Advances in poison management

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This article advances the most current concepts in the management of poisoned patients including the use of ipecac, lavage, activated charcoal, whole-bowel irrigation, and specific antidotes. The benefits vs the risks of each of these procedures are reviewed.

INDEXING TERMS: toxicology • ipecac • gastric lavage • opiates • benzodiazepines • carbon monoxide • charcoal, activated • naloxone • digitalis • flumazenil • acetaminophen • acetylcysteine

Gastrointestinal decontamination, used for centuries in the treatment of poisoned victims, is now undergoing critical reappraisal. The roles of ipecac and gastric lavage have been questioned. Activated charcoal now has an undisputed role in the management of poisoned patients. Recently, the use of ipecac-induced emesis, orogastric lavage, cathartics, activated charcoal, whole-bowel irrigation, and combinations of these treatments has been subjected to limited scientific studies. The results of these analyses are detailed.

Antidotal treatment is useful in certain situations. Naloxone rapidly reverses opiate overdoses, while oxygen is a specific antidote for CO poisoning. Newer antidotes have been developed to reverse toxicity from digitalis (Fab fragment antibodies) and from benzodiazepines (flumazenil). The appropriate indications for the use of these and other antidotes as well as the toxicity associated with their use are reviewed.

Advances in Gastric Decontamination

Interference with absorption of ingested poison from the gastrointestinal tract is the mainstay of poison management. Because few specific antidotes are available to treat poisonings, absorption prevention, observation, and supportive care are the clinician's greatest assets. "Pumping the stomach" has been advocated for the removal of poisons since the beginning of the 19th century. Syrup of ipecac has been used as an emetic for the management of poisoned patients since the 1950s. During the last decade, however, the efficacy and inherent risks of these methods of gastric decontamination have been questioned. Other methods—e.g., activated charcoal in single or multiple doses, cathartics, and whole-bowel irrigation—have been examined as to effectiveness and limitations. This article reviews the various techniques used in gastric decontamination and outlines their risks and benefits.

EFFICACY OF GASTRIC EMPTYING

Several studies [1–3] have demonstrated that gastric lavage is no more effective than ipecac emesis induced in specific instances. Other investigators, however, [4, 5] have challenged those studies on the basis of improper technique. Comparative efficacy is also difficult to evaluate because studies have often been carried out with animals and in nonoverdose situations. However, existing data infer that gastric lavage performed by traditional methods is about as effective as emesis in recovering stomach contents. Use of either gastric-emptying mechanism generally returns ~30% of the stomach contents at 1 h postingestion [6–8]. The effectiveness of both gastric lavage and ipecac in removing stomach contents is time dependent. Unfortunately, many overdose patients do not arrive to the emergency department within 1 h of their ingestions. Although emptying the stomach in the first hour generally works and may be beneficial for several hours, it is usually not helpful beyond 4 h post-ingestion.

Ipecac is contraindicated in ingestions of caustic substances and volatile hydrocarbons, in patients who have decreased gag reflex or altered mental status, and in patients at risk for rapid alteration in consciousness. Complications of ipecac include aspiration pneumonia, lethargy, diaphragmatic rupture, Mallory–Weiss esophageal tears, and intracerebral hemorrhage [9]. Currently, ipecac syrup is rarely used in emergency departments because it may induce prolonged episodes of vomiting, thereby delaying initiation of activated charcoal treatment. Its use is generally limited to the pediatric population, in whom accidental poisonings are usually discovered quickly. Ipecac is also still recommended by poison control centers for use in the home, where early administration can be assured.

Gastric lavage carries potential complications, including aspiration pneumonitis and, rarely, esophageal perforation. Gas-
tric lavage can also promote the rapid passage of tablets into the small bowel rather than removing them. The efficacy of both ipecac and gastric lavage has been questioned, particularly in light of recent clinical outcome studies. Kulig et al. [10], in a prospective study of >592 patients, addressed the issue of whether gastric emptying with either syrup of ipecac or gastric lavage followed by activated charcoal was more effective than activated charcoal alone in overdose emergency department patients. They determined that syrup of ipecac did not alter the outcome of patients who arrived in the emergency department awake and alert. Gastric lavage improved clinical outcome in obtunded patients only if performed within 1 h of ingestion. Several subsequent studies [11, 12] also failed to demonstrate a benefit for patients who underwent gastric emptying before activated charcoal, compared with those who were treated with activated charcoal alone. Thus, individual assessment of the need for gastric emptying by ipecac or lavage should be performed on all potential poisoned patients. Emergency department use of ipecac should be largely relegated to very recent ingestions by small children of substances that would bind poorly to activated charcoal.

Gastric lavage is most effective when performed within several hours of the ingestion and in a manner that would be least likely to lead to complications. A 12–13-mm (36–40 F; IF = 0.3 mm)-diameter orogastric tube should be used in adults. Nasogastric lavage is not adequate for removal of pills or fragments. The patient should be placed in a left lateral decubitus position to decrease drug absorption and reduce the risk of aspiration.

**Activated Charcoal**

Activated charcoal has been used in the treatment of poisonings since 1830, when its effects were first demonstrated by the French chemist Bertrand [13]. Produced by pyrolysis of carbon-containing materials and activated by oxidation with steam at a high temperature, these processed carbon products adsorb most drugs; only very small highly charged molecules or ions resist adsorption to this material [14]. The surface area of most commercially available activated charcoals is ~1000 m²/g. In addition to direct intraluminal binding, activated charcoal can also decrease the resorption of agents that undergo enterohepatic or entero gastric cycling. Convincing evidence also supports the existence of a “gastrointestinal dialysis” effect, whereby the charcoal serves as a large “sink” with movement of toxin molecules across semipermeable membranes from the splanchinic circulation [15]. Traditionally, activated charcoal was used as an adjunct to lavage and ipecac-induced emesis. During the last decade, however, activated charcoal became increasingly popular as a first-line agent for the treatment of poisonings, particularly if more than several hours had passed since ingestion. Activated charcoal is generally considered ineffective against caustics, ethanol, ethylene glycol, methanol, iron, lithium, metals, and petroleum distillates. Complications from activated charcoal are rare but have included aspiration of activated charcoal and gastric contents as well as intestinal obstruction, particularly when repeated doses of activated charcoal are given [16-18].

The use of multiple-dose activated charcoal (MDC) has recently been recommended to enhance the clearance of various drugs—carbamazepine, digitoxin, glutethimide, nadolol, phenobarbital, phenylbutazone, theophylline, and others. Multiple dosing appears to decrease both the absorption and blood concentration of many drugs. However, it still has not been shown whether MDC affects the clinical course. We recommend that MDC be used principally for theophylline overdoses, which carry a high morbidity and mortality: Reducing the blood concentration with MDC can be lifesaving. However, the necessary large clinical studies to demonstrate the benefit of MDC in any of these circumstances have not yet been performed. The multiple-dose regimen consists of an initial dose of 50–100 g followed by maintenance doses of 30–50 g every 2–6 h with or without the administration of a cathartic agent. When multiple doses of cathartics are given repeatedly, patients run the risk of severe fluid and electrolyte disturbances. Cathartics should be given only once or twice in patients who are given MDC. Lists of drugs for which MDC is recommended have been published by Campbell and Chyka [19].

**Cathartics**

Cathartics have long been used as adjunctive therapy for poisonings with the premise that they promote intestinal evacuation of both the drug and the drug–charcoal complex. Despite their widespread use, however, little evidence exists that cathartics alter the outcome of poisoned patients. The most prominent argument is that cathartics prevent constipation caused by charcoal and also hasten the elimination of the charcoal–drug complex, giving less time for the drug to desorb from activated charcoal. The most commonly used cathartics are magnesium sulfate, magnesium citrate, and sorbitol. Sorbitol works the most quickly, causing bowel movements within 1 h. Contraindications to cathartics include caustic ingestions and signs of intestinal obstruction. Magnesium-containing cathartics should be avoided in the presence of renal insufficiency. One dose of a cathartic is generally sufficient. Serious toxicity from cathartics, particularly in children, can be expected with multiple doses of sorbitol or magnesium salts. Associated complications include hypermagnesemia and hypernatremia [20, 21].

**Whole-Bowel Irrigation**

Recently, polyethylene glycol–electrolyte solutions, which once were used for bowel cleansing before surgical procedures, have been applied for gastrointestinal decontamination. These isotomically balanced, nonabsorbable solutions are safe, causing no fluid retention or electrolyte disturbances. Theoretically, whole-bowel irrigation may be useful for managing patients who have taken toxins that are not adsorbed by activated charcoal or sustained-release preparations that continue to be absorbed in the small intestine. The procedure has been advocated for overdoses of agents such as iron, lithium, and enteric-coated or sustained-release medications [22-24]. In practice, hemodynamically stable and cooperative patients are best suited to this intensive cathartic treatment. For the procedure to be effective,
adults should ingest the solution at a rate of 2 L/h, children at 500 mL/h. The solution can also be given through a nasogastric tube. The endpoint of treatment is a clear effluent, which may take 4–6 h to appear. A combination of activated charcoal (without cathartic) and whole-bowel irrigation can be effective in some situations (e.g., for a cocaine body packer), but the polyethylene glycol–electrolyte solution reduces the binding efficacy of charcoal, requiring an increase in the amount of activated charcoal used [25, 26]. One of the risks of polyethylene glycol delivery is vomiting, but this appears to be related to how fast the fluid is given. Contraindications to whole-bowel irrigation include ileus or bowel obstruction.

Laboratory Tests
Although laboratory analysis of various body fluids of overdose patients frequently identifies substances that are clinically unsuspected, these additional findings rarely alter the patient’s clinical course, largely because the presence of a substance does not necessarily correlate with acute toxicity; moreover, analysis can be time-consuming and in most clinical settings falls short of being comprehensive. Most poisoned or overdose patients do well with supportive care alone, extensive testing being most useful in the hemodynamically unstable patient with altered mental status. Finally, no rapidly available, universal screening tool exists. Although some of the newer HPLC methods may approach this ideal in terms of turnaround time and range of detectable substances, if not cost, they do not detect such important toxins as lithium, monoamine oxidase inhibitors, and synthetic narcotics such as fentanyl derivatives. Accordingly, test ordering should be guided by the presence of symptoms and signs characteristic for various toxins; many patients require little, if any, laboratory investigation. Arterial blood gas analysis, serum glucose, and an electrocardiogram can direct test ordering in sicker individuals.

Quantitative testing for specific substances—e.g., acetaminophen, aspirin, anticonvulsants, and theophylline—in blood is readily available by immunoassy, but such tests should be restricted to those patients for whom knowledge of these drugs’ concentrations is likely to make a difference in clinical decision making. Turnaround times of 30–45 min are acceptable for these measurements, because initial treatment will be guided primarily by symptoms. Acetaminophen is probably the sole exception to symptom-guided test ordering, because it does not cause any specific early symptoms. The utility of a very effective antidote, N-acetylcysteine, is strikingly diminished when treatment is delayed beyond 12 h after ingestion; therefore, a serum acetaminophen concentration should be measured early in all suicidal ingestion patients. Other quantitative tests of clinical importance include assays of lithium, the alcohols, and dyshemoglobininemas (e.g., carboxy- and methemoglobin). Although enzymatic assays for methanol and ethylene glycol have reduced the need for gas chromatography, the various instruments necessary for detecting all these agents highlight the difficulty in designing a single “comprehensive” test.

Qualitative assays for many potential toxins are available via various chromatographic methods or immunoassays. Point-of-care testing devices are appealing in their simplicity and their rapid (<10 min) display of results. Unfortunately, many clinicians consider these tests to be comprehensive. They interpret the report of a negative screen as meaning “no drugs present.” Education of clinicians regarding the limits of these technologies (e.g., problems in sample extraction, or cross-reactivity of various immunoassays, or the relatively time-intensive nature of matching positive chromatographic “hits”) is needed. Two-way communication between the laboratory and the clinician, with consideration of the history available and any toxic syndromes present, will determine the best testing strategy for the individual patient and increase the value of the information received.

Rational Use of Antidotes
Antidotes are commonly thought of as chemical or physiological antagonists that prevent the toxicological effect of specific poisons. This differentiates them from agents used to ameliorate the sequela of the toxicological effects of poisons. In most toxicological emergencies, effective antidotes are not available. Symptomatic treatment and supportive care are still the primary approach to treatment; antidotal therapy often plays a relatively minor role. When appropriately used in specific situations, however, antidotes can substantially reduce morbidity and mortality in the poisoned patient.

Oxygen vs carbon monoxide. Oxygen is a specific antidote for CO poisoning. The effects of CO in concentrations encountered clinically are based on its combination with hemoglobin, displacement of oxygen, and consequent disruption of the oxygen transport system. CO competes with oxygen for a binding site in the hemoglobin molecule. The resulting carboxyhemoglobin formed has no practical function as a carrier of oxygen. Because CO affinity for hemoglobin is 230–270 times as great as that of oxygen, the latter is rapidly displaced, and the oxygen-carrying capacity of blood is concomitantly reduced. Thus, very small concentrations of CO cause high concentrations of carboxyhemoglobin. The primary and definitive treatment for CO poisoning is the administration of oxygen: Within the limits of toxicity, the more oxygen given, the more effective the treatment. The immediate therapeutic goal is to reverse cerebral and myocardial hypoxia; the second concern is to accelerate CO elimination. Both goals are achieved simultaneously by adequate oxygen administration. Oxygen is transported in blood, both bound to hemoglobin and dissolved in plasma. Although CO inactivates hemoglobin, it is without effect on dissolved oxygen. In air breathing, the concentration of dissolved oxygen is low but increases with increasing inspired oxygen tensions. One hundred percent oxygen in atmospheric pressure can result in dissolved oxygen content as high as 20.9 mL/L. Given that the whole-body arterial to venous oxygen content difference is usually 50–60 mL/L, administration of 100% oxygen can supply one-third of the oxygen demand in dissolved form [27]. Administration of 100% oxygen should be by use of a non-breathing mask or endotracheal intubation. This can effectively
reduce the half-life of carboxyhemoglobin dissociation from 300 min to between 60 and 90 min.

**Naloxone vs opiates.** Naloxone, the recommended drug of choice for reversal of symptoms of overdosage from opiates, is particularly effective in the presence of respiratory depression, miosis, and coma. Opiates include natural opioids such as morphine and codeine; semisynthetic opioids such as heroin, hydromorphone, oxymorphone, and oxycodone; and synthetic opioids include meperidine, methadone, propoxyphene, and the fentanyls. The opioids act on three specific groups of receptors—the Mu, Kappa, and Delta receptors—all capable of affecting the perception of pain. The Mu-1, Kappa-3, and Delta-2 receptors are found in the brain; the Mu-2, Kappa-1, and Delta-1 receptors are in the spinal cord [28]. Analgesia occurs from stimulating the Mu receptors at a supraspinal level and the Kappa receptors at a spinal level.

In the last 10–20 years, so-called designer drugs have emerged from illicit manufacturers. These drugs include the fentanyl derivatives, which can be 100–3000 times more potent than morphine, and analogs of meperidine. Naloxone is effective in reversing the effects of these opioids and should be given in an initial dose of 2 mg. If reversal is successful, the effective dose may need to be repeated every 20–30 min for several hours to avoid renarcotization, because the half-life of naloxone is much shorter than that of most opioids. Alternatively, continuous infusion of two-thirds of the originally effective dose per hour can be started. The only adverse effect of naloxone in the overdose patient is the risk of precipitating withdrawal symptoms in a narcotic addict. Naloxone can be given through subcutaneous, intramuscular, endotracheal, and sublingual routes. The intravenous route is preferred because its onset of action is more rapid and reliable. Naloxone works as a competitive antagonist to Mu, Kappa, and Delta opioid receptor sites, antagonizing the sedative, analgesic, and miotic effects by displacing the opiate and binding rapidly to its receptors. Higher doses of naloxone are often needed to reverse the effects of synthetic narcotics.

**Fab fragment antibodies vs digitalis.** Specific Fab fragment antibodies, first used to reverse human poisoning in 1976, were proved to be safe and effective by Antman et al. [29] in a multicenter trial of 150 patients with life-threatening digitalis intoxication treated with Fab fragment antibodies. The patients, who ranged in age from 1 day to 94 years, had both acute and chronic overdoses. The median ingested dose of digoxin in acute overdoses was 12.5 mg. The median serum digoxin concentration was 8 ng/mL. Life-threatening complications included refractory ventricular tachycardia, ventricular fibrillation, high-grade atrioventricular block, and hyperkalemia. Most patients improved strikingly when treated with digoxin-specific antibodies: In 80% intoxication resolved completely, and in 10% signs and symptoms lessened. Most dramatic was the resuscitation of overdose patients from cardiac arrest. Thirty of 56 patients (54%) whose digitalis toxicity led to cardiac arrest were successfully resuscitated with Fab antibodies [29], a great improvement over the 100% mortality of similar patients treated with conventional therapy alone [30]. Digoxin-specific Fab antibodies should therefore be administered as soon as possible to patients with digitalis-induced ventricular arrhythmias, high-grade atrioventricular block, and (or) severe hyperkalemia. Patients with digitalis intoxication must be closely monitored and observed. When Fab antibodies are administered, total serum digoxin concentrations rise substantially and cannot be used to guide therapy. Potassium concentrations must be monitored carefully because Fab antibodies can produce hypokalemia. Hypokalemia can become even more serious if additional treatment measures for hyperkalemia (e.g., glucose, insulin, and bicarbonate) have been instituted in addition to Fab antibodies. Treatment with Fab antibodies to counter digitalis effects can also lead to other adverse events: e.g., worsening congestive heart failure or an increase in ventricular rate in patients with atrial fibrillation. However, the benefits of digoxin-specific Fab antibodies far outweigh the risks [31].

**Flumazenil vs benzodiazepines.** Flumazenil is a specific benzodiazepine antagonist with virtually no agonist activity in humans. Flumazenil has been approved and is very effective for antagonism of benzodiazepines after their use in conscious sedation and general anesthesia and for reversal of benzodiazepine overdose. Flumazenil is not recommended for patients who have also ingested cyclic antidepressants or who use benzodiazepines therapeutically to control seizure disorders. When used as recommended, however, flumazenil has an acceptable safety rate and the benefits outweigh the risks, particularly when given to reverse conscious sedation or general anesthesia. Double-blinded placebo-controlled trials in the US have consistently demonstrated the efficacy of flumazenil in reversing benzodiazepine-induced depression of the central nervous system in conscious sedation, in general anesthesia, and in overdoses. Reversal in some cases obviates the need for more-intensive measures such as intubation or mechanical ventilation. The use of flumazenil in benzodiazepine overdose situations, however, presents a risk of seizures if the patient has also taken a proconvulsant such as a tricyclic antidepressant or has been treated chronically with benzodiazepines. Flumazenil, like naloxone, works very quickly but can wear off quickly (<1 h) and may need to be repeated.

**N-Acetylcysteine vs acetaminophen.** N-Acetylcysteine is very effective in preventing hepatotoxicity from overdoses of acetaminophen. The sulfur group of N-acetylcysteine acts as a glutathione substitute or precursor in the liver. Glutathione forms a conjugate with the toxic metabolite of acetaminophen. When hepatic stores of glutathione are depleted in acetaminophen overdoses, the toxic metabolite reacts with hepatocytes to produce necrosis. Administration of N-acetylcysteine prevents the toxic metabolite from binding to liver cells. N-Acetylcysteine is most effective when administered within 8 h of acetaminophen ingestion. However, it may be protective when administered as late as 24 h after acetaminophen ingestion. In a retroactive study of 100 patients with fulminant hepatic failure from acetaminophen overdose, N-acetylcysteine therapy improved clinical outcome
progression of hepatic encephalopathy and (or) fatality, even when administered 36 h after ingestion [32].

Ethanol vs methanol and ethylene glycol. Methanol and ethylene glycol are metabolized in the liver by alcohol dehydrogenase to form their toxic metabolites. Formation of oxalic acid from ethylene glycol causes acute tubular necrosis and renal failure. The metabolites of methanol can lead to severe metabolic acidosis and optic nerve damage. Therapy with inorganic ethanol successfully inhibits the formation of the toxic metabolic products after ethylene glycol and methanol intoxication. Ethanol is a preferential substrate for alcohol dehydrogenase, having a greater affinity for that enzyme than either ethylene glycol or methanol. An optimal blood ethanol concentration of 1000 mg/L should be achieved by giving a loading dose, and this concentration should be maintained until blood concentrations of methanol and ethylene glycol reach zero. Although ethanol therapy prevents further breakdown of ethylene glycol and methanol, it does not affect the toxic metabolites already present. Definitive treatment is achieved with hemodialysis.

There has been a major change in the treatment of poisoned patients, particularly in the area of gastric decontamination. The trend is away from the use of ipecac, except in limited situations such as accidental ingestions in pediatric patients. Similarly, gastric lavage is less beneficial if performed several hours after ingestion. For that reason, activated charcoal has attained a prominent role not only as an adjunct for gastric emptying with either ipecac or gastric lavage but also for use as the sole decontamination agent. Studies have demonstrated that activated charcoal is as effective as ipecac or lavage. Gastric lavage still plays an important role, especially if it can be performed early, or if drugs are involved that may delay gastric emptying. MDC is effective for such dangerous drugs as theophylline and possibly phenobarbital; however, no data are available on clinical outcomes after the use of MDC in drug overdoses. Cathartics hasten the elimination of the toxin and the toxin–charcoal complex. In that regard, sorbitol in a single dose along with activated charcoal probably is of some use. Whole-bowel irrigation is safe and effective in limited situations such as iron, lithium, or sustained-release medications, and for body packers. Antidotes play an important role in specific situations. Oxygen is extremely useful for the treatment of CO. Naloxone is useful for the treatment of opiate intoxication. Fab fragment antibodies are safe and effective for the treatment of digitalis intoxication. However, the use of flumazenil in reversing benzodiazepine overdoses may be risky. In benzodiazepine overdoses involving coingestions or benzodiazepine habituation, there is a risk of precipitating seizures with flumazenil. Therefore, flumazenil should be used cautiously in this situation. N-Acetylcysteine is an effective and safe antidote for acetaminophen poisoning. Alcohol is used effectively as an antidote for methanol and ethylene glycol poisonings. Despite the advances in gastric decontamination and the development of new antidotes, the mainstay of treatment for the poisoning victim remains supportive care and frequent reevaluation for a change in clinical status.

References
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