Review Article

Current Views on Antidotal Therapy in Managing Cases of Poisoning and Overdose

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Abstract
While it is an acknowledged dictum that in poisoning or overdose cases, the emphasis must be on general management comprising supportive measures than the use of specific antidotes in the vast majority of cases, it is nevertheless true that there are some instances where the timely use of a specific antidote or antagonist will dramatically reverse or at least halt the progression of toxicity. For this reason, and also because the indications and the exact manner in which antidotes must be used could be controversial or unfamiliar to the physician, an attempt has been made to review the current concepts on antidotal therapy of poisoning. There is enough evidence that the proper use of specific antidotes when combined with general supportive care does reduce the morbidity and mortality associated with severe poisonings. Common antidotes used in a hospital setting have been discussed in some detail.

INTRODUCTION

In the ancient days, a variety of exotic and even bizarre drugs and potions were suggested as antidotes to various poisonous substances. These antidotes generally referred to as theriacs (Greek), included concoctions of wild thyme, aniseed, fennel, parsley, etc. They were reputed to make people “poison-proof”, especially against bites of venomous animals, the commonest variety of poisoning in those days. The quest for a universal antidote began with the work of the Roman King Mithridates VI of Pontus (132-63 B.C.). He suffered from a paranoid fear of being poisoned by his enemies and performed several toxicity experiments on hapless slaves and criminals, and finally came up with a concoction of 36 ingredients which came to be known as Mithridatum. Regular daily intake of this mixture was supposed to protect against all poisons. Later, the mithridatum was “improved upon” by Andromachus (A.D 37-68) the physician to emperor Nero, who increased the number of ingredients to 73 and proclaimed that it was the best antidote ever made. In fact experiments were conducted on fowl to demonstrate its efficacy, though the exact methodology followed in these experiments may not have been as rigorous as today’s scientific practice! Subsequently, several more theriacs were formulated and enjoyed great popularity as effective antidotes well into the Middle Ages. It was only in the 18th century that for the first time the actual efficacy of these concoctions was questioned. William Heberden published a critical analysis titled Antitheriaka: An Essay on Mithridatum and Theriaka in 1745.

Activated charcoal had its beginnings in the 5th century B.C., when the first adsorbent clay called Serra sigillata obtained from a particular hill on the Greek island of Lemnos was promoted as a universal antidote. This clay was formulated with goat’s blood to make it into a paste. Other substances touted as universal antidotes in ancient times included unicorn horns (actually obtained from rhinoceros), and bezoar stones consisting of gastric or intestinal calculi of goats or cows, impregnated with hair and calcium phosphate.

The principle of modern day charcoal adsorption was enunciated for the first time by Scheele (1773) and Lowitz (1785). The antidotal properties of charcoal were demonstrated by a series of heroic self-experiments conducted in public by French chemist M. Bertrand in 1813. In the 1840s, Garod performed the first controlled study of charcoal when he examined its efficacy on a variety of poisons in animal models. The first charcoal efficacy studies in humans were performed by the American physician B. Rand in 1848. In 1900, the Russian investigator, Obstrejko demonstrated that treating charcoal with super-heated steam significantly enhanced its adsorbing power. This came to be called “activated charcoal.” It finally heralded the dawn of scientifically authentic antidotal therapies, and the end of the era of potions and concoctions imbued with mythical powers.

In the majority of cases of acute poisoning, all that is required is intensive supportive therapy. Specific antidotes are rarely necessary, besides the fact that only a few genuine antidotes exist in actual practice, though there is no denying...
the dramatic results that can be achieved with some of them in appropriate circumstances. Proper antidotal therapy can be life-saving in some situations. Unfortunately, the infrequent presentation of poisoned victims requiring specific antidotes, coupled with the relatively high cost of many of these drugs has resulted in many hospitals stocking inadequate quantities of even the most commonly required antidotes.7

Antidotes work in any one of a number of ways. Common modes of action are as follows:

1. Inert complex formation - Some antidotes interact with the poison to form an inert complex which is then excreted from the body e.g., chelating agents for heavy metals, Prussian Blue for thallium, specific antibody fragments for digoxin, dicobalt edetate for cyanide, etc.

2. Accelerated detoxification - Some antidotes accelerate the detoxification of a poison, e.g., thiosulfate accelerates the conversion of cyanide to non-toxic thiocyanate, acetylcysteine acts as a glutathione substitute which combines with hepatoxic paracetamol metabolites and detoxifies them.

3. Reduced toxic conversion - The best example of this mode of action is provided by ethanol which inhibits the metabolism of methanol to toxic metabolites by competing for the same enzyme (alcohol dehydrogenase).

4. Receptor site competition - Some antidotes displace the poison from specific receptor sites, thereby antagonising the effects completely. The best example is provided by naloxone, which antagonizes the effects of opiates at stereo-specific opioid receptor sites.

5. Receptor site blockade - This mode of action is best exemplified by atropine which blocks the effects of anticholinesterase agents such as organophosphates at muscarinic receptor sites.

6. Toxic effect bypass - An example of this type of antidotal action is provided by the use of 100% oxygen in cyanide poisoning.

Table 1 represents a list of genuine antidotes recommended in toxicological practice today. In addition, there are certain therapeutic agents which are not antidotes as per the accepted definition, but which through their importance and sometimes specific role in the treatment of poisons, border on the concept of “antidotes.” Table 2 represents a list of such substances. Unfortunately in India, cumbersome governmental regulations and a lack of economic incentives for manufacturers have restricted availability of a substantial number of these life-saving drugs. As a result, doctors still use some substances which are more readily available as antidotes, but are generally considered obsolete or even dangerous in Western countries (Table 3). It is imperative that medical professionals strive to phase out these obsolete drugs, while working out strategies to

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Main Indication</th>
<th>Other Applications</th>
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</thead>
<tbody>
<tr>
<td>N-Acetylcysteine</td>
<td>Paracetamol</td>
<td>Amanitin</td>
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<tr>
<td>Atropine</td>
<td>Cholinergic agents</td>
<td>—</td>
</tr>
<tr>
<td>Calcium salts</td>
<td>Oxalates, fluorides</td>
<td>Calcium antagonists</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Malignant hyperthermia</td>
<td>Malignant neuroleptic syndrome</td>
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<tr>
<td>Desferrioxamine</td>
<td>Iron, aluminium</td>
<td>Paraquat</td>
</tr>
<tr>
<td>Dicobalt edetate</td>
<td>Cyanide</td>
<td>—</td>
</tr>
<tr>
<td>Digoxin specific antibody fragments</td>
<td>Digitalis glycosides</td>
<td>—</td>
</tr>
<tr>
<td>Dimeracrol</td>
<td>Arsenic</td>
<td>Copper, gold, mercury</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Methanol, ethylene glycol</td>
<td>—</td>
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<tr>
<td>Flumazenil</td>
<td>Benzodiazepines</td>
<td>—</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Beta blockers</td>
<td>—</td>
</tr>
<tr>
<td>Glucose</td>
<td>Insulin</td>
<td>—</td>
</tr>
<tr>
<td>Hydroxocobalamin</td>
<td>Cyanide</td>
<td>Disulfiram, coprin</td>
</tr>
<tr>
<td>4, Methylpyrazole (fomepizole)</td>
<td>Ethylene glycol, methanol</td>
<td>—</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Opiates</td>
<td>—</td>
</tr>
<tr>
<td>Oximes</td>
<td>Organophosphates</td>
<td>—</td>
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<tr>
<td>Oxyn</td>
<td>Cyanide, carbon monoxide, hydrogen sulfide</td>
<td>—</td>
</tr>
<tr>
<td>Oxygen (Hyperbaric) tetrachloride</td>
<td>Carbon monoxide</td>
<td>Cyanide, hydrogen sulfide, carbon</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Copper</td>
<td>Gold, lead, mercury</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Central anticholinergics</td>
<td>—</td>
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<tr>
<td>Phytomenadione (Vitamin K)</td>
<td>Coumarin derivatives</td>
<td>—</td>
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<tr>
<td>Potassium hexacyanoferrate (Prussian Blue)</td>
<td>Thallium</td>
<td>—</td>
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<tr>
<td>Prostamine sulfate</td>
<td>Heparin</td>
<td>—</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Isoniazid</td>
<td>Ethylene glycol, gyrometrine, hydrazines</td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>Cyanide</td>
<td>Hydrogen sulfide</td>
</tr>
<tr>
<td>Sodium thiosulfate</td>
<td>Cyanide</td>
<td>Bromate, chloride, iodine</td>
</tr>
<tr>
<td>Succimer (DMSA)</td>
<td>Lead, mercury</td>
<td>—</td>
</tr>
</tbody>
</table>
Acid.8-10 There have also been some reports suggesting that tetrachloride, chloroform, pennyroyal oil, and even valproic acid, when given later, it can still ameliorate toxicity. NAC also has an additional benefit because of its non-specific antioxidant effects and free radical scavenging properties.

NAC is potentially beneficial following exposure to certain metals such as cobalt.11

In adults, NAC is usually given as a loading dose of 150 mg/kg in 200 mL of D5W infused over 15 minutes, followed by a first maintenance dose of 50 mg/kg in 500 mL D5W infused over 4 hours, followed by a second maintenance dose of 100 mg/kg in 1000 mL D5W infused over 16 hours. If it is decided to give the NAC orally, the patient should receive a 140-mg/kg loading dose (either orally or by enteral tube), and 4 hours later, 70 mg/kg should be given every 4 hours for an additional 17 doses. The solution should be diluted to 5% with a soft drink to enhance palatability.

If hepatic failure supervenes, IV NAC should be administered at a dose of 150 mg/kg in D5W infused over 24 hours and continued until the patient recovers from hepatic encephalopathy,12 or the international normalized ratio (INR) becomes less than 2.0,13 or the patient receives a liver transplant.14

Oral NAC often causes nausea, vomiting, flatus, and diarrhoea; generalized urticaria occurs rarely. Anaphylactoid reactions can occur after IV NAC dosing.15

Atropine

Atropine is a competitive antagonist at both central and peripheral muscarinic receptors, and is effective in the treatment of exposures to muscarinic agonists and acetylcholinesterase inhibitors such as organophosphate and carbamate pesticides, as well as some chemical warfare agents. Like scopolamine (hyoscine), atropine is a tropane alkaloid found in Datura and some other related plants, and has a tertiary amine structure that allows CNS penetration. This is an advantage that some other antimuscarinic agents such as glycopyrrolate, ipratropium, and tiotropium do not have, which are unable to cross the blood-brain barrier.16

Organophosphate and carbamate pesticides, as well as some chemical warfare nerve agents are cholinesterase inhibitors, and prevent the breakdown of acetylcholine by acetylcholinesterase, thereby increasing the concentration of acetylcholine at cholinergic receptors. These receptors are composed of muscarinic and nicotinic components. Muscarinic agonists such as muscarine, methacholine, and pilocarpine stimulate muscarinic receptors, and do not have any effect on nicotinic receptors. Atropine is a competitive antagonist of acetylcholine primarily at muscarinic receptors.17 These receptors are coupled to G proteins

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**Table 2: Adjunctival antidotes**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated charcoal</td>
<td>For most poisons</td>
</tr>
<tr>
<td>Benztropine</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Psychotic states</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Convulsions</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Myocardial depression, vascular relaxation</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Anaphylactic shock, cardiac arrest</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Fluid retention, left ventricular failure</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Psychotic states</td>
</tr>
<tr>
<td>Heparin</td>
<td>Hypercoagulability</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Cerebral oedema, fluid retention</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Convulsions</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Bronchoconstriction</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Metabolic acidosis</td>
</tr>
</tbody>
</table>

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**Table 3: Obsolete antidotes**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper sulfate</td>
<td>Phosphorus</td>
</tr>
<tr>
<td>Cysteamine</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Diethylthiocarbamate</td>
<td>Thallium</td>
</tr>
<tr>
<td>Fructose</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Levallorphan</td>
<td>Opiates</td>
</tr>
<tr>
<td>Nalorphine</td>
<td>Opiates</td>
</tr>
<tr>
<td>Silibinin</td>
<td>Amanitin</td>
</tr>
<tr>
<td>Tocopherol</td>
<td>Paraquat</td>
</tr>
<tr>
<td>Universal antidote</td>
<td>Ingested poisons</td>
</tr>
</tbody>
</table>

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Given the complexity of antidotal management of poisoned patients and problems that can arise in the use of many antidotes, consultation with a medical toxicologist or poison control centre should always be considered. A brief discussion on some of the common specific antidotes follows. Uncommonly indicated or unavailable antidotes have not been discussed.

**N-acetylcysteine**

Although paracetamol possesses an excellent safety profile at therapeutic doses, a rapidly progressive hepatic failure leading to death can occur following large overdoses, when appropriate treatment is delayed. Toxicity results from paracetamol’s metabolism via cytochrome p450 to N-acetyl-p-benzoquinoneimine (NAPQI). At therapeutic doses, NAPQI is detoxified by glutathione to non-toxic conjugates. However, with excess dosing, exhaustion of glutathione reserves occurs, with accumulation of NAPQI, initiating a cascade of events leading to fulminant hepatic failure.

N-acetylcysteine (NAC) prevents NAPQI-induced hepatotoxicity through several mechanisms. Firstly, it acts as a glutathione (GSH) precursor that increases GSH availability, as well as providing inorganic sulfate that enhances paracetamol metabolism through the nontoxic sulfation pathway. NAC also directly converts NAPQI to relatively non-toxic cysteine and intercaptop conjugates, besides reducing NAPQI back to paracetamol, which is then eliminated by other non-toxic routes. NAC also offers additional benefit because of its non-specific antioxidant effects and free radical scavenging properties.

If administered early in the course of exposure, NAC can prevent significant paracetamol-induced toxicity. Even when given later, it can still ameliorate toxicity. NAC also has a role in limiting toxicity caused by glutathione depletion and free radical formation from poisoning due to carbon tetrachloride, chloroform, perryroyal oil, and even valproic acid.8-10 There have also been some reports suggesting that...
and either inhibit adenyl cyclase (M₄, M₅) or increase phospholipase C (M₂, M₄, M₅). They are widely distributed throughout the peripheral and central nervous systems.

A precise dosage regimen of atropine for organophosphate/carbamate pesticide poisoning has never been arrived at for lack of randomized controlled trials, and hence there is considerable confusion. However, the usual practice is to begin atropine in doses of 1-2 mg IV for mild-to-moderate poisoning, and 3-5 mg IV for severe poisoning with altered consciousness. This dose can be doubled every few minutes. The endpoint for adequate titration. Over-administration of atropine can give rise to as an IV infusion every hour, with frequent evaluation and titration. Over-administration of atropine can give rise to hypotension, shock, erythema, and urticaria that occurred when DFO was infused rapidly, resulted in the current recommendations for less rapid IV infusions of DFO not exceeding 15 mg/kg/h. However, higher rates have been administered successfully in critically ill patients without much toxicity.

Acute lung injury (ALI) has been described in the setting of acute iron overdoses following IV administration of DFO (15 mg/kg/h) therapy for >24 hours. The mechanism for development of pulmonary toxicity is unclear, but may be due to excessive DFO chelation of intracellular iron and depletion of catalase, resulting in oxidant damage or generation of free radicals.

DFO therapy is known to result in infections from a number of unusual organisms, including Yersinia enterocolitica, Zygomycetes, and Aeromonas hydrophilia. This may be because the DFO-iron complex acts as a siderophore for their growth.

Cyanide antidotes:

1. Amyl and Sodium nitrites and Sodium thiosulfate—

Amyl and sodium nitrite are highly effective cyanide antidotes; but they must be administered without delay. Amyl nitrite is a volatile liquid which is available in some Western countries in ampoules that can be broken, and the vapour is inhaled by the patient until intravenous sodium nitrite can be begun.

Cyanide acts by binding to the ferric iron in cytochrome oxidase, paralysing energy production throughout the body. However, the ferric iron in methaemoglobin has preferential affinity for cyanide, and combines with it to form cyanmethaemoglobin. This helps to free cyanide from cytochrome oxidase. In order to induce methaemoglobinemia, nitrites are administered, which oxidize the iron in haemoglobin to produce methaemoglobin. There are other agents such as 4-dimethylaminophenol and hydroxylamine, which are also efficient inducers of methaemoglobinemia and can be used as cyanide antidotes. Unfortunately, in India, none of these antidotes are available. Amyl nitrite falls under the category of banned drugs on account of its abuse potential, while sodium nitrite is only available as a laboratory chemical, which is not of pharmaceutical grade.

The usual dose of sodium nitrite in adults is 300 mg (10 mL of 3% solution), which should be given intravenously at a rate of 2.5-5 mL/min. Half this dose can be repeated if symptoms of cyanide toxicity reappear. If amyl nitrite is available, it should be administered first. Break the amyl nitrite ampoule and hold it in front of the patient's mouth for a few seconds. Amyl nitrite should be discontinued when sodium nitrite therapy is begun.

For children, the dose of sodium nitrite is 6-8 mL/m² (~0.2 mL/kg) of 3% sodium nitrite solution intravenously. The administered dose must not exceed 10 mL, or 300 mg. Half this dose can be repeated if symptoms of cyanide toxicity reappear. If amyl nitrite administration is decided upon, the same procedure must be followed as for an adult.

Administration of sodium nitrite should always be followed by sodium thiosulfate. Sodium thiosulfate (which is also available in India only as a laboratory chemical) acts by donating a sulfur entity, which with the help of the enzymes cyanide sulfurtransferase (formerly called rhodanese) and mercaptopyruvate sulfurtransferase, transports sulfane sulfur to bind with cyanide, producing thiocyanate. Thiocyanate is relatively non-toxic, and is harmlessly
require 52 g of hydroxocobalamin to bind 1 g of cyanide.34 Into consideration the molecular weights of each, it would 1 mole of hydroxocobalamin binds 1 mole of cyanide. Taking methaemoglobinaemia must be avoided at all costs.33 Nitrites are also potent vasodilators, and usually cause significant hypotension. Sodium thiosulfate has relatively few side effects, and most of them are minor in nature (mild hypotension, nausea, and vomiting).

Nitrites, while being effective cyanide antidotes, act as double edged swords. It is a fact that methaemoglobinemia is helpful in the treatment of cyanide toxicity, but too much methaemoglobinemia can itself be lethal! Therefore, the nitrite dose must be carefully worked out, and excessive methaemoglobinemia must be avoided at all costs.33 Nitrites are also potent vasodilators, and usually cause significant hypotension. Sodium thiosulfate has relatively few side effects, and most of them are minor in nature (mild hypotension, nausea, and vomiting).

2. Hydroxocobalamin –

Hydroxocobalamin has been used as a cyanide antidote in some European countries, most notably France, for many years, either as a sole agent or in combination with sodium thiosulfate.34 It is not yet being used in India, though it can easily be employed. The mechanism of action is related to its cobalt content which is a known antidotal agent for cyanide. The cobalt in hydroxocobalamin combines with cyanide to form the relatively nontoxic cyanocobalamin.35 Other cobalt chelators, such as dicobalt EDTA have been used in some countries, but their margin of safety is very narrow.30 One mole of hydroxocobalamin binds 1 mole of cyanide. Taking into consideration the molecular weights of each, it would require 52 g of hydroxocobalamin to bind 1 g of cyanide.34 The combined employment of hydroxocobalamin with sodium thiosulfate is synergistic, and is as efficacious as the use of sodium nitrite with sodium thiosulfate.36

The usual dose of hydroxocobalamin suggested is 70 mg/kg (to a maximum of 5-10 g initially) administered intravenously over 30 minutes. This dose can be repeated (up to a maximum total dose of 15 g) as necessary.37 The second and subsequent doses should be administered over a longer period (6-8 hours), except in severe cases. The adult dose of sodium thiosulfate is as explained earlier: 12.5 g (50 mL of 25% solution) administered intravenously as either a bolus injection or infused over 10 to 30 minutes. While hydroxocobalamin has a remarkably low incidence of adverse effects even at massive doses, red discolouration of mucous membranes, plasma, and urine may occur and last from 12 hours to a few days after therapy. Prior exposure to hydroxocobalamin or cyanocobalamin (for treatment of vitamin B12 deficiency) may rarely predispose a patient to allergic reactions, including anaphylaxis.34

Metal chelating agents

Most chelating agents have similar mechanism of action. Soft metal ions, such as Hg2+, Au+, Cu+, and Ag+ have large ionic radii with a large number of electrons in their outer shell. Therefore, they form the most stable complexes with sulfur donors and are referred to as sulfur seekers.38 Chelating agents such as BAL (British Anti Lewisite) form a coordinate bond with the metal by donating a pair of free electrons. Hard metals such as Na+, K+, Mg2+, Ca2+, and Al3+ are referred to as oxygen seekers and form complexes with chelators containing a carbonyl (COO-) group, such as calcium disodium edetate (CaNa2EDTA).39 Borderline metal ions, such as Pb2+, Cd2+, Cu2+, As3+, and Zn2+, prefer nitrogen-donating ligands but will also react with both hard and soft ligands. Antidotes for metal poisoning often contain more than one type of donating group, making them effective for more than one type of metal.39

1. B.A.L (British Anti Lewisite; Dimercaprol)

BAL is available as a yellow, viscous liquid with a sulfur-like odour, in 3-mL ampoules containing 100 mg/mL of BAL, 200 mg/mL of benzyl benzoate, and 700 mg/mL of groundnut oil. It is given by deep intramuscular injection, and is useful in the treatment of toxicity resulting from arsenic, mercury, and lead (in combination with CaNa2EDTA).

The recommended dose of BAL for inorganic arsenic poisoning is 3 mg/kg IM every 4 hours for 48 hours, followed by twice daily for 7-10 days. Alternatively, 3-5 mg/kg IM can be administered every 4-6 hours on the first day, followed by gradual tapering of the dose and frequency. Some investigators suggest decreasing the number of injections by day 2, and termination of therapy within 5-7 days.

For poisoning due to inorganic mercury salts, the dose of BAL is 5 mg/kg IM initially, followed by 2.5 mg/kg every 8-12 hours for 1 day, followed by 2.5 mg/kg every 12-24 hours, for a maximum of 10 days.

The dose of BAL for lead encephalopathy is 75 mg/m² IM every 4 hours for 5 days.40 The first dose of dimercaprol should precede the first dose of CaNa2EDTA by 4 hours. Subsequently, CaNa2EDTA is given IV in a dose of 1500 mg/m²/d (up to a maximum of 2-3 g) as a continuous infusion, or divided into 2-4 doses.

Adverse effects resulting from BAL are dose dependent, and also dependent on urinary pH. Acidic urine leads to dissociation of the BAL-metal chelate, and hence it should be alkalinized with hypertonic NaHCO₃ to a pH of 7.5-8.0.

Common adverse effects comprise pain at the injection site, nausea, vomiting, headache, fever, burning sensation of lips, mouth, throat, and eyes, lacrimation, rhinorrhea, salivation, and myalgia. In some cases, there may be burning and tingling of extremities, toothache, sweating, and rarely chest pain. Hypertension and tachycardia can occur with high doses.41 Doses greater than 25 mg/kg can
give rise to hypertensive encephalopathy with convulsions and coma.

It is important to note that unless hepatotoxicity encountered in a patient is arsenic-induced, hepatic dysfunction is a contraindication to BAL use.

BAL is not useful in methylmercury poisoning, because animal studies have shown a redistribution of mercury to the brain.42

Unintentional IV infusion of BAL can cause fat embolism, lipid pneumonia, and chylothorax.43

2. Calcium disodium edetate (CaNa₂EDTA)

Calcium disodium edetate (CaNa₂EDTA) is practically the only chelating agent that is used in India for the treatment of lead poisoning, though in most Western countries it has been replaced to a large extent by its safer counterpart, succimer (2,3-dimercaptosuccinic acid). There is evidence to show that CaNa₂EDTA is capable of reducing blood lead concentrations, enhancing renal excretion of lead, and reversing the effects of lead on haemoglobin synthesis,44 but no rigorous clinical studies have ever been performed to evaluate its actual efficacy.45 One study of children with moderately high blood lead levels, who were given 5 days of CaNa₂EDTA, showed hardly any difference in blood lead, bone lead, or erythrocyte protoporphyrin concentrations, when compared to pretreatment values.46 The once popular CaNa₂EDTA mobilization test which was recommended as a diagnostic aid for assessing the potential benefits of chelation therapy has now been abandoned as useless.47

The recommended dose of CaNa₂EDTA depends on the patient’s body surface area or weight, the severity of the poisoning, and the status of renal function. For patients with lead encephalopathy, the dose of CaNa₂EDTA generally recommended is 1500 mg/m²/d by continuous IV infusion, starting 4 hours after the first dose of dimercaprol. Combined dimercaprol and CaNa₂EDTA therapy is given for 5 days, followed by cessation for 2 to 4 days, which permits lead redistribution. Blood lead concentration should be measured 1 hour after the CaNa₂EDTA infusion is discontinued, to avoid falsely elevated blood lead concentration determinations.

In children without evidence of lead encephalopathy, the dose of CaNa₂EDTA is 1000 mg/m²/d, in addition to dimercaprol at 50 mg/m² every 4 hours. In most Western countries however, succimer is the chelator of choice in lead-poisoned children without encephalopathy.48 CaNa₂EDTA should be administered at 0.5% concentration by continuous IV infusion over 24 hours in 5% dextrose or 0.9% NaCl. Concentrations greater than 0.5% may lead to thrombophlebitis and must be avoided. In children with lead encephalopathy, BAL must be started 4 hours prior to CaNa₂EDTA.49

The main adverse effect of CaNa₂EDTA is related to renal function. Therefore, it is important to monitor renal function closely during CaNa₂EDTA administration, and to adjust the dose and schedule accordingly. Nephrotoxicity can be minimized by taking care to ensure that the total daily dose of CaNa₂EDTA does not exceed 1 g in children or 2 g in adults, as far as possible. Other, less common adverse effects include malaise, loss of appetite, chills, fever, myalgia, dermatitis, headache, increased urinary frequency, rhinorrhea, lacrimation, glycosuria, and anaemia.41

Extravasation may result in the development of painful calcnosis at the injection site. Depletion of endogenous metals, particularly zinc, iron, and manganese, can result from chronic therapy.49

3. Succimer (2,3-Dimercapto Succinic Acid)

Chinese investigators first reported on the beneficial effects of IV succimer in the treatment of lead and mercury poisoning, after which several studies were conducted around the world, which finally led to FDA approval in 1991 in the United States of America for the treatment of lead-poisoning.50-52 Since then, a large body of evidence has accumulated clearly indicating the efficacy of succimer, and its superiority over CaNa₂EDTA in the treatment of lead poisoning.53-55

Succimer can also be used for the treatment of arsenic and mercury toxicity.56,57 There is one study from India demonstrating the efficacy of succimer in arsenic poisoning.58 The tragedy is that succimer is at present not available in India, and has to be imported from the West. In the US, succimer is available under the brand name Chemet®, in the form of 100-mg bead-filled capsules. For patients who find it difficult to swallow the capsule, it can be opened out, and the contents sprinkled onto juice, or ice cream, or soft food. The recommended dose is 350 mg/m² in children, 3 times a day for 5 days, followed by 350 mg/m² twice a day for 14 days. In adults, it can be administered at 10 mg/kg, following the same regimen as above.

Succimer is generally well tolerated, and does not appear to have any serious adverse effects.60 Common problems are gastrointestinal in nature, comprising nausea, vomiting, flatus, diarrhoea, and a metallic taste. Rarely, chills, fever, urticaria, rash, reversible neutropenia, and eosinophilia may occur.61,62

Oximes

The most commonly used oxime for organophosphate pesticide (OP) poisoning in India is pralidoxime (2-hydroxyiminomethyl-1-methyl pyridinium chloride, pyridine-2-aldoxime methiodide, P₂AM or PAM). The others, axonime and obidoxime are not available in India. Pralidoxime must invariably be administered together with atropine in the management of OP poisoning.

Organophosphate pesticides are powerful inhibitors of carboxylic esterase enzymes, especially acetylcholinesterase, which is found in red blood cells, nerve cells, and skeletal muscle, as well as plasma cholinesterase or butyrylcholinesterase, which is found in plasma, liver, heart, pancreas, and brain). The former is often referred to as true cholinesterase, and the latter as
pseudocholinesterase. Organophosphorus pesticides bind to the serine-containing esteratic site of either enzyme, inactivating it by phosphorylation.63 This results in the accumulation of acetylcholine at muscarinic and nicotinic synapses of the central and peripheral nervous systems, leading to cholinergic excess. The enzyme is subsequently inactivated, and may undergo one of three reactions: hydrolysis of the phosphorylated enzyme; reactivation by a strong nucleophile, or aging, which is a process that renders the phosphorylated molecule inactive.

Hydrolysis of OP compounds can be quite slow, and is generally considered to be insignificant in contrast to the rapid hydrolysis of most carbamate (CM) pesticides. Oximes have the ability to reactivate cholinesterase bound to OP compounds.64 Pralidoxime is capable of a nucleophilic attack on the phosphate moiety, successfully competing for it and releasing it from the acetylcholinesterase enzyme.65 This enables the restoration of enzymatic function. Previously it was believed that pralidoxime therapy can succeed only if started within 24-48 hours of exposure to the OP compound, and that later, the acetylcholinesterase would be irreversibly inactivated. But recent information suggests that oximes can be beneficial even when started much later.66,67

In the case of carbamate (CM) poisoning, the acetylcholinesterases which are inactivated, usually get reactivated spontaneously over a few hours, though in severe cases, symptoms may persist for 24 hours or more.68 Pralidoxime is therefore rarely required for carbamate poisoning; but it is important to note that it is NOT contraindicated as was previously suggested. Such an erroneous conclusion was based solely on data derived from the study of a single carbamate (carbaryl). There are several studies which demonstrate the beneficial effects of oximes in treating most kinds of carbamate exposure.69 Pralidoxime should therefore not be withheld in a seriously poisoned patient out of concern that a carbamate is involved.70

Though obidoxime is not available in India, it is actually 10-20 times more effective in reactivating acetylcholinesterase than is pralidoxime.71 To improve the central effects of pralidoxime, a new derivative known as pro-2-PAM, which is actually the dihydropyridine derivative of pralidoxime was synthesized and introduced into practice. It has the ability of passing through the blood-brain barrier. After passage across the membrane, in vivo oxidation converts it to its active form, demonstrating a 13-fold higher level of PAM in the brain, than when PAM itself is administered directly.72 Some organophosphates which are used as chemical warfare nerve agents can only be tackled by the H series of oximes (named after Hagedorn). They demonstrate far greater efficacy against sarin, VX and some other newer pesticides.73-75 They are however not as efficacious in traditional OP poisoning.

There is a great deal of controversy regarding the exact dosage regimen for pralidoxime in OP poisoning. Conventionally, the recommended initial adult dose is 1-2 g in 100 mL of 0.9% saline given IV over 15-30 minutes. The paediatric dose is said to be 20-40 mg/kg (up to a maximum of 2 g) given IV over 30-60 minutes.76 These doses can be repeated in 1 hour if muscle weakness and fasciculations are not controlled. Additional doses may be given every 4-8 hours if signs of poisoning keep recurring. An alternative regimen involves administration of a loading dose of pralidoxime, followed by a continuous IV infusion.77 Severe cases may require a continuous infusion of 500 mg/h in adults and 10-20 mg/kg/h (up to 500 mg/h) in children. Pralidoxime therapy should be continued for a minimum of 24 hours after symptoms have resolved.

Pralidoxime does not have serious adverse effects when given at recommended doses. There may be mild vertigo, diplopia, and hypertension in some cases.78 Rapid IV administration can rarely cause sudden cardiac and respiratory arrest because of laryngospasm and muscle rigidity.79

Ethanol

Ethanol is used as an antidote in those cases where a particular toxic substance is metabolized by alcohol dehydrogenase, for e.g., methanol and ethylene glycol. It acts by competitive inhibition as a result of which toxic metabolites of methanol and ethylene glycol are not formed, and the parent compound is excreted unchanged. The affinity of ethanol for alcohol dehydrogenase is 67 times that of ethylene glycol and 15.5 times that of methanol.80 A relatively smaller quantity of ethanol is required to inhibit the metabolism of ethylene glycol, when compared to the amount required to block the metabolism of methanol, since the affinity of ethylene glycol for alcohol dehydrogenase is much less than that of methanol.81 The usual recommendation is to maintain a serum ethanol concentration of 100 mg/dL, or at least a 1:4 molar ratio of ethanol to methanol or ethylene glycol, whichever is greater.82

Ethanol can be given orally or intravenously. The usual concentrations recommended for oral and IV administration are 20-30% and 5-10% respectively. Intravenous administration is always preferable since it leads to complete absorption, does not produce GI effects, and can be administered to an unconscious patient. The main problem is the difficulty in obtaining and preparing an IV ethanol solution. The amount of ethanol absorbed after oral administration depends on a number of factors, such as nutritional status, rate of gastric emptying, sex and age of the patient, genetic factors, chronic alcoholism, etc. Adequate concentration is usually achieved with 0.8 g/kg of ethanol given orally over 20 minutes.83

Mode of administration84

10% ethanol at a dose of 10 ml/kg administered IV over 30 minutes, followed by 1.5 ml/kg/hr, so as to produce and maintain a blood ethanol level of 100 mg/100 ml. Blood ethanol levels should be maintained at 100 to 130 mg/100 ml (21.7 to 28.2 mmol/L). Alternatively, 1 ml/kg of 95% ethanol in fruit juice (180 ml) can be given orally over 30 minutes. For maintenance, administer 0.17 to 0.28
Flumazenil is a competitive antagonist for benzodiazepine receptors. While it does not directly reverse the respiratory depression induced by benzodiazepines, it is very effective in reversing CNS depression. An important point to note is that since the duration of action of flumazenil is shorter than that of most benzodiazepines, repeat doses are usually necessary at relatively short intervals. Flumazenil is also said to be effective for zolpidem and zaleplon overdoses, which interact with a subclass of benzodiazepine receptors.87,88

Even though flumazenil is very effective in benzodiazepine overdose, its actual use in practice is controversial, primarily because of the low morbidity and mortality associated with benzodiazepine poisoning. One double-blind controlled study covering 702 cases over a 14-year period demonstrated a mortality of only 0.7%.89 In fact, the mortality rate for nonbenzodiazepine-related overdoses was more (1.6%). Therefore the current view is to use flumazenil only in the small minority of "seriously overdosed" patients, and to rely only on supportive measures in all other cases. If it is decided to be given, the usual dose is 0.1 mg/min by slow IV titration, to a total dose of 1 mg. Re-sedation may occur in half hour to 2 hours, and re-administration of flumazenil may be necessary.

The main problems associated with flumazenil use include precipitation of seizures in benzodiazepine-dependent patients, unmasking of arrhythmias in patients who coingest benzodiazepine with tricyclic antidepressants, and the need for frequent re-administration.

**Naloxone**

Naloxone is a pure competitive opioid antagonist at the mu (µ) receptor, while nalmefene and naltrexone act at the kappa and delta receptors. Naloxone is most commonly used in opioid overdose, and is available in India. The usual dose is 0.05 mg IV to begin with, increasing it as indicated to 0.4 mg, 2 mg, and up to a maximum of 10 mg. Continuous monitoring is necessary for the return of respiratory depression, and if this happens, repeated doses of naloxone will have to be given. Alternatively, another bolus followed by a continuous infusion may be embarked upon.90 Naloxone is best administered intravenously in normal saline. It can also be given by intramuscular, subcutaneous, endotracheal, intranasal, and intralingual routes, as well as in the form of nebulization.

Adverse effects associated with naloxone (excluding withdrawal and re-sedation), are rarely encountered. Patients tolerant to opioids may manifest withdrawal reaction, characterized by yawning, lacrimation, sweating, rhinorrhea, piloerection, mydriasis, vomiting, diarrhoea, etc. There are rare reports of acute lung injury (non-cardiogenic pulmonary oedema), hypertension, and cardiac arrhythmias.

Naltrexone is administered orally in chronic opioid abusers following detoxification, to maintain opioid abstinence. Nalmefene is a new entrant whose duration of action falls between that of naloxone and naltrexone.

**Methylene Blue**

Methylene blue is a very effective antidote for toxins causing methaemoglobinemia. Symptomatic methaemoglobinemia usually occurs when the methaemoglobin level exceeds 20%, and in such cases, methylene blue is given at a dose of 1-2 mg/kg IV over 5 minutes, followed immediately by a fluid flush of 15-30 mL to minimize local pain. The onset of action is rapid, but repetitive dosing may be required in association with GI overdoses.
decontamination, in the case of drugs such as dapsone, which is one of the commonest agents implicated in methaemoglobinemia in the toxicological setting.\textsuperscript{93}

It is important to note that methylene blue has the paradoxical ability of itself inducing methaemoglobinemia when given in excess. This means that there is normally an equilibrium between the ability of methylene blue to oxidize haemoglobin directly to methaemoglobin, and to reduce methaemoglobin to haemoglobin through the NADPH and NADPH methaemoglobin reductase pathway, and leukomethylene blue production. The equilibrium gets disturbed when excessively large doses of methylene blue are administered or when the NADPH methaemoglobin reductase system is abnormal.\textsuperscript{92} Other major adverse effects of methylene blue include tachypnoea, chest discomfort, bluish discolouration of skin and mucous membranes, paraesthesias, restlessness, nausea, and vomiting. Urine and vomitus usually have a bluish tinge. Intravenous methylene blue is quite painful, and may cause local tissue damage even in the absence of extravasation.\textsuperscript{93}

Vitamin K

Vitamin K is an essential fat-soluble vitamin, and is actually a generic term that includes two distinct natural forms: vitamin K\textsubscript{1} (phytonadione, phylloquinone) and vitamin K\textsubscript{2} (menaquinones) comprising a series of compounds with the same 2-methyl-1,4-naphthoquinone ring structure as phylloquinone, but with a variable number (1-13) of repeating 5-carbon units on the side chain. Most of the dietary vitamin K is in the form of phytonadione.

Phytonadione is antidotal in nature for reversing elevated prothrombin time/international normalized ratio (INR) induced by toxins or drugs such as warfarin, or long-acting anticoagulant rodenticides (LAARs), such as brodifacoum. It is usually given orally, because IV administration of vitamin K\textsubscript{1} is associated with anaphylactoid reactions. Subcutaneous administration may be considered if a patient is unable to tolerate oral vitamin K, and is not seriously poisoned enough to necessitate IV vitamin K.\textsuperscript{94}

Oral anticoagulants are vitamin K antagonists that interfere with the vitamin K cycle, causing the accumulation of vitamin K 2,3-epoxide, an inactive metabolite. Warfarin is a strong irreversible inhibitor of the dithiol-dependent vitamin K reductases (epoxide reductase and quinone reductase), which maintain vitamin K in its active (quinol, hydroquinone) form.\textsuperscript{95} The superwarfarins (long acting) are even more potent inhibitors. NADPH-dependent quinone reductase is an enzyme capable of reducing vitamin K\textsubscript{2} to its active hydroquinone form, but it is incapable of regenerating vitamin K from vitamin K epoxide following carboxylation of the coagulation factor. Thus, in the presence of warfarin or superwarfarin, additional vitamin K\textsubscript{1} must be administered to supply this active cofactor for each and every carboxylation step, as it can no longer be recycled.\textsuperscript{96}

The usual dose of vitamin K\textsubscript{1} in LAAR poisoning varies from 50 to 250 mg daily for weeks to months.\textsuperscript{97} The recommended starting dose is 25 to 50 mg orally, 8\textsuperscript{th} or 6\textsuperscript{th} hourly, for one or two days. The INR should be constantly monitored, and the dose adjusted if necessary. When the INR drops below 2, a downward titration of vitamin K\textsubscript{1} can be made, based on factor VII analysis. In the case of brodifacoum poisoning, serum levels of brodifacoum may be helpful in deciding the duration of treatment.\textsuperscript{98}

Intravenous administration of vitamin K\textsubscript{1} should be reserved for life-threatening bleeding. In such a case, the patient may be supplemented with prothrombin complex concentrate. If it is not available, fresh-frozen plasma or recombinant factor VIIa can be considered as alternatives. Vitamin K\textsubscript{1} can be begun at a dose of 10 mg, taking care to dilute with preservative-free 5% dextrose, normal saline, or 5% dextrose in saline, and administered slowly, at a rate not exceeding 1 mg/min, to minimize the risk of an anaphylactoid reaction. The dose may have to be repeated 3 to 4 times daily.

When given orally, vitamin K\textsubscript{1} is virtually free of adverse effects, except for overcorrection of the INR in the setting of a patient who requires maintenance anticoagulation. Intravenous administration has resulted in death secondary to anaphylactoid reactions, probably as a result of the preparation’s colloidal formulation.\textsuperscript{98}

REFERENCES


