Treatable drug overdoses

Modern research in pharmacology has provided remarkable new treatments for the drug overdose patient. The recent approval of the antidigoxin antibody for treatment of digoxin poisoning (Digibind, Burroughs Wellcome) is the most recent example of a drug that can dramatically reverse an otherwise fatal overdose.[1] This new therapeutic agent joins well-established drugs such as naloxone (Narcan) as a specific antidote able to rapidly and effectively reverse a drug intoxication with minimal risk.

See also the case report by Verilli et al (pp 289–295)

Other treatments for drug overdose have developed from an understanding of drug metabolism. As the review of ethylene glycol poisoning in this issue notes, ethanol can effectively block the metabolism of ethylene glycol to its toxic metabolites, glycolic, glyoxylic, and oxalic acids. In fact, it is these toxic metabolites that are responsible for the severe metabolic acidosis and organ toxicity associated with ethylene glycol ingestion. The reason that ethanol can successfully block ethylene glycol metabolism is that ethanol has a 100-fold greater affinity for the alcohol dehydrogenase enzyme, which metabolizes both compounds. Therefore, almost any amount of ethanol can block metabolism of large quantities of ethylene glycol. In the absence of ethanol, acid production may reach 150 mEq/hr, rapidly overwhelming body buffering capacity. Because of the continued production of acids, the consequences of the overdose become worse as time goes on.[2] Early recognition of the problem and treatment with a can of beer or a shot of whiskey can be lifesaving. In the case presented, recognition of the clinical problem was delayed for many hours.

The clinician dealing with the drug overdose patient should have a hierarchy of diagnoses in mind when he confronts the individual patient. Some problems must be recognized immediately because delay in recognition and treatment will quickly result in death or permanent disability of the patient. The three most common overdoses for which this is the case are cyanide, carbon monoxide, and insulin poisoning. These three poisonings are catastrophic because they deny either oxygen or glucose to the brain, with rapid and permanent neurologic consequences. Furthermore, specific therapies are available. In the case of carbon monoxide, the most practical therapy is intubation followed by ventilation with 100% oxygen. For cyanide, the therapy involves using sodium nitrite to convert a portion of the hemoglobin in red cells to methemoglobin. The ferric iron in methemoglobin will pull the cyanide from the cells where it is interfering with oxidative metabolism. Glucose, of course, is the antidote for insulin poisoning.

After this category of intoxication, there are about a dozen drugs for which specific therapy can change the morbidity and mortality of the overdose. As noted above, the toxic alcohols ethylene glycol and methanol are treated with ethanol infusion and hemodialysis. The narcotic antagonist naloxone is a pure antagonist with a high affinity for the morphine receptor so that doses as small as 2 mg can reverse 50 mg to 100 mg of a pure agonist such as morphine or heroin. Interestingly, when the partial agonist, partial antagonist drugs propoxyphene (Darvon) or pentazocine (Talwin) are taken in overdose, much higher quantities of naloxone are required because of the higher receptor affinity of these partial agonists.

The analgesic acetaminophen (Tylenol) can destroy the liver when taken in overdose. A remarkable series of studies in animals led to the current effective use of N-acetylcysteine for acetaminophen overdose. In mice, acetaminophen was shown to be metabolized in part via a cytochrome P-450 pathway, and the reactive metab-

olites formed by this pathway were reduced to benign compounds by glutathione. In overdose, however, the supply of glutathione was exhausted and the reactive metabolites bound to the liver and destroyed it. By providing a sulfhydryl-containing glutathione equivalent, such as cysteamine or N-acetylcysteine, the researchers showed that liver damage and death could be prevented.[3] As with all poisonings made worse by metabolism, early intervention is critical and the initial loading dose of N-acetylcysteine is certainly the most important.

Anticholinergic poisoning with atropine, scopolamine, or tricyclic antidepressants is common. Although the central and peripheral cholinesterase inhibitor physostigmine can reverse signs of anticholinergic poisoning by increasing the available acetylcholine, such therapy is dangerous because physostigmine can induce seizures and can complicate an already dangerous situation. Physostigmine is in no way a specific diagnostic test for atropinic overdose. Because acetylcholine is an excitatory neurotransmitter, it can induce increased neural activity after a variety of drug overdoses. The use of physostigmine should be discouraged. Organophosphosate insecticides and nerve gases such as Soman work as cholinesterase inhibitors. Very high doses of atropine up to 100 mg may be needed to dry secretions produced by the use of these compounds. Pralidoxine can sometimes reverse the skeletal muscle blockade associated with anticholinesterase intoxication. Heavy metals such as mercury, lead, copper, and iron may be removed with chelating agents such as D-penicillamine, British anti-Lewisite, and deferoxamine. The dopamine-blocking actions of antipsychotic drugs such as chlorpromazine (Thorazine) or haloperidol (Haldol) can be ameliorated to some extent by anticholinergic drugs including diphenhydramine (Benadryl).

Most other drugs taken in overdose including the sedative hypnotics are best managed by supportive care. Hemodialysis may have value in salicylate and phenobarbital overdoses, but most of these cases can be managed conservatively. Charcoal hemoperfusion has received a good deal of attention as a technique for removing drugs taken in overdose.[4] Although the rate of drug removal can be accelerated two- to three-fold over that spontaneously occurring, this rate of accelerated drug removal usually does not justify the use of this technique over simply supporting the patient and waiting for time to pass. One exception to the use of charcoal hemoperfusion might be in the case of theophylline overdose with a long-acting theophylline preparation like Theodur. With this agent, drug levels may continue to rise perhaps to dangerous levels even after the patient is admitted to the hospital. Because rising levels present an increased risk of seizures and death, it may be wise to try to bring the level down as quickly as possible. Even with charcoal hemoperfusion, however, the rate of elimination is only two- to three-fold greater than that by metabolism alone. Another technique for drug removal is the use of continuous oral charcoal administration to draw the drug from the bloodstream back into the gut. This therapy has been shown to increase the removal of drugs such as phenobarbital by up to a factor of two.[5] Although a more benign treatment than charcoal hemoperfusion, this method is of limited clinical value because overdose patients often have a paralytic ileus, and the administration of charcoal, fluids, and sorbitol may lead to electrolyte disturbances.

Deciding what makes a good drug antidote or drug removal technique can be difficult and may be a matter of opinion. The digoxin antibody is an example of a major breakthrough in drug therapy because that antibody shortens the risk of sudden death from a matter of days to a few minutes. The use of ethanol and hemodialysis in the methanol and ethylene glycol overdoses is absolutely indicated because there is no other way except prolonged diuresis to get rid of the alcohols whose metabolism leads to toxic and potentially fatal consequences. On the other hand, drug removal techniques like charcoal hemoperfusion that accelerate the removal of a drug by a factor of two can rarely justify the risk of anticoagulation and the cost of the hemoperfusion methodology.

Clever use of pharmacologic agents and manipulations of drug metabolism have provided a number of lifesaving treatments for drug overdose. The problem for the practicing physician is first to recognize the overdose and then to intervene promptly. The physician must be willing to resist the temptation to use interventions of marginal value, like charcoal hemoperfusion, in patients with sedative hypnotic overdose. New therapies, such as immunotherapy for botulism poisoning and refined antibodies for snakebite, are likely in the near future. Refined understanding of drug action and metabolism should con-

tinue to yield new treatments for perplexing drug overdose problems.

References

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