

Seventeen Superior Ways to Manage Your Poisoned Patient

Toxicology update 2007

Much has changed in the young specialty of toxicology in the last few years, bringing new clarity to previously cloudy issues. Fortunately, most of the changes make treatment simpler and safer rather than more complex. I've singled out seventeen changes that are most likely to affect the way family physicians, pediatricians and internists treat their poisoned patients.

1. **Cathartics are out.** We reasoned speciously for decades that it would be helpful to purge poisoned patients in the hope that poisons could be hastened through the intestine and out of the body. Unfortunately, not a single study has shown any benefit from cathartics. Most drugs and toxins are absorbed within 30-90 minutes and most laxatives take hours to work. Furthermore, dangerous fluid and electrolyte shifts have occurred, causing a few infant deaths. The mortality of a poisoned child who reaches the hospital alive is only 0.05 percent; therefore, this treatment fails the old caveat that the treatment should not be worse than the disease.

2. **Gastric emptying**, whether by ipecac or lavage, is **out**. Multiple studies have shown no advantage over activated charcoal in decreasing absorption. Ipecac can lead to prolonged vomiting, which dehydrates the patient and prevents timely administration of oral antidotes. In addition, many overdoses eventually produce a diminished level of consciousness, which increases the risk of aspiration. Gastric lavage is a time consuming procedure which also risks aspiration as well as esophageal injury, but it may still be useful when the clinician suspects the toxin has not yet passed the pylorus, especially when the toxin is a substance not adsorbed by charcoal. In general there is no advantage to gastric emptying once 60 minutes have elapsed since the ingestion. Cathartics and gastric emptying both contribute to dehydration and decreased renal clearance of toxins. Adequate hydration is part of good supportive care, and urine output of 1-3 cc per kilo per hour is a reasonable goal. Over hydration should also be avoided, and forced diuresis has also fallen into disfavor.

3. Activated **charcoal** is definitely **in**. It's safe, inexpensive, and it adsorbs most toxins. It should be administered in a dose of 1-2 grams per kilogram in water rather than sorbitol (an unnecessary and noxious laxative, especially if inadvertently repeated with each dose of charcoal). The ideal dose of charcoal is 10 grams for each gram of poison ingested. Multiple dose activated charcoal (MDAC), that is q4h charcoal, may be useful for a few drugs which undergo enterohepatic circulation, such as theophylline. Studies have shown decreases in half life of these drugs; disappointingly, however, clinical benefit has not been established. Unfortunately, charcoal does not adsorb every poison, particularly alcohols, metals, acids, alkalis and hydrocarbons. Charcoal should be administered as soon as possible after the ingestion. Most absorption occurs within 30-90 minutes, so charcoal is generally ineffective if more than 2 hours have elapsed.

4. **Whole bowel irrigation (WBI)** is **in**, but it is messy and time consuming and should be reserved for life threatening intoxications from sustained release ("CR, SR, LA, XL") beta blockers, calcium channel blockers, and lithium, as well as for iron and lead. Oral charcoal followed by WBI is also the safest way to decontaminate body packers and stuffers of illegal drugs. It does accelerate gastrointestinal transit much better than laxatives and does reduce the time for absorption, especially when sustained-release preparations are ingested. An added benefit--because a polyethylene glycol solution is used--is no net shift of fluids or electrolytes across the intestinal wall. The patient is given approximately 20 cc's per kilogram per hour which means about two liters per hour for adults; about half a liter per hour for children. The end point is a clear rectal effluent which usually requires four to six hours. Few patients are able to drink this quantity of fluid; most will require a NG tube and an antiemetic. Useful intravenous antiemetics for patients older than 12 years include 10 mg prochlorperazine (Compazine®) or 1 mg/kg metoclopramide (Reglan®). The popular but puny dose of 10 mg of Reglan is inadequate for most adults. Young children should receive only 0.1 mg/kg of metoclopramide. More effective--though more expensive--antiemetics are the 5-HT₃ antagonists (ondansetron, granisetron, dolasetron). According to the Medical Letter (March 29, 2004), ondansetron (Zofran®) in a dose of 8 mg IV is the most effective and least expensive of these new drugs. An additional advantage of this newer antiemetic is the absence of dystonic reactions, which are an occasional annoyance with Compazine and Reglan, especially in children.

5. **N-acetylcysteine (NAC)**, is **in** more than ever. It is now available as both oral Mucomyst® and intravenous Acetadote®, If administered within eight hours of an acetaminophen overdose, mortality is zero, but some benefit is obtained if treatment is delayed over 24 hours, so never withhold NAC because you think it's too late. Even late administration during hepatic encephalopathy decreased mortality from 58 percent to 37 percent in a British study. Early benefit is credited to glutathione regeneration, but other mechanisms account for late benefits. NAC may function as an anti-oxidant, protect the microcirculation and thereby decrease cerebral edema. In the past we have rigidly held to the 72 hour oral regimen requiring 18 doses of NAC. A new consensus is that oral Mucomyst can be safely stopped at 36 hours if the following criteria are met:

- * the prothrombin time is normal
- * the AST is normal
- * the acetaminophen level is less than 10 mcg/ml

The FDA approved the intravenous preparation of N-acetylcysteine in 2004 (Acetadote®, Cumberland Pharmaceuticals), which allows timely administration of the antidote to patients with persistent vomiting or other impediment to oral administration. Another advantage of the IV preparation is shorter administration time: 21 hours vs. 36-72 for the oral protocol.

A four hour acetaminophen level of 150 mcg/ml is still the criterion for initiating NAC therapy. However, if the time or amount of ingestion is in any doubt, it's always best to give the loading dose until the potential for hepatotoxicity can be clarified later. If you suspect that the patient is presenting late (>12 hours post ingestion), administer NAC and measure the prothrombin time (PT) and a transaminase such as AST. The PT is the earliest serum marker of hepatic injury, followed by transaminases, which begin to rise as early as 16 hours following ingestion. Don't be falsely reassured by a falling acetaminophen level. The parent compound, acetaminophen, may be falling, but the unmeasured toxic metabolite, NAPQI, is certainly rising. A toxic four level of 150 mcg/ml can fall to a therapeutic level (<20) in just 11 hours, so a patient who presents late with a normal acetaminophen level can still develop serious or even lethal hepatotoxicity.

Many toxicologists feel that because young children are more resistant to acetaminophen toxicity, it may not be necessary to treat toddlers if the level is less than 200. Certainly if the level is 149 or less, I would not repeat the level or worry about missing the exact peak in a child. The level of 150 was already set low so as not to miss any patients with potential liver toxicity. Only 25 percent of adults with a level >200 mcg/ml will develop hepatic toxicity.

NAC has recently been shown to reduce the risk of contrast nephropathy. Contrast media are the leading cause of drug-induced renal failure in hospitals. Older patients with elevated creatinine (>1.5) or diabetes mellitus are at increased risk. Two doses of 600 mg of Mucomyst given 12 hours apart—starting the day before a contrast study—reduced the incidence of contrast nephropathy from 21% to 2%. It remains to be proven whether a single dose administered immediately before a contrast study or shortly after has any benefit. Adequate hydration of the patient (intravenous flush of 500-1000 cc before the study if the patient can tolerate a fluid load) remains the best way to avoid renal injury.

6. **Flumazenil (Romazicon®)**, should not be used routinely to awaken an unconscious patient. Although flumazenil will reverse benzodiazepine toxicity, it is most useful in reversing the therapeutic doses used for procedural sedation. Unfortunately, most overdoses are polydrug with more than one CNS depressant, so flumazenil has failed to find a role in the treatment of the unknown, unconscious overdose patient. Moreover, the solitary benzodiazepine overdose is rarely fatal. Serious complications of flumazenil have now been recognized—including seizures, ventricular arrhythmias and benzodiazepine withdrawal in patients who are addicted. It should not be used if a pro-convulsant drug has been co-ingested. Dozens of common drugs cause seizures in overdose, including tricyclic antidepressants, meperidine, propoxyphene, carbamazepine, MAO inhibitors, cyclosporine, chloral hydrate, cocaine, isoniazid, and cyclobenzaprine. If partial reversal of benzodiazepine intoxication is deemed necessary, in order to prevent aspiration, avoid intubation, or reduce time in ICU, then the smallest possible dose—0.05-0.1 mg—should be diluted in 10 cc saline or D5W and given slowly IV over several minutes. Meaningful goals are respiratory sufficiency and verbal responsiveness, not complete arousal.

7. **Dopamine** is still in. For over two decades this has been the most popular drug for treating hypotension of most etiologies. However, it is not the drug of choice for every case of toxin-induced hypotension. Dopamine requires conversion to a vasoactive catecholamine. It may be ineffective or even contraindicated in some overdoses. For example, it is ineffective for treating the hypotension associated with Antabuse reactions. Conversion of dopamine into norepinephrine is blocked. Many overdoses such as cocaine, amphetamine, and tricyclic antidepressants cause catecholamine depletion making dopamine less effective. Dopamine is also contraindicated in toxicity associated with MAO inhibitors where it is either ineffective or can cause adrenergic storm. If dopamine is used for toxin-induced hypotension, it should be used in higher doses (>10 mcg/kg/min) and rapidly titrated and promptly discarded if no effect is achieved. Increase the dopamine infusion in 5 mcg/kg/min increments every 5-10 min until the desired blood pressure (usually 90 mm Hg) is achieved. Infusion rates in excess of 50 mcg/kg/min are sometimes needed. **Norepinephrine**, brand name Levophed®, may be a more effective vasopressor in some cases. Norepinephrine acts directly, requiring no conversion. It is the pressor of choice for tricyclic antidepressant hypotension. High doses may be needed so rapid titration is advisable. Ephedrine or phenylephrine should be considered if the poisoned patient is pregnant because those two drugs cause less uterine vasoconstriction. A new antidote for hypotension secondary to beta blocker or calcium channel blocker overdose has been validated: **insulin**. Infusion of 0.5-1.0 u/kg/hr increases myocardial contractility, cardiac output, and blood pressure. Adults on insulin drips usually require 15-30 gms glucose/hour (D10 or more).

8. **Phenytoin (Dilantin®)** is out. For the treatment of drug and toxin-induced seizures phenytoin is often ineffective. In the case of theophylline, it actually worsens seizures. **Benzodiazepines** are in. They are the drugs of choice for toxin-induced seizures. They are safe, effective and inexpensive, as well as familiar to all clinicians. In the case of cocaine or amphetamine intoxication, they not only treat seizures but also exert a central sympatholytic effect and thereby ameliorate the hypertension and tachycardia associated with these drugs. If benzodiazepines alone are ineffective, barbiturates should be administered next. If seizures are refractory, then **pyridoxine** should be empirically given in a dose of 5 grams. Pyridoxine is especially effective in isoniazid-induced seizures and those induced by monomethyl hydrazine mushrooms (*Gyromitra* species).

9. **Type 1a and 1c antiarrhythmic drugs** are out. These drugs affect the sodium channels which are already poisoned in many overdoses so they worsen AV conduction and exacerbate ventricular arrhythmias. 1a drugs to avoid include quinidine, procainamide and disopyramide. 1c drugs include encainide, flecainide and propafenone. **Lidocaine** is a class 1b drug and is still in favor. According to the most recent ACLS guidelines, "lidocaine is the antiarrhythmic of choice in most cases of drug-induced monomorphic VT or VF." However, the antiarrhythmic that is in is **sodium bicarbonate**. The list of cardiotoxic overdoses for which bicarbonate is effective is growing. Sodium bicarbonate should be considered for any toxic wide-complex tachycardia. Sodium bicarbonate reverses the membrane stabilizing effects of various toxins and counteracts QRS widening as well as AV block and hypotension. The goal is an arterial pH of 7.50 to 7.55. Bicarbonate should be considered in the following overdoses: TCA's, cyclobenzaprine, orphenadrine, procainamide, disopyramide, quinidine, quinine, chloroquine, encainide, flecainide, propafenone, mexiletine, amantadine, thioridazine, mesoridazine, carbamazepine, cocaine, bupivacaine, propoxyphene, diphenhydramine, chlorpheniramine, pyrilamine, arsenic, and taxine (yew plant ingestion). Another antiarrhythmic drug to consider in toxin-induced VT or VF is **magnesium sulfate**, especially when QT prolongation is present. The dose is 2 grams in adults and 25 mg/kg in children, administered over 2 minutes.

10. **Pacemakers** are definitely out for treating bradyarrhythmias secondary to digitalis toxicity. Studies have shown a high complication rate—36 percent—when pacemakers are used, because the myocardium is already irritable. Pacemakers may still be needed for treating bradycardias from beta blocker and calcium channel blocker overdose. Digoxin-specific Fab fragments (Digibind® or Digifab®) are definitely in for the treatment of digitalis intoxication. In the past they were reserved for immediately life threatening arrhythmias, but should probably be given earlier. Digibind does not work as quickly as naloxone (Narcan®). It takes many minutes rather than seconds and

definitely should be given whenever pacing is considered. Another indication for Fab fragment treatment is a potassium level greater than 5.0, since rising potassium correlates highly with increasing mortality.

11. Several killing combinations of drugs have been recognized and should be avoided. First, never combine a MAO inhibitor with a selective serotonin re-uptake inhibitor (SSRI) such as Prozac®, or with meperidine, tramadol, dextromethorphan or codeine. The combination can result in the deadly **Serotonin Syndrome**, marked by the rapid onset of rigidity, hyperthermia and altered level of consciousness. MAOI's include Marplan (isocarboxyzid), Nardil (phenelzine), Parnate (tranylcypromine), and Eldepryl (selegiline). Allow at least a two-week washout between MAOI's and SSRI's, TCA's and other antidepressants. Repeated use of meperidine also results in accumulation of its toxic metabolite, normeperidine, which causes seizures. Because of meperidine's drug interactions and toxicity, it may be best to avoid its use entirely in emergency medicine. Second, avoid beta blockers in the setting of cocaine intoxication, especially in patients complaining of chest pain. The combination has been shown to increase blood pressure and cause coronary artery vasoconstriction from unopposed alpha stimulation. In the setting of a cocaine-associated myocardial infarction, benzodiazepines and nitroglycerin should be used first. If chest pain persists, then 1 mg of phentolamine can be given IV.

12. **Ethanol** is **out** for the treatment of ethylene glycol (EG) and methanol poisoning. These chemicals are common ingredients of windshield washer fluid as well as radiator and gas line antifreeze. Though inexpensive, ethanol usually made patients sick (and children hypoglycemic), and it was difficult to maintain therapeutic levels. **Fomepizole (Antizol®)** was approved by the FDA in late 1997 for the treatment of EG poisoning, and in early 2001 for the treatment of methanol poisoning. Fomepizole is a competitive inhibitor of alcohol dehydrogenase, which catalyzes the metabolism of ethylene glycol--itself non-toxic--to toxic metabolites such as glycolic, oxalic, and other acids, which cause a high anion gap acidosis and renal failure. Alcohol dehydrogenase also catalyzes the conversion of methanol to formic acid, which damages the optic nerve, causing blindness. Fomepizole is indicated for suspected EG and methanol poisoning or for levels > 20 mg/dl. Hemodialysis is still recommended for patients whose level exceeds 50 mg/dl. Many case reports and future studies will probably confirm the safety and effectiveness of fomepizole alone for treatment of patients with higher levels of EG or methanol.

13. The **Physicians Desk Reference (PDR)** is **out**. Guidance for overdoses is limited and sometimes outdated. Poison centers are definitely in. Poison centers are manned by full time poison information specialists (nurses or pharmacists) backed up by MD toxicologists. Information is available 24 hours a day at no cost. Regional poison centers all use a computer data base that is updated every three months, thus two years more current than the latest toxicology textbooks. For any poisoning, I recommend you call the Poison Center at 1-800-222-1222 for the most recent updates on poisoning treatment.

14. **Octreotide (Sandostatin®)** is now recommended for the treatment of persistent hypoglycemia secondary to sulfonylurea overdose. It is much more reliable and effective than hypertonic glucose infusion, which often requires a central line and is associated with rebound hyperinsulinemia and hypoglycemia. It works by blocking insulin release from pancreatic islet cells. The dose for adults is 100 mcg subcutaneously q8h x 3 doses. Give children 1-2 mcg/kg. Studies have shown the need for far fewer rescue doses of D50 with octreotide than with hypertonic glucose. The patient should be followed frequently with an Accucheck measurement of blood glucose (q2-4h when awake, q1-2h when asleep).

15. **Carnitine (Carnitor®)** is **in** as a new antidote for valproic acid (Depakote®) intoxication. Valproic acid, formerly just an anticonvulsant, is now commonly prescribed as a mood stabilizer in bipolar disorder and other psychiatric conditions. Valproic acid intoxication depletes the body of carnitine, resulting in hypoglycemia, hyperammonemia, cerebral edema, and death. Carnitine should be administered oral or IV in a dose of 50 mg/kg q6h. Carnitor® is supplied as 330 mg tablets, 1 gram per 10 cc oral solution, or 1 gram/5 cc IV injection. Hemodialysis should also be considered for massive valproic acid ingestions.

16. **Wyeth's rattlesnake antivenom** is **out**. For decades this was the only antidote available to treat North American rattlesnake bites. Unfortunately, it was a whole IgG product derived from horse serum, so allergic reactions and serum sickness were all too common. **CroFab** is now **in**. This new product, manufactured by Protherics, is an ovine (sheep) product, and the active antigen-binding fragment of IgG (Fab) is split off and purified, so allergic reactions are much less troublesome. Four to six vials should be given within 6 hours of envenomation, and 2 vials should be administered at 6-hour intervals for three more doses. The price of progress is substantial: 12 vials cost approximately \$9300.

17. **Lilly's Cyanide Kit** is **out**; **Cyanokit® (hydroxocobalamin)** is **in**. The old product—a combination of amyl nitrite, sodium nitrite, sodium thiosulfate--was not only cumbersome to administer but also caused methemoglobinemia and hypotension, effects which dangerously limit oxygenation and perfusion. The new product, also known as Vitamin B12a, binds cyanide into a relatively harmless complex that can be excreted in the urine. Cyanokit became available in the United States early in 2007. Ten-year studies of its use in France demonstrated increased survival of smoke inhalation victims when administered prehospital. Because cyanide levels are unavailable in most clinical settings, Cyanokit should be administered empirically to suspected victims of severe cyanide intoxication, who tend to be hypotensive (<90 mm Hg), acidotic (pH < 7.2, lactate > 10), and unconscious (GCS < 8). Side effects are mild: temporary red-staining of urine, skin, and mucosa; increased blood pressure, nausea, headache, and occasional, usually mild allergic reactions. The initial dose is 5 grams for adults, 70 mg/kg for children.

It's wise to remember, despite impressive progress in treatment, that most poisoning victims are saved by good supportive care rather than by specific antidotes. For most of the 100,000 drugs and chemicals in common use worldwide, no specific antidotes exist.

Finally, for further information on treating victims of intoxication, I recommend reading or referring to the following recent toxicology publications:

1. Olson KR. *Poisoning and Drug Overdose*, 5th edition, McGraw Hill, 2007.
2. Flomenbaum N. *Goldfrank's Toxicologic Emergencies*, 8th edition, 2006.
3. Again, it's best to call the Poison Center at 1-800-222-1222 for the most recent recommendations, as most publications are 2-3 years behind current practice.

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