrhea, caused by a toxin (iron and lithium). Finally, elevated transaminases may be a clue to a late-presenting acetaminophen overdose or represent toxicity from any number of other hepatotoxins. While likely not as critical as a CMP, a complete blood count (CBC) can provide useful information. Hemoglobin is helpful in caustic or iron ingestions, which can cause gastrointestinal hemorrhage and blood loss. In some cases, leukocytosis or leukopenia may be encountered and give clues to the etiologic agent, such as with iron and colchicine, respectively (although colchicine may cause an early leukocytosis). The importance of a blood glucose level has been discussed and will not be examined further. Obtaining a measured osmolality and comparing this to the calculated value for an osmolality gap may indicate a toxic alcohol exposure [3, 4, 6, 8]. There are many ways to calculate an osmolality gap, as well as many pitfalls, and the reader should have experience with this laboratory analysis or seek guidance from a medical toxicologist or poison center. Many poisonings result in rhabdomyolysis, and a creatine phosphokinase should be obtained in these cases [9]. Urine drug screens (UDS) are often ordered in the workup of suspected poisoned patients. UDS should be interpreted with caution for the following reasons. Positive results are often based on drug metabolites, which may remain after clinical effects of the drug have subsided, and thus a positive UDS does not necessarily indicate intoxication; also, the UDS is plagued by many false positives and negatives, and the findings infrequently change management [3, 4, 6, 8].

Some specific drug and other laboratory levels can be obtained in real time to aid in diagnosis and management. Examples include acetaminophen, salicylates, iron, lithium, theophylline, carboxyhemoglobin, methemoglobin, valproic acid, digoxin, and phenobarbital [5, 10]. This is not a comprehensive list. These should not be sent on every undifferentiated patient but should be ordered based on the patient's medication list, history of ingestion, or within the clinical context of the toxidrome or physical exam findings. One possible exception to this rule is acetaminophen levels. Data show a small number of potentially toxic acetaminophen ingestions are found with a routine screening of patients presenting with intentional ingestions [11–13]. Initial acetaminophen poisoning may be asymptomatic or only present with nonspecific findings, making clinical diagnosis difficult, if not impossible. Also, N-acetylcysteine is a highly effective antidote, but its efficacy decreases if the administration is greater than 8 hours out from ingestion [5]. For these reasons, some advocate universal testing of acetaminophen concentrations in all intentional ingestions. The small number of significant ingestions found, however, leads others to argue against routine screening.

Radiographic imaging, although less frequently than laboratory evaluation, can be useful in the poisoned patient as well. A chest X-ray can identify aspiration pneumonitis, a common complication of poisoning [4, 5, 9]. Certain substances (iron, halogenated hydrocarbons, lead, mercury, salicylates) are radiopaque and can be identified on routine abdominal radiographs to help confirm or quantitate exposure [4, 5]. Computed tomography (CT) of the head is helpful in undifferentiated patients with alterations in mental status.

Many toxins cause bradycardia, tachycardia, and various dysrhythmias, as well as changes in intervals such as the QTc, QRS, and variable degrees of heart block [3, 5, 6]. An electrocardiogram is invaluable in identifying life-threatening cardiovascular effects, as well as aiding diagnosis of certain classes of drugs such as beta-blockers, calcium channel blockers, sodium channel blockers, cardiac glycosides, and other cardioactive drugs.

Decontamination

Decontamination is a core tenant of toxicology. The primary route of most toxic exposures is via ingestion [14]. Consequently, techniques for GI decontamination are discussed below. Dermal and ocular exposures do occur, and remediation is still crucial in these cases. Generally, irrigation of skin with saline or slightly soapy water (if the substance is hydrophobic) is adequate. Dry or powdered substances should be brushed off the patient, as dissolution in water may cause burns if the substance is caustic. Ocular exposures should be aggressively irrigated with saline until pH is within the normal range or symptoms improve/resolve.

Activated Charcoal

Activated charcoal (AC) is formed by the burning of variable plant matter to form charcoal. This charcoal is subsequently processed to increase its surface area, forming "activated" charcoal [15]. It is by far the most commonly used method for decontamination of those discussed below [14]. AC is known to adsorb many compounds and decrease the percent systemically absorbed in a time-dependent fashion [16]. It is not recommended for use with ingestion of metals, ions, toxic alcohols, or corrosives secondary to poor binding or increased risk of aspiration [3, 9, 17].

Of the randomized trials comparing AC versus none, which examined clinically meaningful endpoints, none demonstrated a benefit [18, 19]. In one study by Merigian et al. among a subgroup analysis of self-poisoned patients who were ultimately discharged from the emergency department, those who received AC had a shorter length of stay (about 3 hours) versus those who did not [20]. There was no statistically significant difference between AC versus none among all admitted patients, however [20]. Numerous other studies and reports of AC use in poisoning exist. These have been well reviewed by Chyka et al. and will not be discussed here.

There are many potential reasons (small sample size, exclusion of significantly ill patients, the inclusion of patients with delayed presentation) why these studies did not show any benefit for AC. Despite this, AC is still recommended, owing to its ability to reduce absorption, its relative safety, and theoretical benefit. AC is recommended when potentially toxic substances have been ingested within the last hour [15]. Some substances may have delayed absorption in overdose (salicylates or anti-muscarinic compounds). These and sustained- or extended-release preparations of drugs may benefit from more delayed administration of AC [21]. Optimal dosing is dependent on the specific substance, but adults are typically administered 50–100 g of AC. Classically, the major concern with the administration of AC is aspiration leading to a pneumonitis. As such, AC is contraindicated in those without an intact airway (seizing or patients with CNS depression) or who are expected to vomit from their specific ingestion. Forced administration to an awake but noncompliant patient is likely to have an unfavorable risk/benefit ratio. Patients with gastrointestinal perforation or hemorrhage should also not receive AC [15].

Whole-Bowel Irrigation (WBI)

Administration of large amounts of polyethylene glycol electrolyte solution (PEG-ES) can be used to clear the gastrointestinal (GI) tract of ingested substances. This clearance ultimately can reduce drug absorption and at least theoretically be of benefit in the poisoned patient [22]. PEG-ES is used, as it does not cause clinically significant fluid or electrolyte shifts [23]. A single study has shown the benefit of WBI on clinically relevant endpoints. Patients receiving WBI had a decreased odds ratio (OR) for developing seizures (all from venlafaxine overdose) versus those without any decontamination, although the OR did cross one. WBI and AC combined were superior to either alone, also suggesting a benefit to WBI [24]. Multiple, randomized volunteer studies have been performed, looking at pharmacokinetic data. Interpretation of this data is difficult. Some studies showed statistically significant decreased absorption [25–27], whereas others did not [28, 29], and another did not compare WBI to a control [21]. Another study of WBI in venlafaxine overdose showed a benefit of AC and WBI compared to AC alone. WBI used alone did not result in a reduction of absorbed dose, however [30]. Multiple case reports of WBI with PEG-ES have been published; many of these are reviewed in a position statement on WBI by the American Academy of Clinical Toxicology and European Association of Poison Centres. Conclusions are difficult to draw, owing to the nature of case reports. The reader is referred to the position statement for a synopsis of these reports and their citations [22].

Indications for WBI include ingestions of sustained-release preparations, large ingestions of substances not adsorbed to charcoal, iron, and for body stuffers/packers [22].

In adults, the goal is to administer 1–2 liters of PEG-ES an hour until the patient passes clear rectal effluent. In children, 500–1000 milliliters an hour is recommended [22]. In compliant patients, this may be from typical oral ingestion (although the total amount ingested is often below the goal) or via a nasogastric (NG) tube in intubated patients. An NG tube can undoubtedly be forcefully inserted into a noncompliant patient for WBI. However, the risk–benefit ratio may not be in favor of this and should be assessed on a case-by-case basis within the clinical context. Contraindications include bowel obstruction/perforation/hemorrhage, ileus, or an unprotected airway [22].

Gastric Lavage and Syrup of Ipecac

Neither gastric lavage nor induced emesis with syrup of ipecac is routinely recommended, and they will not be reviewed further here [31, 32].

Elimination

Even after a substance has been absorbed into the systemic circulation, techniques exist to increase its rate of elimination, depending on the specific agent involved. Increasing the rate of elimination of toxic compounds can reduce the time of exposure and total body burden of a toxic substance. Whether to institute enhanced elimination techniques depends on the inherent toxicity of the specific drug or chemical involved, dose ingested (or however otherwise exposed), existence and efficacy of specific antidotes, and endogenous methods of elimination and their integrity. Common methods to increase elimination are discussed below.

Extracorporeal Elimination

Multiple methods for the extracorporeal elimination of foreign and endogenous substances exist. These include but are not limited to intermittent hemodialysis (HD), hemoperfusion (HP), and various methods of continuous renal replacement therapy (CRRT). Hemodialysis is by far the most frequently employed technique [14, 33]. Other techniques include exchange transfusion, liver dialysis, and plasmapheresis, but these are rare and will not be reviewed here [14, 34]. In general, substances that are amenable to extracorporeal removal are of small size, have low protein bind-

ing, and a small volume of distribution (V_d) [34–36]. In HD, solutes are eliminated through a semipermeable membrane from the blood. These membranes have certain size pores through which the solute must be eliminated. This limits which solutes, or toxins, can be effectively removed in this manner [34]. The specifics of the size have changed as technology advances [33, 37]. The pore size of filters used in CRRT is larger than in HD, and to some extent, larger molecules may be removed via this methodology [34, 35, 38]. Another benefit is its use in hemodynamically unstable patients. These benefits are tempered by its slower clearance of drugs [35]. In HP, blood is forced through a column (charcoal or resin), which adsorbs drugs and toxins. This technique allows for the elimination of larger compounds, as well, but is limited by availability and an increased rate of complications [34, 35, 39, 40]. In addition, as alluded to above, advancements in HD have negated some of the benefits of HP versus HD [33, 37].

Protein-bound substances are often too large for effective extracorporeal removal [37]. In some cases (Valproic acid), protein binding becomes saturated at high doses and the amount of free drug becomes large enough to make extracorporeal removal beneficial [34].

The V_d describes the relative partitioning of various compounds into water and fat. As the vasculature (a major water compartment) is the location of extracorporeal removal, substances that distribute more to the water compartment are more amenable to extracorporeal removal [37]. Compounds with a V_d less than 1 liter per kilogram are considered amenable to extracorporeal removal [35]. Substances with a higher V_d have greater distribution into fat and are not available for extracorporeal removal.

Other pros and cons of these methods exist but will not be reviewed here. The decision of when and which technique to use should be made in conjunction with a nephrologist.

Examples of more commonly dialyzed substances include lithium, metformin, salicylates, toxic alcohols, and valproic acid [33, 35]. This is not a comprehensive list. Determination of the utility of extracorporeal techniques for other specific substances should be made with the aid of toxicologists, the local poison center, and nephrologists.

Multidose Activated Charcoal

Rather than limiting absorption, as with single-dose activated charcoal (SDAC), multidose activated charcoal (MDAC) is used to increase the elimination of certain substances. It entails the administration of at least two doses of AC (in practice, often many more). A study by Mckinnon et al. helps to explain how MDAC works. Mckinnon et al. showed that AC could increase the clearance and decrease the half-life of intravenously (IV) administered theophylline. As the theophylline was given IV, there is obviously no drug in the GI tract for the AC to bind. As theophylline has some biliary excretion, there is the possibility that AC may bind some theophylline excreted in the bile, preventing its reabsorption and accounting for the above findings. Mckinnon addressed this in his study via biliary drainage (in human and animal subjects), which interrupted the enterohepatic recirculation of theophylline. Thus, any increase in theophylline clearance would be from some other route. Mckinnon found only very small amounts of the administered dose of theophylline (less than 2%) in the bile. This is too small of an amount to explain the increased clearance and decreased half-life of theophylline with AC. Rather, the thought is that the AC interrupts what is called the enteroenteric recirculation of drugs. In the same study, McKinnon demonstrated that theophylline given IV resulted in the presence of theophylline in jejunal aspirate. The thought is that drugs will diffuse down their concentration gradient out of the circulation into the GI tract. In the presence of AC, this diffused drug is bound, preventing later reabsorption but also maintaining a favorable gradient for continued diffusion of a toxin into the GI tract for more binding to AC [41]. Other studies have shown similar results [42, 43].

Unlike with SDAC, there are some randomized studies showing benefit in clinically meaningful endpoints in patients treated with MDAC

versus not. One study by Brahmi et al. found a statistically significant decrease, with respect to MDAC vs. SDAC, in length of coma, mechanical ventilation, and stay for patients presenting with carbamazepine poisoning [44]. Another study analyzed the benefit of MDAC in yellow oleander poisoning. The control population received sterile water, rather than MDAC, and both groups received SDAC and gastric lavage. Statistically significant decreases in mortality, intensive-care-unit admissions, need for digoxin-specific antibodies, cardiac pacing, presence of life-threatening arrhythmias, and mean dose of atropine given were found [35]. In contrast, a study by Eddleston et al. found no benefit to MDAC vs. SDAC vs. no decontamination with respect to mortality [19].

Current guidelines recommend the use of MDAC for life-threatening ingestions of carbamazepine, dapsone, phenobarbital, quinine, and theophylline. These recommendations were based on the review of multiple animal, volunteer, and case reports/series. MDAC can increase the clearance of digoxin, but given its large V_d and other effective treatment modalities (mainly digoxin-specific antibodies), it is not currently recommended [45]. Contraindications are the same as those for SDAC.

Urinary Alkalinization

Urinary alkalinization is the administration of IV sodium bicarbonate to alkalinize the urine and thereby increase the excretion of certain substances. An alkaline, or high pH, environment will favor the charged form of acidic substances. This charged state reduces passive reabsorption through the hydrophobic cell membrane of kidney tubule endothelial cells. This is sometimes referred to as ion trapping. The substance in question must have some significant renal elimination for this treatment to work. Increasing renal elimination for a drug with minimal-to-small renal elimination is unlikely to offer any clinical or even theoretical benefit.

Urinary alkalinization has been examined with respect to various compounds, as reviewed by Proudfoot et al. [10]. Of these compounds, the more commonly encountered include phenobarbital, methotrexate, and salicylates. Current guidelines recommend the use of urinary alkalinization as first-line therapy for salicylate toxicity in those not meeting indications for extracorporeal elimination. Although urinary alkalinization does significantly increase the elimination of phenobarbital, it is not recommended as first-line due to the superior effectiveness of MDAC [10, 46]. Similarly, urinary alkalinization has been shown to increase the clearance of methotrexate, but these studies were case reports, series, or had no controls, making it difficult to draw concrete conclusions [47–51]. As such, urinary alkalinization cannot be recommended as first-line treatment for methotrexate poisoning [10].

Definitive Management

Supportive care, much of which will have been addressed in the initial stabilization of the ABCs, is often adequate to support patients through their poisoning. Certain drugs and toxins, however, have specific antidotes which should be administered with the guidance of a medical toxicologist or local poison center. Please see Table 4.2 for a

Table 4.2 Antidotes

Toxin	Antidote
Acetaminophen	N-acetylcysteine
Anti-muscarinic compounds	Physostigmine
Benzodiazepines	Flumazenil
Beta blockers	Glucagon
Cardiac glycosides	Digoxin Specific Antibodies
Cyanide	Hydroxocobalamin
Isoniazid	Pyridoxine
Methemoglobinemia	Methylene blue
Opioids	Naloxone
Organophosphates	Atropine, pralidoxime
Sulfonylureas	Octreotide
Toxic alcohols (ethylene glycol, methanol, propylene glycol)	Fomepizole

References: [5, 6, 9]

list of the more commonly used antidotes. Some patients may be assessed, treated, and ultimately cleared from a medical perspective, but it is important to involve psychiatry in the care of patients presenting with intentional ingestions or exposures.

Conclusion

- Poisoning is a significant cause of mortality in the United States.
- Initial stabilization focuses on the ABCs.
- Toxidromes can help identify an etiologic poison.
- Decontamination and elimination techniques should be considered.
- Supportive care is often adequate, but various antidotes exist for select poisonings.

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