

Review article

# New developments in the therapy of intoxications

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## Abstract

There has been a significant evolution in the clinical management of the poisoned patient over the last decade. Interventions that were once the cornerstone of treating the poisoned patient have become passé or have come under intense scrutiny. The advent of evidence-based medicine has forced clinical scientists to re-evaluate standard therapies. Gastrointestinal decontamination with either emesis or gastric lavage was the foundation of the initial management of most poisoned patients. Examination of the published literature demonstrated that neither emesis nor lavage changed the ultimate outcome of poisoned patients, and most poison centers have abandoned their use. Even the use of activated charcoal has been questioned. A multitude of studies demonstrated that the effectiveness of activated charcoal diminished significantly 30–60 min after the ingestion of a poison. No study has demonstrated that charcoal changed patient outcome. Cathartics have been deemed to be ineffective and potentially dangerous and are never indicated. Whole bowel irrigation should not be used routinely in the management of the poisoned patient. Multiple dose activated charcoal and urinary alkalization, commonly used to enhance the elimination of some poisons, have limited usefulness. While these ‘old’ and more general methods of ‘detoxification’ have thus failed in most cases to improve or change patient outcome, the use of more specific antidotes, tailored to the exact cause of intoxication is to be considered. Very few antidotes, however, are used on a consistent basis in the management of poisoned victims. The indiscriminate use of antidotes may even be harmful to the patient and incur an inordinate expense. In addition to the commonly known antidotes *N*-acetylcysteine (acetaminophen, paracetamol), naloxone (opioids) and flumazenil (benzodiazepines), new antidotes include fomepizole to treat ethylene glycol and methanol poisoning and Crotalidae Polyvalent Immune Fab (Ovine) for pit viper envenomation. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

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## 1. Introduction

Poisonings are a universal problem. The majority of poisoning exposures are unintentional, involve children less than six years of age and have a positive outcome without the need for medical intervention (Litovitz et al., 2000). Until recently

there was major emphasis on the use of gastrointestinal decontamination to manage patients who ingested poisons. However, contemporary evidence suggests that gut decontamination using some conventional techniques (emesis, gastric lavage, cathartics) has little or no impact on patient outcome and should be abandoned. There may be a hypothetical role for the use of activated charcoal and whole bowel irrigation (WBI), but their intrinsic value has not been demonstrated

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with any degree of scientific or clinical certainty. Even the use of traditional techniques to enhance elimination is being questioned. Antidote use has diminished and is limited to a select number of agents that are used with any frequency. The purpose of this manuscript is to explore and resolve the controversies associated with the use of gastrointestinal decontamination, the enhanced elimination of poisons with noninvasive techniques and to address contemporary antidote development.

## 2. Gastrointestinal decontamination

Ipecac syrup is an effective emetic; gastric lavage assists in the retrieval of stomach contents; activated charcoal binds a multitude of compounds *in vitro*; agents such as sorbitol produce a brisk catharsis; and WBI flushes the length of the gastrointestinal tract. While these treatment modalities produce gratifying technical outcomes for the intervening clinician and have been used for decades, do they change patient outcome? Recently published evidence-based position statements from the world's two largest clinical toxicology societies (American Academy of Clinical Toxicology and the European Association of Poisons Centers and Clinical Toxicologists) cast significant doubt on the effectiveness of these time-honored interventions (Krenzelok and Vale, 1997).

### 2.1. Ipecac syrup

Ipecac syrup, derived from the dried rhizomes and roots of *Cephalis acuminata* or *Cephalis ipecacuanha*, has been promoted throughout the world, but especially in the United States, as an emetic for patients who have ingested poisons. Following the ingestion of 120–240 ml of water, the administration of ipecac syrup 15–30 ml produces emesis within approximately 15–25 min. The early studies evaluated dose-response relationships and even compared emesis to lavage with regard to the retrieval of marker substances such as barium or sub-toxic doses of medications. However, there was no emphasis on patient out-

come since it was assumed that emesis would eliminate some portion of the poison and reduce morbidity and mortality.

An extensive review of the literature exposed the limitations of ipecac syrup (Krenzelok et al., 1997). For example, in experimental studies that involved the use of marker agents, the amount of the various markers that were retrieved was highly variable and diminished with time (an expected conclusion since emesis does not remove gastric debris that has moved beyond the stomach). The clinical studies did not demonstrate that ipecac syrup improved patient outcome. While the adverse effects associated with ipecac syrup-induced emesis are not significant, there does not appear to be any merit based on risk:benefit analysis to justify the use of ipecac syrup in the management of acute poisoning emergencies. Its use should be abandoned.

### 2.2. Gastric lavage

Similar to ipecac syrup-induced emesis, gastric lavage has been a cornerstone in the management of poisoning emergencies. Gastric lavage has been a featured intervention for over 180 years. In recent decades, it was used in patients with a decreased level of consciousness who were not candidates for being treated with ipecac syrup (for fear of aspiration and resultant complications). During the early days of gastric lavage research, little attention was paid to the diameter of the lavage tube. Research during the decades of the 70's and 80's focused on the importance of utilizing a large bore orogastric hose with a diameter of 34–40 French in the adult patient, with appropriately large tubes for children. Comparing the efficacy of lavage, emesis and activated charcoal consumed considerable research attention. However, the focus continued to be on the comparative quantitative effectiveness of the techniques with respect to their removal of a marker agent, not patient outcome.

The hypothetical effectiveness of gastric lavage is related directly to the presence of the poison in the stomach—if there is little or no poison in the stomach, lavage will have limited or no usefulness. It is estimated that patients who suffer from

self-inflicted intentional poisoning do not present to the emergency department until they are at least 2–3 h post-exposure. It is unlikely that appreciable amounts of the poison remain in the stomach after such a delay. Therefore, it is quite remarkable that gastric lavage survived the scrutiny of clinical scientists for so long. Neither the experimental nor the clinical studies support the universal use of gastric lavage. Conceivably, it may be of benefit if the patient ingested a life-threatening quantity of a poison and less than 60 min have elapsed between the time of ingestion and the implementation of gastric lavage—an unlikely scenario. However, in the general poisoned patient gastric lavage has no role (Vale, 1997).

### 2.3. *Single-dose activated charcoal*

Activated charcoal is the product of the pyrolysis of a variety of forms of organic matter, including petroleum, which is ‘activated’ through a cascade of steps that include heating it in steam, air or carbon dioxide at 600–900 °C, washing with organic acids and drying. The final product is a highly porous form of carbon with a surface area of 950–2000 m<sup>2</sup>/g that is capable of adsorbing poisons. Activated charcoal has its highest affinity for compounds with a molecular weight of 100–1000 Da. The rationale for using activated charcoal in the poisoned patient is to bind poisons, thereby minimizing their absorption and the risk of morbidity and mortality. For activated charcoal to be effective, it must come into direct contact with the poison. Therefore, if the administration of activated charcoal is delayed, its effectiveness will be reduced. In essence, if the poison is not in the stomach, single-dose activated charcoal administration is unlikely to have a positive impact on patient outcome. The typical dose of activated charcoal for single use is 25–50 g given as an aqueous slurry in 120–240 ml of water.

Unlike the research on ipecac and lavage, there has been more of a propensity to evaluate the clinical effectiveness of activated charcoal. But in similar fashion, the volunteer studies, demonstrated that the effectiveness of activated charcoal

decreased with time and the greatest benefit was derived (hypothetically) when it was administered within one hour of the ingestion of a poison that was known to be adsorbed by activated charcoal (Chyka and Seger, 1997). However, there is no evidence that activated charcoal actually improves patient outcome. Despite these apparent limitations, activated charcoal continues to be used in the management of poisonings that are associated with increased morbidity and mortality (e.g. acetaminophen, calcium channel blockers, salicylates, tricyclic antidepressants, etc.). The definitive study to determine the impact of activated charcoal on patient outcome has yet to be conducted. Until that time, medical/legal concerns rather than evidence-based medicine will dictate the indications for activated charcoal.

### 2.4. *Cathartics*

The sole use of cathartics to enhance purging the bowel of poisons has never been embraced universally. The concurrent use of cathartics with activated charcoal was the perceived standard of care until recently. The rationale for using cathartics (especially sorbitol) with activated charcoal was to enhance the palatability (gritty texture) and thereby increase compliance, and to result in the expedited expulsion of the activated charcoal:poison complex from the bowel. There was considerable emphasis on this process to prevent the desorption (and resultant reabsorption) of poisons from activated charcoal.

The aggressive use of cathartics with activated charcoal was a relatively recent phenomenon. Charcoal was combined most commonly with sorbitol in commercial products or mixed extemporaneously with saline cathartics such as magnesium or sodium sulfate. Research focused on which cathartic was most effective and whether cathartics interfered with the adsorptive capacity of activated charcoal instead of patient outcome. There is no evidence that supports the use of cathartics as an adjunct in the management of the poisoned patient (Barceloux et al., 1997). Furthermore, cathartics have the potential to cause fluid and electrolyte imbalance. There is absolutely no role for the use of cathartics in the management

of the poisoned patient, its use is without merit and constitutes a risk in unstable patients. The use of cathartics should be abandoned.

### 2.5. *Whole bowel irrigation*

Whole bowel irrigation cleanses the bowel through the enteral administration of large amounts of iso-osmotic polyethylene glycol solution. Long known as an effective means of evacuating the bowel prior to surgery, WBI use in the management of patients who ingested poisons became popular only during the last three decades. It is the least studied and the least used of the gastrointestinal decontamination modalities. There are no dose:response studies, but the typical dose is the administration of 500–2000 ml/h either orally or via a nasogastric tube. The hypothetical endpoint is the presence of clear effluent that signifies that gastrointestinal evacuation is complete. The endpoint is not valid and there is no way to know that the bowel has been cleansed unless the poison is radiopaque and can be quantified.

From both a clinical and scientific perspective, WBI is not a procedure that is used routinely in the management of the poisoned patient (Tenenbein, 1997). Anecdotal reports support its use in a limited number of poisonings but there is no evidence that demonstrates a positive impact on patient outcome. Despite the lack of solid supportive evidence, WBI remains a viable treatment option following the ingestion of significant amounts of iron and potentially toxic ingestions of sustained-release and enteric-coated pharmaceuticals. Another proposed indication is to force the elimination of illicit drug packets that have been swallowed for the purpose of drug smuggling or to avoid arrest—if the patient is symptomatic or if the drug containers have the potential to rupture or leak.

## 3. Enhanced elimination

### 3.1. *Forced alkaline diuresis*

Forced alkaline diuresis was introduced into clinical practice at a time when clinicians were

desperate to find a way to enhance the elimination of poisons from the body. Extracorporeal means of removal such as hemodialysis were not available universally as they are today. The rationale for forced alkaline diuresis was based on increasing the rate of flow of filtrate in the nephron which reduced the time that a toxin spent in the renal tubule and resulted in a reduction of toxin reabsorption. The elimination was further enhanced through the manipulation of urinary pH that resulted in ionization of the poison—ionized chemicals are not reabsorbed. Therefore, alkalinization of the urine would hypothetically ionize acidic compounds and the induced diuresis would enhance elimination of the ionized poison. For ionization to be effective, the pH of the urine must exceed the pH of the blood by approximately one pH unit. Considering that the normal blood pH is approximately 7.35, the urine pH would have to exceed pH 8 to be effective. This is difficult to achieve clinically.

Early research focused on the merits of using forced alkaline diuresis in the treatment of salicylate poisoning (Savege et al., 1969; Morgan and Polak, 1971; Prescott et al., 1982). A variety of regimens were devised, but despite all of the research, there is no evidence that demonstrates that forced alkaline diuresis is superior to urinary alkalinization alone. Furthermore, patients with mild salicylism will not benefit from urinary alkalinization nor will patients suffering from serious salicylism. The complications (pulmonary edema, cerebral edema, alkalemia, hypokalemia, hypocalcemia, etc.) associated with forced alkaline diuresis outweigh the perceived benefits of using this treatment in salicylism and most other forms of poisoning that involve acidic compounds. Forced alkaline diuresis may have but one indication—the treatment of serious chlorophenoxy herbicide poisoning (Bradberry et al., 2000).

### 3.2. *Multiple-dose activated charcoal*

Multiple-dose activated charcoal therapy involves the repeated administration of oral activated charcoal to enhance the elimination of drugs that are present systemically in a toxic concentration. Drugs that have a prolonged half-

life and a relatively small volume of distribution may undergo enterogastric secretion. Other compounds may be subject to significant enterohepatic circulation. The administration of multiple doses of activated charcoal (25–50 g every 4–6 h) has been demonstrated to adsorb those drugs, enhance their elimination and thereby reduce their absorption. Theoretically, reduced drug reabsorption would reduce morbidity and mortality. Despite impressive reduction of drug half-life and increased total body clearance, there is no evidence that demonstrates convincingly that morbidity and mortality are reduced.

While the clinical evidence is lacking, there are five drugs whose clearance may be enhanced through the use of multiple-dose activated charcoal—carbamazepine, dapsone, phenobarbital, quinine and theophylline (Vale et al., 1999). This may eliminate the need to use an invasive extracorporeal technique (e.g. hemodialysis) to enhance elimination in serious poisoning. As with single-dose activated charcoal, cathartics should never be used with multiple-dose activated charcoal. Fluid and electrolyte imbalance would be magnified through the use of multiple doses of a cathartic.

#### 4. Antidote development

With the exception of *N*-acetylcysteine (acetaminophen, paracetamol), naloxone (opioids) and flumazenil (benzodiazepines), very few antidotes are used on a consistent basis in the management of poisoning victims. The indiscriminate use of antidotes may be harmful to the patient and incur an inordinate expense. Two relatively new antidotes (fomepizole and Crotalidae Polyvalent Immune Fab) have the potential to reduce morbidity and mortality.

##### 4.1. Fomepizole

Methanol and ethylene glycol poisoning result in both significant morbidity and mortality through the production of profound metabolic acidosis and organ specific toxicity. While neither parent compound is highly toxic, alcohol dehydrogenase

metabolizes the substrates to toxic metabolites. Methanol is metabolized to formaldehyde and formic acid, and if untreated, blindness and death are not uncommon sequelae. Ethylene glycol is metabolized to glycoaldehyde, glycolic acid and oxalic acid. Renal failure and death may ensue.

The traditional therapy of methanol and ethylene glycol poisoning has been ethanol therapy (Barceloux et al., 1999; Cobaugh et al., 1999). When ethanol is introduced concurrently with either methanol or ethylene glycol, alcohol dehydrogenase will metabolize preferentially the methanol and ethylene glycol, preventing their conversion to the toxic metabolites. An ethanol serum concentration of approximately 100 mg/dl will provide sufficient ethanol substrate for alcohol dehydrogenase. Since methanol and ethylene glycol metabolism are impaired in the presence of ethanol, their elimination half-lives are long and conventional wisdom dictated that hemodialysis should be used to eliminate the toxic alcohols. Ethanol is metabolized via Michaelis–Menten kinetics which necessitates hourly oral replacement or constant intravenous infusion of the ethanol to maintain the inhibitory concentration. An ethanol loading dose of 600–700 mg/kg followed by 110–125 mg/kg/h are necessary. The dose of ethanol must be increased during hemodialysis because it is also removed effectively.

A more convenient solution to the treatment of toxic alcohol poisoning is the use of fomepizole (Brent et al., 1999, 2001). Fomepizole (4-methylpyrazole, 4-MP, Antizol<sup>®</sup>) is a competitive inhibitor of alcohol dehydrogenase. A loading dose of 15 mg/kg intravenously is followed every 12 h by 10 mg/kg for 48 h and then 15 mg/kg thereafter since fomepizole induces its own metabolism. If hemodialysis is employed, the dose of fomepizole must be adjusted to replace the amount lost during dialysis. Fomepizole is safe and effective and eliminates the many challenges associated with ethanol therapy. While it is an expensive intervention, its use eliminates the necessity of obtaining frequent ethanol concentrations and in stable patients, hemodialysis is often unnecessary. These advantages offset the cost of fomepizole.

#### 4.2. *Crotalidae polyvalent immune fab (Ovine)*

In addition to aggressive supportive care, the cornerstone of managing a patient suffering from severe snake envenomation is antivenom. Until 2000 the only antivenom available in the United States for pit viper envenomation was *Crotalidae* polyvalent antivenin-derived from horse serum. The current manufacturer of the antivenin has ceased production and supplies are dwindling rapidly. However, a new antivenom (CroFab<sup>®</sup>) *Crotalidae* Polyvalent Immune Fab (Ovine) is now available commercially. This product is produced by inoculating sheep with the venoms of four North American pit vipers and then harvesting the antibodies which are purified to produce a final product that contains the immune Fab fragment. Not all venomous snakebites need to be treated with the antivenom. A minimal number of bites are dry bites where no venom is injected by the snake. Envenomation is signaled by the presence of pain, swelling and ecchymosis. Early administration of the *Crotalidae* Polyvalent Immune Fab will reverse or prevent local tissue injury as well as systemic effects such as coagulopathy (Dart and McNally, 2001). The recommended dose is the intravenous administration of 4–6 vials, infused over 60 min given at a progressively greater rate once it is determined that the patient is not allergic to the product. An additional 4–6 vials should be administered if initial control is not achieved. Once the local and systemic effects are controlled, an additional three maintenance doses of two vials should be administered to prevent exacerbation of the toxic effects as venom is released slowly from the envenomation site. In contrast to the traditional horse serum antivenin, *Crotalidae* Polyvalent Immune Fab is tolerated better with fewer allergic manifestations and without the classical serum sickness that occurs in many patients.

#### 5. Summary

The first tenet of patient management is to do no harm. The second principle is to improve patient outcome. Many of the traditional manage-

ment interventions do not improve patient outcome and subject the patient to some degree of risk. Single-dose activated charcoal therapy may be of benefit to the patient if administered within 60 min of ingesting a life-threatening amount of a poison. Multiple-dose activated charcoal may enhance the elimination of a limited number of drugs. The judicious use of antidotes such as fomepizole and *Crotalidae* Polyvalent Immune Fab (Ovine) may reduce morbidity and mortality, when they are used appropriately.

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