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Clinical Applications of Commonly Used Contemporary Antidotes

A US Perspective

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Summary

Poisonings are a common problem. In 1995, over 2 million exposures were reported to American poison information centres alone. The majority of poisoning exposures can be treated without major therapeutic intervention. If therapy is indicated, it is usually in the form of gastrointestinal decontamination with activated charcoal, to prevent absorption of the toxin and the subsequent toxicity that may occur.

In a limited number of cases, more aggressive life-support measures may be necessary to treat the adverse effects of poisons. Occasionally, that intervention may include the use of pharmacological antagonists, more commonly referred to as antidotes.

According to the American Association of Poison Control Centers, the most commonly used antidotes are acetylcysteine, naloxone, atropine, deferoxamine

(desferrioxamine) and antivenins. Overall, 17 antidotes account for 99% of all antidote use and those agents are reviewed in this article.

With the exception of naloxone, most antidotes have pharmacological effects that are independent of their inherent antidotal properties. Therefore, antidotes should be used judiciously because their pharmacological properties may exacerbate pre-existing toxicity and only in rare circumstances are they used prophylactically. Some antidotes, such as digoxin-specific antigen binding fragments (digoxin immune Fab), are very expensive, and both the risk : benefit ratio and the associated cost should be considered before the antidote is administered.

The principle aims are to 'treat the patient, not the poison' and to do no harm to the patient. Antidotes should be used only when they are indicated and may help a patient.

Over 2 million poisonings were voluntarily reported to US poison centres in 1995.[1] However, it is estimated that this number only represents about 40% of all poisoning exposures,[2] as a result of under-reporting of frequently used antidotes. The primary reason for this is that healthcare professionals traditionally contact poison centres only when they require information regarding the administration of an antidote in unfamiliar situations. Therefore, the statistical bias inherent in the reporting system to poison centres should be considered in the literature evaluation of these poisoning reports.

Approximately 30% of accidental and intentional poisonings are treated in healthcare facilities. Therefore, it is important for all medical care professionals, including physicians, pharmacists, nurses, medical toxicologists and other emergency care personnel, to be familiar with the most frequently used antidotes. This article is intended to update healthcare professionals on the present use of antidotes, and to address considerations for optimal care of the toxicological patient.

Many institutions have antidote areas in their pharmacy and/or emergency department, but there is great uncertainty as to which antidotes to keep and in what quantities. Of course, the final decision concerning which antidotes to stock will depend upon the patient population and the logistical area in which the institution is located. This article will address some of the most frequently asked questions regarding the common practice of using antidotes in the US. It is hoped that this review will facilitate the provision of optimal pharmaceutical care and clinical outcomes for patients affected by a toxic substance.

A summary of the most frequently reported antidotes used in the US from 1983 to 1994, according to the American Association of Poison Control Centers National Data Collection System[2-13] is presented in table I. Interestingly, 98% of reported antidote use involves only 16 pharmaceutical agents. This review will address the 16 most commonly used pharmacological antagonists (excluding hyperbaric oxygen), based upon actual usage as reported to US poison information centres, together with succimer; the latter is an agent that is widely used, although this is not yet reflected in current data. Also, included in table I are the conventional poisoning indications for each antidote.

It is important to note that not all agents listed in table I are necessarily efficacious. For example, thioctic acid has not shown efficacy in the treatment of *Amanita* mushroom poisonings and is no longer used for this indication. Therefore, it should be stressed that not all agents reported in table I are supported by literature recommendations.

While antidotes are important therapeutic interventions in the management of poisoned patients, their importance should not be overstated – they are adjuncts to patient care in most such patients. The cornerstones of therapy are aggressive supportive care and prevention of further absorption of the poison(s). When there is the opportunity to

Table I. Reported use of antidotes in the US between 1983 and 1994 (actual number of cases is probably much higher). Data collected from the American Association of Poison Control Centers National Data Collection System[2-13]

Antidote	No. of patients	Percentage	Cumulative percentage	Common poisoning indications
Acetylcysteine (oral and intravenous)	62 306	36.9	36.9	Paracetamol (acetaminophen)
Naloxone	56 412	33.4	70.2	Opioid agonists, clonidine
Atropine	7468	4.4	74.7	Organophosphate or carbamate insecticides or synthetic choline esters
Deferoxamine (desferrioxamine)	6744	4.0	78.7	Iron, aluminum
Antivenins:	5983	3.5	82.2	
crotalidae polyvalent				Pit vipers, including *crotalus* and *sistrurus* rattlesnake species, copperhead, cottonmouth water moccasin, *Agkistrodon halys* (Korea/Japan), fer-de-lance, cantil and bushmaster (*Lachesis mutus*)
black widow spider (*Latrodectus mactans*)				Black widow spider (*Latrodectus mactans*)
North American coral snake (*Micrurus fulvius*)				Elapidae including Texas coral snake (*Micrurus fulvius tenere*), Eastern coral snake (*M. fulvius fulvius*) bites
Flumazenil	5135	3.0	85.2	Benzodiazepines
Ethanol	4939	2.9	88.2	Ethylene glycol, methanol
Hydroxocobalamin	3130	1.9	90.0	Cyanide
Physostigmine salicylate	2991	1.8	91.8	Anticholinergic agents
Pralidoxime chloride	2028	1.2	93.0	Organophosphate insecticides
Digoxin-specific antigen binding fragments (digoxin immune Fab)	2016	1.2	94.2	Digoxin, digitoxin, foxglove (*Digitalis* species), oleander (*Nerium oleander*)
Pyridoxine	1678	1.0	95.2	Isoniazid, hydrazine, *Gyromitra* mushroom, ethylene glycol
Dimercaprol (British anti-lewisite; BAL)	1652	1.0	96.2	Lead, arsenic, gold, inorganic mercury, arsine, antimony, bismuth, chromium, copper, nickel
Penicillamine	1089	0.6	96.8	Lead, copper, mercury, arsenic, bismuth, gold, zinc, iron, cadmium
Hyperbaric oxygen	1046	0.6	97.4	Carbon monoxide, cyanide
Methylene blue (methylthioninium chloride)	1043	0.6	98.0	Methaemoglobinaemia (dapsone, nitrates, phenazopyridine, etc.)
Cyanide antidote kit	928	0.5	98.5	Cyanide
Edetic acid	919	0.5	99.0	Lead, copper, cadmium, zinc
Phytomenadione (vitamin K)	713	0.4	99.4	Warfarin, indandione rodenticides
Calcium salts	224	0.2	99.6	Hydrofluoric acid, fluorides, calcium antagonists, black widow spider bites
Folic acid	162	0.1	99.7	Methanol
Succimer	148	0.1	99.8	Lead, mercury, arsenic
Sodium thiosulfate	117	0.1	99.9	Cyanide
Sodium nitrite	87	0.1	100.0	Cyanide
Glucagon	29	0.0	100.0	β-Blockers, calcium antagonists, insulin
Thioctic acid	21	0.0	100.0	*Amanita* mushroom toxicity[a]
Neostigmine	3	0.0	100.0	Anticholinergic agents[b]
Total	169 011	100.0	100.0	

a Thioctic acid has never demonstrated efficacy. This agent is no longer used for this indication.

b Physostigmine is the preferred agent. Neostigmine is no longer used for this indication.

prevent the absorption of poisons, the traditional techniques should be considered: syrup of ipecacuanha (ipecac)–induced emesis, gastric lavage, activated charcoal administration and whole bowel irrigation. These treatment modalities have been reviewed elsewhere.[14]

In general, ipecac use is reserved for patients who have ingested a poison; ipecac-induced emesis can be achieved within 60 minutes of the ingestion. In the US, it is usually used in children in the home setting. Gastric lavage is reserved for patients who have ingested agents associated with significant morbidity and mortality [e.g. tricyclic antidepressants (TCAs)] and for patients with a decreased level of consciousness. Use of activated charcoal is gaining popularity, and it is now considered to be a first-line agent in preventing the absorption of many pharmaceuticals, and other organic and inorganic poisons. In most patients, it is used instead of emesis or lavage. Whole bowel irrigation has limited indications, and finds its greatest application in treating patients who have ingested large quantities of iron, sustained-release pharmaceuticals or illicit drugs. Except in unusual circumstances, supportive care and gastrointestinal decontamination measures are instituted before the use of pharmacological antagonists is considered.

One final factor that must be considered is the cost of the antidote. In an era in which cost-containment has become such a critical element in patient care, it is necessary to consider cost-benefit analysis as it relates to both the quantities of antidotes stocked by the institution and the clinical justifications of administering the antidote. In evaluating these costs, it is important to consider not only those associated with drug administration, but also costs associated with reducing length of stay or the need for expensive and/or invasive procedures (i.e. intubation, dialysis), which contribute to the total cost of patient care and perhaps an alteration in clinical outcome.

Assessment of the economic benefits derived from the expense of using the product is more important than the price tag on the drug itself. For example, from a cost perspective, naloxone can be and is administered rather injudiciously.[15] However, the acquisition cost of digoxin-specific antigen binding fragments (digoxin immune Fab) is over 100 times that of naloxone! Therefore, criteria for its use are generally more well defined. While patient care and positive outcomes are the goals of therapy, antidotes should only be administered when indicated.

The acquisition costs of treatment with the most commonly used antidotes, based on 1995 average wholesale prices, are shown in table II. This table was devised with due consideration of antidote decision-making issues and compliance with medical care standards. Hopefully, this will aid the clinician in the most appropriate use of antidotal therapy.

The remainder of this article is a review of the 16 most commonly used antidotes plus succimer, and their place in pharmaceutical practice.

1. Acetylcysteine

1.1 Indication

In the US, paracetamol (acetaminophen) is the most commonly reported analgesic taken in overdose, alone or in combination.[12] Toxicity may become apparent when patients acutely ingest approximately 7.5g or 140 mg/kg, whichever is less;[17] 13 to 25g of paracetamol is considered a potentially lethal dose.[18] It is frequently very difficult to determine the actual amount of paracetamol that a patient has consumed and the ingestions are often mixed, since paracetamol is in many combination products. Acetylcysteine is an effective antidote when administered to a patient with paracetamol toxicity.

The development of paracetamol toxicity occurs in 4 stages. Symptoms range from mild gastrointestinal complaints to severe hepatic damage and death. For a discussion of paracetamol toxicity staging, the reader is referred to the article by Lewis and Paloucek.[18]

Table II. Acquisition cost for average therapy of selected antidotes. Traditional doses of antidote are based on a single course of therapy (as appropriate for adults or children). Cost calculations are performed solely based on drug average wholesale price as quoted in the Redbook, 1995 (administrative and professional costs are not included)[16]

Agent	Usual regimen	Bodyweight (kg)[a]	1995 Cost ($US)
Acetylcysteine	140 mg/kg PO initially, then 70 mg/kg PO 4-hourly for 17 doses	70	208.69[b]
Antivenin, crotalidae	Minimal envenomation 5 vials IV	70	1129.80
	Moderate envenomation: 10 vials IV	70	1883.00
	Severe envenomation: ≥20 vials IV	70	4707.50
Atropine	Moderate poisoning: 2mg IV every 10-30 minutes; severe poisoning: 2-5mg IV every 10-30 minutes	70	109.94[b]
Cyanide antidote kit	1 kit (inhaled amyl nitrate, followed by sodium nitrite 300mg IV over 15-20 minutes, then sodium thiosulfate 12.5g IV	70	140.29
Deferoxamine (desferrioxamine)	1g IV, then 500mg IV 4-hourly for 2 doses at rate not to exceed 15 mg/kg/h IV; *or* 30 mg/kg IV over 1 hour, then 15 mg/kg/h IV	70	159.24
Digoxin-specific antigen binding fragments (digoxin immune Fab)	For digoxin overdose of unknown quantity, administer 20 vials IV	70	8039.80
Dimercaprol (British anti-lewisite; BAL)[d]	3-5 mg/kg IM 4-hourly for 2 days, then 2.5-3 mg/kg 6-hourly for 2 days, then 2.5-3 mg/kg 12-hourly for 7 days	23	297.00[b]
Ethanol	600mg/kg IV (7.6 ml/kg of 10% ethanol) initially; maintenance dosage 66 mg/kg/h IV (0.83 ml/kg/h of 10% ethanol)[c]	70	0.71
Flumazenil	0.2mg IV over 15 seconds initially, then 0.3mg IV after 30 seconds, then 0.5mg IV after a further 30 seconds; the latter dose repeated to a maximum dose of 5mg (average dose 3mg)	70	134.31
Hydroxocobalamin[e]	Cyanide poisoning: 50 mg/kg IV	70	1386.45[b]
	Nitroprusside-induced cyanide toxicity: 25 mg/h for 24 hours	70	237.00
Methylene blue (methylthioninium chloride)	1-2mg IV over 5 minutes	70	7.00[b]
Naloxone	0.4-2mg IV or IM initially, repeated every 2-3 minutes (maximum dose 10mg; average dose 5mg)	70	13.69[b]
Penicillamine	15-40 mg/kg/day PO to maximum of 500mg 4 times daily for 4-12 weeks	70	174.13
Physostigmine	1-2mg IV initially by slow injection, repeated every 10-30 minutes	70	9.26
Pralidoxime chloride	1-2g IV over 15-30 minutes; repeat after 1 hour if muscle weakness still present; then titrate up to 12g/24 hours according to response	70	577.13
Pyridoxine	1g pyridoxine IV for each gram of isoniazid ingested[f]; give dose over 15 to 30 minutes	70	17.32[b,g]
Succimer	10 mg/kg (350 mg/m^2) PO 8-hourly for 5 days, then 10 mg/kg 12-hourly for 14 days	23	314.82

a 1kg = 2.21lb; 70kg indicates adult dosage, 23kg indicates child dosage.

b Price based on using entire ampoules/vials for each dose. It is assumed that the remainder of the dose is discarded.

c For patients without alcoholism not undergoing haemodialysis; if haemodialysis is required, maintenance dosage is 169 mg/kg/h IV (2.13 ml/kg/h of 10% ethanol). Maintenance dosages in patients with alcoholism are 154 mg/kg/h IV (19.6 ml/kg/h of 10% ethanol) without haemodialysis and 257 mg/kg/h (3.26 ml/kg/h of 10% ethanol) with haemodialysis.

d Dimercaprol must be co-administered with sodium calcium edetate [edetate calcium disodium; calcium disodium ethylenediamminetetraacetate (EDTA)].

e Hydroxocobalamin is investigational for cyanide poisoning in the US; it is not commercially available in the appropriate concentration.

f If isoniazid dose unknown, 5g every 30 minutes until seizures are controlled.

g Price based on single 5g dose.

Abbreviations: IM = intramuscularly; IV = intravenously; PO = by mouth.

1.2 Mechanism of Action

Approximately 96% of paracetamol is metabolised in the liver, with only 2 to 4% excreted in the urine unchanged. 90% of the hepatically metabolised drug is converted to a nontoxic glucuronide or sulfate conjugate product. A fraction of the paracetamol is metabolised to a toxic intermediate, *N*-acetyl-imidoquinone. This metabolite has been implicated as the cause of hepatocyte necrosis that is the ultimate cause of death following paracetamol overdose. At therapeutic doses, *N*-acetyl-imidoquinone undergoes glutathione conjugation, yielding a nontoxic metabolite. However, in toxic doses, glutathione stores become depleted, thereby shifting the reaction towards greater production of *N*-acetyl-imidoquinone.[18] As an antidote to paracetamol toxicity, acetylcysteine serves to detoxify *N*-acetyl-imidoquinone by working as a glutathione precursor or surrogate by contributing sulfhydryl groups to this metabolic reaction, thus:

- enhancing glutathione stores
- promoting glutathione conjugation
- preventing accumulation of the toxic metabolite.

1.3 Administration Guidelines

The Rumack-Matthew nomogram has been a major influence in identifying the severity of paracetamol poisonings. It is an adaptation of published data obtained from patients who were treated at the Regional Poison Treatment Centre of the Royal Infirmary of Edinburgh, Scotland.[19] Although the Rumack-Matthew nomogram has recently been revised,[20] the original version is the most widely used nomogram for the treatment of paracetamol toxicity.

To determine the potential for hepatotoxicity, a 4-hour post-ingestion plasma paracetamol concentration should be obtained. This value is plotted on the Rumack-Matthew nomogram to determine if a potentially hepatotoxic concentration exists. Toxic concentrations can be treated with acetylcysteine,[21] as outlined in the next paragraph. It should be noted that the Rumack-Matthew nomogram is only useful in patients with acute ingestion; chronic paracetamol consumption cannot be evaluated using this nomogram.

In patients with acute paracetamol poisoning, oral acetylcysteine 140 mg/kg is administered orally, followed by 70 mg/kg every 4 hours for 17 doses. If the patient vomits within an hour of a dose, it should be re-administered. Intravenous acetylcysteine is used in most western countries outside the US.

1.4 Adverse Effects

Oral acetylcysteine is not usually associated with severe adverse effects; nausea and vomiting occur most frequently. However, intravenous administration of acetylcysteine has been associated with rare reports of anaphylactoid adverse effects, including angioedema, bronchospasm, hypotension and tachycardia. Patients with asthma should be monitored more closely, since they may be at increased risk. Further discussion of the intravenous use of acetylcysteine in patients with paracetamol toxicity is described in section 1.6.

1.5 Precautions and Contraindications

Known acetylcysteine hypersensitivity is the only contraindication to oral administration of acetylcysteine in the treatment of paracetamol overdose.[22]

If a patient experiences severe vomiting after paracetamol ingestion, administration of acetylcysteine may worsen the vomiting. In these situations, the use of an antiemetic (such as ondansetron) or intravenous acetylcysteine should be considered.

1.6 Other Considerations

Acetylcysteine should be mixed to a 5% solution in juice or cola, then placed in a cup with ice, and covered. The patient should sip the mixture through a straw. This may help to alleviate some of the malodorous sulphur aroma, and reduce the risk of nausea and vomiting associated with smelling the acetylcysteine mixture. If the patient is noncompliant,

acetylcysteine may be administered through a nasogastric tube. Dilutions should be consumed within 1 hour. Remaining undiluted solutions may be stored in a refrigerator for 96 hours.[22]

There exists some controversy regarding the use of oral acetylcysteine in conjunction with activated charcoal. Theoretically, it has been suggested that activated charcoal would interfere with the absorption of acetylcysteine, thus reducing its effect in paracetamol intoxication. Some authors have advocated a larger loading dose to compensate for any acetylcysteine that is adsorbed to the activated charcoal.[23] Others oppose increasing the dose of acetylcysteine for those patients receiving activated charcoal.[24,25]

In general, most authors believe that activated charcoal *is* useful in patients with an acute overdose, without the requirement for larger acetylcysteine doses.[17,26-28] There are several reasons for these opinions.[28] First, the dosage of acetylcysteine has been established empirically; the amount of acetylcysteine required to effectively prevent hepatotoxicity is yet to be determined. Second, it has never been established that there is any relationship between plasma acetylcysteine concentrations and the reduction in hepatotoxic effects. Finally, one study has shown that acetylcysteine has a lesser affinity than paracetamol for activated charcoal.[27] Thus, combination therapy using activated charcoal and acetylcysteine is generally recommended as initial treatment of acute paracetamol toxicity.

Only the oral formulation of acetylcysteine is approved for use in the US, where intravenous administration of acetylcysteine is considered investigational; however, an intravenous preparation has been available in the UK and Canada for many years. There are 2 investigational intravenous protocols used in the US. In the first, a regimen of 150 mg/kg is infused over 15 minutes, followed by 50 mg/kg over 4 hours and 100 mg/kg over the remaining 16 hours, for a total of 300 mg/kg over 20 hours.[29] A second intravenous protocol consists of a loading dose of 140 mg/kg, followed by 12 doses of 70 mg/kg every 4 hours; all doses are administered over 1 hour.[30] Both regimens are considered equally efficacious. Further study is required to identify the ideal protocol.

Originally, it was believed that for patients with paracetamol overdose who present more than 15 hours after ingestion, acetylcysteine therapy was futile. However, it is now known that it is always worth giving acetylcysteine within 24 hours of ingestion if paracetamol concentrations are in the toxic range. Although antidotal therapy may be of limited benefit when initiated more than 24 hours after ingestion, there is been some evidence to suggest that acetylcysteine should be considered in patients with severe paracetamol-induced hepatotoxicity. Treatment with intravenous acetylcysteine may decrease the risk of developing grade III or IV coma, cerebral oedema or hypotension requiring inotropic support; mortality may also be reduced in these patients.[31,32] It has been theorised that the mechanisms by which acetylcysteine exerts its effect are related to its antioxidant activity, resulting in: (i) the scavenging of free radicals; (ii) an improvement in oxygen delivery and extraction in hypoxic tissues; and (iii) the replenishment of glutathione stores.[28]

Infants and young children appear to be more resistant to the toxic manifestations of paracetamol, despite the ingestion of doses well above the toxic range for older children and adults. Rarely do they develop hepatotoxicity.[33] It has been suggested that early emesis and differences in paracetamol metabolism, related to the prematurity of hepatocyte development, contribute to their altered response.[34-36]

Susceptibility to paracetamol toxicity may be increased in patients receiving enzyme-inducing drugs, while patients with alcoholism may be at greater risk of developing hepatotoxicity.

In summary, the use of oral acetylcysteine has become the standard of care for managing patients with paracetamol toxicity in the US. Activated charcoal is recommended for use in conjunction with acetylcysteine to promote adsorption of paracetamol to the charcoal, thus reducing systemic absorption. Appropriate monitoring of serum

paracetamol concentrations and other patient parameters will assist in determining further treatment modalities. The intravenous formulation, although used in other parts of the world, has not yet been approved by the US Food and Drug Administration (FDA).

2. Naloxone

2.1 Indications

Naloxone is well established as the agent of choice in the treatment of opioid overdose. Agents of the opioid family are frequently prescribed for their analgesic, cough suppressant, antidiarrhoeal and sedative properties. Because of the easy accessibility of these agents, and the tolerance and physical dependence characteristics that they possess, abuse of these agents is common. The classic triad of CNS depression, respiratory depression and miosis is a standard manifestation of opioid ingestions. High-dose naloxone administration is necessary in some patients with severe intoxication who exhibit symptoms such as coma, apnoea and respiratory depression.

Another situation in which naloxone has been used is in the postprocedural or postanaesthesia reversal of opioid administration. Naloxone has been further used with limited success in the treatment of clonidine toxicity.[37,38] Investigative nontoxicological uses for naloxone include acute spinal cord injury, septic and haemorrhagic shock[39] and intractable pruritus.[40] Further study is necessary to determine the role of naloxone in these indications.

2.2 Mechanism of Action

The major mechanism by which naloxone exerts its effect is by antagonising the activity of opioid agents by competitive binding to the μ opiate receptors. To a lesser extent, its antagonistic property also occurs at the κ and σ receptors.[41] Besides its effects against exogenous opioids, the activity further extends to the endogenous endorphins. Because naloxone is a pure antagonist, it does not exhibit any intrinsic activity.

As a result of the pharmacokinetic and pharmacodynamic properties of naloxone, repeat administration or continuous infusion is necessary to maintain opioid reversal. The duration of action of naloxone is generally much shorter than the opioids for 2 reasons: first, studies comparing the metabolism of naloxone with that of morphine show that the brain metabolises naloxone more quickly than morphine;[42] second, many opioids have pharmacologically active metabolites that increase their duration of activity. In combination products such as diphenoxylate/atropine, the atropine component may delay absorption of diphenoxylate, thereby extending the time before which manifestations of opioid toxicity occur. Delayed toxicities also develop after methadone overdose with its longer time to peak effect. Another situation often requiring repeated bolus administration or continuous infusion of naloxone is the ingestion of sustained-release morphine preparations. Nalmefene, a long-acting opioid antagonist, may eventually replace naloxone infusions; however, the cost associated with its use in the treatment of most acute opioid overdoses is prohibitive compared with naloxone.

2.3 Administration Guidelines

Definitive guidelines regarding the ideal dose of naloxone have been difficult to establish. The most appropriate dose is a function of the quantity of opioid ingested and its affinity for the receptor site Generally, an initial bolus of naloxone 0.4 to 2mg is administered intravenously, with repeated boluses at 2- to 3-minute intervals until the desired effect is obtained.[43] Titration is the key to optimal clinical response.

Alternatively, a continuous intravenous naloxone infusion of 0.4 mg/h may be used in adults or children[44] to eliminate the need for multiple-bolus administration. The dosage of this infusion should be titrated every 30 minutes based on clinical response. The duration of the infusion is a function of the duration of action of the ingested drug, the quantity ingested and patient response.[45] Infusions may be necessary to treat patients with opioid

overdose who use agents that have excessively long therapeutic half-lives (e.g. methadone).

Others have proposed an administration nomogram for continuous intravenous infusion.[46] To determine the quantity of the initial naloxone dose, the authors recommend that a bolus dose be administered until reversal of symptoms occurs. 50% of this total dose should then be administered over 15 minutes, followed by a continuous infusion of two-thirds of the initial bolus dose per hour. Other naloxone infusion protocols have been described in the literature.[47] For acute clonidine ingestions, the usual maximum 2mg dose of naloxone may be insufficient to produce an effect. Higher than average doses are commonly required. In children, an initial intravenous dose of 0.1 mg/kg has been suggested.[39]

2.4 Adverse Effects

In patients who are not dependent on opioids, naloxone has an excellent tolerability profile. The most frequently reported adverse effect is opioid withdrawal with symptoms of nausea, vomiting and anxiety.

It is generally considered that precipitous cardiovascular effects do not occur following the use of naloxone in acute opioid overdosage. However, in one recent retrospective review of diamorphine (heroin) overdoses it was estimated that between 4 and 30 serious complications (including cardiac arrhythmias) could be expected in every 1000 patients with clinically diagnosed overdoses of diamorphine or diamorphine mixtures.[48]

Case reports of hypertension, cardiac arrest, and atrial and ventricular arrhythmias have been documented following naloxone administration after anaesthesia. Likewise, reports of excruciating pain have been reported after naloxone administration in patients with cancer who were receiving opioids for chronic pain management. It is suspected that naloxone abruptly unmasks the pain, resulting in a massive surge of catecholamines and potentially severe cardiac dysrhythmias.[49,50] If naloxone administration is warranted, caution should be exercised in patients with underlying chronic pulmonary or cardiac disease.[39]

2.5 Precautions and Contraindications

Caution is required when administering naloxone to patients who are dependent on opioids, since the precipitation of withdrawal symptoms may be significant.

For paediatric clonidine ingestions, naloxone should be administered slowly, using small incremental doses. Hypertensive effects have been reported with rapid naloxone administration in this subset of patients.[51]

2.6 Other Considerations

Endotracheal administration of naloxone has been shown to be effective when timely administration using the intravenous route was not possible.[52,53] Ordinarily, doses of 2 to 2.5 times the intravenous dose have been employed.

Sustained-release opioid preparations that are crushed or chewed have resulted in the immediate release of the entire dose, resulting in massive overdose. Patients should be informed of proper handling procedures associated with sustained-release preparations and warned of potential adverse effects.

Patients receiving naloxone as a continuous infusion should be monitored closely. It should never be assumed that the infusion is sufficient to maintain adequate reversal of the agent.

The use of naloxone as part of the 'coma cocktail' has recently been re-evaluated.[54] Previously, the standard practice was to administer the combination of naloxone, dextrose and thiamine to all patients with altered mental status. The basis for this recommendation lies with the relative safety of these agents and their diagnostic value. However, administration of naloxone to a more selective patient population may reduce its overall use. Hoffman and colleagues[15] proposed that naloxone should only be administered to patients with altered mental status and respiratory depression (respiratory rate of 12 breaths/minute or less). In their report, they state that 75 to 90% of naloxone

administration could be eliminated if these criteria were adapted. This has many benefits, including decreasing the cost of therapy, reducing the development of adverse effects and minimising the confusion incurred from an equivocal patient response to naloxone. Therefore, the use of naloxone in all patients with altered mental status is considered controversial.

Nalmefene is a newer opioid antagonist with similar properties to naloxone. To date, the agent has been efficacious and well tolerated.[55] However, the proposed benefit of a longer half-life may be questioned, since precipitation of withdrawal symptoms for a protracted time and the unmasking of pain postoperatively may occur with nalmefene, possibly making an agent with a shorter half-life preferable. In contrast, the long term action of nalmefene may reduce the requirement for a continuous infusion. The definitive comparison of naloxone versus nalmefene, regarding the amount of time spent in the intensive care unit, has not been published. Further studies evaluating these issues, as well as addressing the tolerability and efficacy profiles of nalmefene and naloxone, are necessary in order to determine the comparative benefits and risks of the 2 agents.

In summary, naloxone is an opioid antagonist that has been used for many years in the clinical setting to reverse the effects of opioid overdose. When administered for an appropriate indication, the tolerability profile of this agent is excellent. Caution should be exercised in patients who are in the postanaesthetic period and in those with cancer who are receiving opioids for chronic pain management, because of risk of unveiling severe pain and the potential development of cardiac manifestations, and in individuals who are dependent on opioids, in order to prevent precipitation of acute withdrawal.

3. Atropine

3.1 Indication

The American Association of Poison Control Centers reports that organophosphates and carbamates are responsible for a large percentage of insecticide- and pesticide-related poisonings in the US.[12] Organophosphate poisonings may produce irreversible inhibition of acetylcholinesterase, while carbamates produce reversible inhibition. The effects of these processes result in accumulation of acetylcholine, thereby overstimulating muscarinic, nicotinic and CNS cholinergic receptor sites.

A characteristic finding of toxicity caused by organophosphate and carbamate insecticides is a hypersecretory syndrome (salivation, diaphoresis, etc.), followed by coma, seizures or cardiac arrhythmias. Other manifestations that have been associated with organophosphate poisonings include the Intermediate Syndrome (paralysis of various muscle groups up to 4 days after apparent recovery from organophosphate toxicity),[56-60] followed by a delayed polyneuropathy.[58] Respiratory failure is usually the cause of death.

Patients with carbamate insecticide poisoning display manifestations that are similar to organophosphate toxicities. However, the clinical presentation is different in 2 respects: first, overall symptoms may be less severe and of shorter duration compared with organophosphate toxicity; second, the carbamates exhibit fewer CNS adverse effects as a result of their inability to penetrate the blood-brain barrier.[61]

The treatment of carbamate poisoning requires only atropine administration, whereas organophosphate poisoning may require the use of both atropine and pralidoxime chloride. Additionally, diazepam is an effective agent for patients who develop seizures in association with organophosphate toxicity.[62]

3.2 Mechanism of Action

Atropine is used in the treatment of organophosphate or carbamate poisoning, primarily for control of muscarinic manifestations, such as hypersecretion and bradycardia. It acts to antagonise acetylcholine at the muscarinic receptor site. There are at least 3 muscarinic receptor subtypes, labelled M_1, M_2 and M_3. Atropine is a nonselective muscarinic

antagonist, but may have some preferential selectivity toward M_1 receptors. Generally, lower doses are required to inhibit M_3 receptors (salivation), while higher doses are needed to display the cardiac effects that are associated with inhibition of the M_2 receptor subtype.[63]

3.3 Administration Guidelines

In mild poisonings, the recommended intravenous atropine doses are 1mg for adults and 0.01 mg/kg for children. Adult patients with moderate poisoning should receive 2mg intravenously every 10 to 30 minutes until muscarinic symptoms disappear. The standard atropine regimen for severe poisoning in adults is 2 to 5mg intravenously every 10 to 30 minutes until symptom resolution.[64] The paediatric dose for moderate or severe poisonings is 0.02 to 0.05 mg/kg intravenously, again until muscarinic symptoms disappear.

A typical patient with mild or moderate poisoning may require 40 to 60mg of atropine daily;[65] while severe toxicity may warrant several grams over several weeks.[66] Prolonged atropinisation is necessary because the regeneration of erythrocyte acetylcholinesterase is limited by the rate of generation of new erythrocytes. When atropine is administered over several days, it should be continued (at a dosage titrated against clinical effects) 24 hours beyond the time of resolution of the symptoms of organophosphate toxicity.

3.4 Adverse Effects

An important consideration in the use of large amounts of atropine is the presence of the preservatives benzyl alcohol or chlorobutanol, which may produce their own toxicity. Therefore, it is imperative that the atropine used in these patients is preservative-free in order to prevent potentially serious adverse effects.

The most common adverse effects associated with atropine are typical of anticholinergic toxicity, and include disorientation, tachycardia, and dilated or unresponsive pupils. The patient should be observed closely for signs of atropine toxicity.

3.5 Precautions and Contraindications

Since ventricular fibrillation may develop in anoxic patients, atropine is contraindicated in these situations. Anoxia must be corrected before atropine administration.[64]

Atropine therapy should be withdrawn slowly in order to prevent a rebound phenomenon that may result in pulmonary oedema. This is of particular concern in patients with lipophilic organophosphates.

Atropine should not be administered prophylactically (before the symptoms of organophosphate toxicity have appeared), since it may mask organophosphate toxicity.

3.6 Other Considerations

Theoretically, glycopyrrolate may have certain advantages over atropine in the treatment of organophosphate poisonings, including better control of secretions and less tachycardia. It is a quaternary ammonium compound that does not readily cross the blood-brain barrier; therefore, it is associated with fewer CNS effects.[67]

Anecdotal reports of the use of 2 other formulations of atropine have been described in the literature. An aerosolised formulation of atropine has been used as an initial antidote during military use of organophosphates, as adjunctive treatment of nerve gas poisonings or in patients with toxicity that is refractory to injectable atropine. Nerve gas is a particularly potent variety of organophosphate, with the potential to cause death even after moderate exposure. In 1991, the aerosolised formulation provided an alternative to intramuscular administration in Operation 'Desert Storm', when chemical warfare with nerve gas was impending.[65] A case report describing the use of nebulised atropine in a patient with malathion poisoning suggested that some improvement in bronchorrhoea and respiratory distress was noted.[68] The success in using aerosolised atropine is predominately based on anecdotal reports, so the efficacy of this formulation cannot be determined until further studies are conducted.[65]

A formulation of atropine combined with pralidoxime chloride was designed for intramuscular self-administration using a special autoinjector device. It has been used in the past by the US Army to treat nerve gas toxicities. The autoinjector delivers atropine 2mg/0.7ml and pralidoxime chloride 600mg/2ml. Two devices are available from Survival Technology in Bethesda, Maryland, US, marketed under the brand names, Mark I® and Combopen MC®.[66]

In summary, atropine is a useful agent in the treatment of organophosphate and carbamate poisonings. However, it only neutralises the muscarinic receptor effects of these agents. Unusually high doses may be warranted to induce a response. Concomitant therapy with pralidoxime chloride is required in patients with moderate or severe organophosphate poisonings, when nicotinic or CNS effects occur.

4. Deferoxamine (Desferrioxamine)

4.1 Indication

Deferoxamine (desferrioxamine) has been used adjunctively as a treatment for iron toxicity for many years. Iron overload may occur either in the acute overdose situation or in chronic medical conditions, such as primary or secondary haemochromatosis. In acute iron overdose, 4 stages of iron toxicity have been described.[69] Clinical manifestations include gastrointestinal symptoms, metabolic acidosis and hypotension. If a patient progresses to stage 4, multisystem organ failure, coagulopathies and gastrointestinal scarring may ensue. For a discussion of the staging of iron overdose, the reader is referred to the review by Mills and Curry.[69]

Another indication for deferoxamine is the reduction of high plasma aluminium concentrations, primarily in patients undergoing haemodialysis. Aluminium has been known to cause problems such as neurological disease, osteodystrophy[70] and microcytic anaemia.[71]

4.2 Mechanism of Action

The major mechanism of action of deferoxamine is its ability to chelate with ferric iron (Fe^{+++}) from ferritin and haemosiderin, which are 2 iron-storage forms in the body. Binding with ferric ions results in the formation of ferrioxamine, which can be eliminated through the kidneys. In an analogous manner, aluminium is mobilised from extra-osseous tissue. Despite its high binding affinity for ferric iron and aluminium ions, its affinity for other metal ions is relatively low.[70] Therefore, ions such as calcium, magnesium, zinc and copper are virtually unaffected by deferoxamine administration.

4.3 Administration Guidelines

After acute ingestion, patients who are symptomatic (section 4.1) or who have peak serum iron concentrations above 500 μg/ml are candidates for intravenous administration of deferoxamine 1g, followed by 500mg 4-hourly for 2 doses at rate not to exceed 15 mg/kg/h.[69,72] Some toxicologists have promoted the use of a 30 mg/kg loading dose over 1 hour before commencing the maintenance infusion of 15 mg/kg/h.[72]

The duration of deferoxamine therapy does not commonly need to exceed 24 hours. It is appropriate to discontinue deferoxamine therapy when the following criteria are met: (i) the patient no longer exhibits signs and symptoms of systemic iron poisoning; (ii) the corrected serum iron concentration is normal or low; (iii) for those patients in whom an initial abdominal radiographic test indicated multiple radio-opacities, suggesting the presence of iron in the stomach, a repeat abdominal radiograph test should demonstrate the disappearance of ingested iron; (iv) the vin-rose coloured urine that usually accompanies deferoxamine administration in iron-overloaded patients should have disappeared.[69] Disappearance of the vin-rose coloured urine is frequently used as the sole determinant for discontinuing deferoxamine; however, false negatives have been reported. Thus, all 4 criteria should be met before stopping treatment with deferoxamine.

Subcutaneous administration of deferoxamine over 6 to 12 hours on a daily basis is the preferred method in patients with chronic iron overload. In children less than 6 years of age, a subcutaneous infusion of 40 to 50 mg/kg/day 5 to 6 days weekly is generally adequate to treat transfusional iron overload.[73] Adults usually require deferoxamine doses of 50 to 100 mg/kg/day.[74]

Doses of deferoxamine in the treatment of aluminium toxicity vary from 20 to 80 mg/kg/week intravenously, intramuscularly or intraperitoneally, in single or divided doses.[70]

The use of deferoxamine in patients undergoing maintenance haemodialysis and continuous ambulatory peritoneal dialysis has been reported.[75] Both methods achieved a satisfactory response to therapy.

4.4 Adverse Effects

Overall, deferoxamine has a very good safety profile, although there are limited concerns over haemodynamic effects related to the rate of administration. Rapid intravenous injection has been associated with hypotension, requiring discontinuation of therapy. However, once blood pressure is maintained, deferoxamine can be re-introduced slowly. Urticaria and erythema are uncommon adverse effects.

Ocular and auditory neurotoxicity have been documented in patients receiving long term therapy (i.e., not for the treatment of acute iron poisoning).[76] Careful monitoring of visual and auditory response is recommended.

Pulmonary manifestations, including adult respiratory distress syndrome, have been reported.[77-79] It has been proposed that pulmonary toxicity may result from continuous deferoxamine infusions.[78,79] However, intermittent deferoxamine infusions have been administered, with little success, in an attempt to diminish these pulmonary effects.

Yersinia enterocolitica is a ubiquitous organism that is generally of low pathogenicity in the general population, as a result of its high iron requirements for survival. However, patients with chronic iron overload who are receiving deferoxamine are more susceptible to *Y. enterocolitica* infection, since iron from tissues becomes more available once deferoxamine is administered. Patients receiving deferoxamine who develop any infection should undergo blood culture testing for this pathogen. Antimicrobial agents should be initiated before obtaining results. Agents of choice include cotrimoxazole (trimethoprim/sulfamethoxazole), tetracycline, gentamicin, cefotaxime or ciprofloxacin.[80]

4.5 Precautions and Contraindications

Controversy exists regarding the use of deferoxamine in pregnant women. Animal studies of deferoxamine therapy during the early stages of pregnancy have revealed skeletal abnormalities in fetuses. Furthermore, growth retardation has been reported in prepubescent patients. Other experimental studies in humans and animals have shown that neither ferric ion nor deferoxamine crosses the placenta, which places the fetus at a lesser risk of toxicity. Anecdotal case reports have appeared in the literature describing the successful treatment of pregnant women with iron poisoning using intravenous deferoxamine.[81,82] Most recent recommendations state that deferoxamine should be administered during pregnancy in the presence of acute iron poisoning,[69] since survival of the fetus is dependent upon the health and survival of the mother.

The interaction between deferoxamine and prochlorperazine has been reported to result in coma in humans and animals.[83] Concomitant administration of these agents is not advisable.

4.6 Other Considerations

The use of total iron-binding capacity (TIBC) as a method of evaluating iron toxicity is considered invalid, since TIBC may become falsely elevated either in the presence of high serum iron concentrations or with deferoxamine therapy. No study has proven the contention that toxicity only occurs when the serum iron concentration is greater than TIBC.[69]

Oral administration of deferoxamine is not recommended,[69] because it may increase the dissolution

rate and absorption of iron, resulting in increased serum iron concentrations.[84] Furthermore, as a result of a considerable decrease in the bioavailability of oral deferoxamine, the dosage requirements to achieve sufficient metal : chelate ratios make it impractical for use.

In the acute overdose situation, it is important to note the iron salt formulation that was ingested. The elemental iron content of the different salts is 12% in ferrous gluconate, 20% in ferrous sulfate and 33% in ferrous fumarate. This may influence the anticipated serum iron concentrations and therapy decisions.

Patients with impaired renal function who receive deferoxamine for chronic aluminium toxicity may require iron supplements and epoetin alfa, since deferoxamine-induced iron loss may occur.

In summary, deferoxamine is a valuable agent in the toxicologist's armamentarium of pharmacological antidotes. Its selective efficiency as a chelator of iron and aluminium has made it the agent of choice in acute or chronic scenarios. The agent is generally well tolerated in the acute situation; however, during long-term administration, ocular and auditory manifestations should be monitored. It should not be used prophylactically or indiscriminately in acute iron poisoning – always 'treat the patient, not the poison'.

5. Antivenins and Antitoxins

5.1 Indication

Antivenins/antitoxins are the fifth most commonly reported antidotes administered in the US. This category includes antivenins for snakebites, black widow spiders, scorpions and others. The focus of this section will be the crotalidae polyvalent antivenin, which is most commonly used. Crotalidae antivenin is effective in treating patients who are bitten by poisonous snakes of the pit viper family, including rattlesnakes, copperheads and cottonmouths (water moccasins).

In cases of actual envenomation (30 to 70% of bites), local reactions consisting of swelling, pain and tissue necrosis may occur. Systemic symptoms include hypovolaemic shock, renal failure and coagulopathies. After supportive care, antivenin is considered the mainstay of pit viper snakebite therapy provided that it is clinically justified. While morbidity associated with pit viper envenomation is high, death is rare.[85] The degree of envenomation should be assessed before therapy to assist in determining the most appropriate dosage.[86] If oedema and erythema do not occur within the first 4 hours after the snakebite, it may be assumed that the patient does not have a pit viper envenomation.[87] Envenomation does not occur with every pit viper bite.

5.2 Mechanism of Action

Pit viper venom is composed of 90% water, 5 to 15 enzymes and a large number of peptides. These enzymatic proteins may cause proteolysis and haemolysis. The major enzymes include phospholipase A_2, hyaluronidase, amino-acid esterase and the proteolytic enzymes ribonuclease, deoxyribonuclease and 5′-nucleotidase.[88]

Crotalidae antivenin is prepared by hyperimmunising horses with multiple snake venoms. The antivenin globulins act to neutralise the enzymes present in the venom of pit viper snakes. For a comprehensive description of the diagnosis and management of venomous snakebites, the reader is referred to the articles by Gold and Barish,[87] and Gold and Wingert.[88]

5.3 Administration Guidelines

Before antivenin administration, skin testing should be performed to identify those patients who may be sensitive to the horse serum in the antivenin. Included in the antivenin package is a sample of horse serum that is designed for this purpose. It is important to note that the skin test has been associated with false positive and false negative results. Those patients with a positive skin test may be premedicated with diphenhydramine. Another alternative would be to administer epinephrine (adrenaline) concomitantly with the antivenin. As with most clinical decisions, the risk of anaphylaxis

must be weighed against the potential benefit of crotalidae antivenin.

Initially, crotalidae antivenin should be administered by slow intravenous injection. The manufacturer recommends intravenous administration of a 1 : 1 or 1 : 10 dilution of reconstituted antivenin in either sodium chloride injection, USP, or 5% dextrose, USP. The first 5 to 10ml of the total solution should be administered over 3 to 5 minutes. The patient should be carefully observed for signs and symptoms of an adverse reaction.[89] Dilute solutions are preferred, but more concentrated solutions can be administered if fluid volume is a consideration. The rate and concentration may be gradually increased until the entire dose is administered.[90] The goal is to reach the maximally safe rate for intravenous administration. Patients who tolerate the antivenin should receive 1 vial every 5 to 10 minutes until the total dose has been given. The first 5 vials should be administered over 30 to 60 minutes.[91]

The amount of antivenin required is highly variable and is dependent on:

- the snake species
- the amount of venom
- the patient's age
- the site of envenomation
- the health status of the patient
- the patient's response
- resolution of systemic reactions, pain and oedema.

Generally, antivenin is not required in up to 40% of patients.[87] Treatment recommendations are controversial, and it is advised that a regional poison information centre be contacted for administration guidelines. A commonly employed guideline for the number of crotalidae antivenin vials required in adults is: (i) 5 vials for patients with minimal symptoms without systemic involvement; (ii) 10 vials for patients with moderate symptomatology; and (iii) 20 or more vials for those with severe symptoms.[88] Children usually require a much higher total dose of antivenin as a result of a larger volume of envenomation in relationship to their total body surface area. The total dose should be given over a 4- to 6-hour period.

Antivenin should never be administered prophylactically to asymptomatic patients. When indicated, it is best to administer the antivenin within 4 hours of the snakebite. However, in serious situations, antivenin has been administered successfully up to 24 hours after the snakebite.

5.4 Adverse Effects

Often, it is difficult to distinguish adverse effects caused by the antivenin from those effects of the snakebite itself. Mild reactions to the antivenin infusion, such as tachycardia, hypotension and hyperthermia, can develop in some patients. Generally, adverse effects are more prevalent when the rate of infusion is greater than 1 vial over 10 minutes.[91] As mentioned in section 5.3, antivenin is a horse serum derivative that may produce a serious allergic reaction in a sensitive individual.

A common adverse effect associated with antivenin administration is a delayed hypersensitivity, or serum sickness, reaction that occurs in 50 to 80% of patients receiving crotalidae antivenin.[92] This is a dose-related phenomenon, with an increasing incidence among patients receiving 5 or more vials.[87] In contrast to anaphylactoid reactions, serum sickness usually occurs 5 to 24 days after administration. Symptoms include lymphadenopathy, fever, arthralgias and/or rash. Oral corticosteroids are effective in treating the symptoms.

5.5 Precautions and Contraindications

Administration of antivenin for all pit viper bites is not necessary. Proper assessment of the bite and clinical manifestations are required before antivenin administration.

Pregnancy is not a contraindication for crotalidae antivenin administration. Antivenin may prevent envenomation-induced abortions in pregnant women after severe envenomation.[93]

5.6 Other Considerations

People who have been bitten by a snake should be informed that the delayed hypersensitivity reaction from the antivenin may occur within 1 to 3 weeks. If such signs or symptoms become evident, a physician should be contacted immediately.

Recent work using the new Therapeutic Antibody Incorporated antivenom (TAI) Fab product has been reported in the literature.[94] Studies in sheep have shown that this agent is more efficacious than the standard crotalidae polyvalent antivenin preparation currently in use. Since the Fab product is not of equine origin, it is suspected that the serum sickness reactions that occur with the crotalidae polyvalent antivenin preparation will not manifest with the new Fab product. In a similar study, using a purified ovine Fab antivenin in 10 patients, the authors concluded that the new antivenin was well tolerated and effective; however,[95] repeated doses were required because of the very short half-life of the product. Further studies are necessary to substantiate the use of this product as a standard of care in the treatment of crotalidae snakebite. However, the results of these studies[94,95] suggest that this agent has potential in the future treatment of crotalidae snakebites.

Other pharmacological agents that are used not as antidotes, but as standard-of-care treatment of snakebites include tetanus immune globulin, tetanus toxoid and antibacterials. Superficial scratches may require topical antibacterial administration. If local tissue damage is present, quinolone antibacterials may be required to prevent infection from Gram-negative and Gram-positive bacilli.[88]

In summary, the treatment of pit viper snakebites is largely supportive. Antivenin, which aids in neutralising the venom, may cause anaphylactic reactions as a result of its equine origin. Often, adjusting the rate of administration and careful patient monitoring may permit administration of the antivenin to a patient who is hypersensitive to it. The decision regarding the suitability of a patient for antivenin should be evaluated by weighing the issues of risk versus those of benefit.

6. Flumazenil

6.1 Indication

Flumazenil is a benzodiazepine antagonist with traits that are analogous to the opioid antagonist properties of naloxone. In many cases, the risks of flumazenil outweigh its benefits; thus, there are few indications for this agent. Flumazenil is cautiously indicated in the management of benzodiazepine overdose, as serious adverse effects (such as ventricular dysrhythmias and seizures) have been reported. In patients with a benzodiazepine overdose, it has been suggested that flumazenil may confer greater risk than benefit. Another indication for flumazenil is the reversal of the benzodiazepine-induced CNS depression that is associated with sedation induced during outpatient procedures or after procedures involving a general anaesthetic.[96]

Overdoses with zolpidem, a nonbenzodiazepine sedative hypnotic, have been successfully treated with flumazenil.[97] Oral and intravenous flumazenil administration have further been employed in the management of patients with hepatic encephalopathy.[98] More studies are required to substantiate its use in these indications.

6.2 Mechanism of Action

Flumazenil is a 1,4-imidazodiazepine that inhibits the effects of benzodiazepines by competing for the benzodiazepine recognition site on the γ-aminobutyric acid (GABA)/benzodiazepine receptor complex.[96] Its effects are specific for central benzodiazepine receptors.[99] Similar to naloxone, flumazenil has no intrinsic agonist activity. The effects of anxiolysis, sedation and hypnosis are a function of benzodiazepine receptor occupancy. An anxiolytic effect occurs when approximately 20% of benzodiazepine receptors are occupied, while sedative and hypnotic effects generally occur at occupancy rates of 30 to 50% and 60%, respectively.[100]

6.3 Administration Guidelines

The usual dosage of flumazenil in adults is 0.2mg administered intravenously over 15 seconds, then 0.3mg after 30 seconds and 0.5mg after a further 30 seconds; administration of the latter dose is repeated to a maximum of 5mg.[54] The onset of response to flumazenil usually occurs within 1 to 2 minutes. Total doses greater than 5mg rarely provide any additional benefit.[54] The optimal dose is ultimately titrated according to the level of consciousness.

The shorter half-life of flumazenil in comparison with many benzodiazepines may warrant the administration of flumazenil as a continuous infusion. A randomised, double-blind, placebo-controlled trial of 51 patients showed that an infusion of flumazenil 0.5 mg/h maintained patients at an optimal level of consciousness after benzodiazepine-induced coma. Higher dosages may be required in more severely poisoned patients.[101] Similar to naloxone, the duration of a continuous flumazenil infusion will vary depending upon the amount of benzodiazepine ingested, the half-life of the benzodiazepine and pharmacokinetic differences among patients (including those with hepatic impairment).

Reported use in the paediatric and neonatal populations is limited. Some have proposed a 0.01 mg/kg dose of flumazenil for paediatric patients.[98] Further studies are necessary in this patient population to determine safety and efficacy. To date, use in children has not yet been approved by the FDA.

6.4 Adverse Effects

Reports of major adverse effects with flumazenil are relatively uncommon. However, one serious effect is the development of seizures, particularly when the benzodiazepine was originally prescribed as an anticonvulsant. If a patient has a seizure after flumazenil administration, phenobarbital (phenobarbitone) or additional benzodiazepine administration has been attempted. However, it is unlikely that this will be effective; moreover, higher than usual doses of benzodiazepines have been used without great success.[102]

The Flumazenil in Benzodiazepine Intoxication Multicenter Study Group[103] reported that the most common adverse effects associated with flumazenil administration were agitation (7%), vomiting (7%), abnormal crying (4%) and nausea (4%). All of these effects were reported in placebo recipients to a lesser degree. More serious adverse effects included seizures and cardiac arrhythmias. However, the adverse effects appear to be more consistent with withdrawal effects from the benzodiazepine as opposed to effects induced by flumazenil itself.

Resedation is most commonly found after flumazenil administration when the elimination half-life of the benzodiazepine exceeds that of flumazenil. As previously described, repeat bolus administration or continuous maintenance infusions of flumazenil may be required to maintain its effects until the benzodiazepine can be effectively eliminated.

6.5 Precautions and Contraindications

There are several contraindications to the use of flumazenil after acute ingestion.[54] Flumazenil is contraindicated in patients for whom benzodiazepines were originally prescribed for seizure prevention or those who had been receiving benzodiazepines as maintenance therapy, since it may obliterate the therapeutic effects of the benzodiazepine. It is also contraindicated in situations in which use of benzodiazepines may be anticipated such as for sedation, muscle relaxation or seizure control. Patients with severe head trauma should also not receive flumazenil, since these patients are at greater risk of developing seizure activity, and additional benzodiazepine administration may be warranted.[54] Furthermore, flumazenil has been known to increase intracranial pressure and reduce cerebral perfusion pressure.[98]

Patients with mixed overdoses, particularly the combination of TCAs and benzodiazepines, should not receive flumazenil; the benzodiazepine often serves to protect the brain from fatal seizure activity, and

the morbidity and mortality associated with benzodiazepine overdose is much lower than that of TCAs. By removing the protective activity of the benzodiazepine, life-threatening seizures from the TCA overdose may develop.[104]

6.6 Other Considerations

Initiating therapy with higher doses may increase the incidence of agitation and withdrawal. Therapy should begin with smaller doses of flumazenil, re-administered as needed. In patients with mixed overdoses that include benzodiazepines with other agents, the effects of flumazenil may not be fully realised because of the effects of other agents (opioids or other agents with sedative properties).

As with any pharmacological antidote, the administration of flumazenil is not intended to replace the institution of basic life support measures and gastrointestinal decontamination. All patients with substantial ingestions should be continually monitored, since rapid changes in patient status may occur.

In summary, flumazenil is an agent that has primarily been useful in the management of benzodiazepine ingestions. Judicious use of this agent in mixed overdoses is recommended, as the cardioprotective and neuroprotective properties of the benzodiazepines may provide some benefit. The actual incidence of mortality with benzodiazepine overdose is quite low, so the risk of benzodiazepine overdose must considered alongside the risk of unmasking the toxic effects of other agents.

7. Ethanol

7.1 Indication

Although methanol (methyl alcohol) and ethylene glycol ingestions are less common than the above listed poisonings, they are often associated with serious toxicity. Methanol is a common component of antifreeze, paint removers and windshield washer fluids. In 1993, it ranked 22nd by volume among chemicals produced in the US.[105] Ethylene glycol is commonly found in antifreeze, coolant fluids, and as a preservative and sweetener in selected products.[106]

Metabolic acidosis and visual complaints, including retinal oedema and blindness, are serious manifestations of methanol poisoning. The course of ethylene glycol poisoning generally follows 4 stages, which have been described elsewhere.[107-109] The major characteristic of methanol and ethylene glycol poisonings is an increased osmolal gap and anion gap metabolic acidosis. The severity of acidosis often correlates with outcome.[110] However, the absence of a gap (deviation from a normal value) should not eliminate the possibility of methanol or ethylene glycol ingestion.

Toxicity from these agents usually results from their respective metabolites (section 7.2) instead of the parent compounds. Therefore, the effects of methanol and ethylene glycol toxicity may not manifest immediately, since it may take time to convert these parent compounds into their toxic metabolites. Ethanol therapy is indicated if the serum methanol or ethylene glycol concentration is greater than 200 mg/L, even in asymptomatic patients.[111]

7.2 Mechanism of Action

To understand the mechanism of action of ethanol in methanol and ethylene glycol ingestions, a brief discussion of normal methanol and ethylene glycol metabolism will be described.

Methanol is metabolised in the human body by alcohol dehydrogenase and aldehyde dehydrogenase to form the toxic metabolite, formic acid. Formic acid is converted to carbon dioxide and water through a slow process that requires the vitamin cofactor, folic acid. Ethylene glycol is also metabolised by alcohol dehydrogenase and aldehyde dehydrogenase to form glycolic acid, which is also toxic. Glycolic acid is enzymatically metabolised to glyoxylic acid by lactate dehydrogenase glycolic acid oxidase. Glyoxylic acid is subsequently metabolised to glycine, oxalic acid, formic acid and α-hydroxy-β-ketoadipate; pyridoxine and thiamine are vitamin cofactors for the conversion of glyoxylic

acid to glycine, and of glycine to α-hydroxy-β-ketoadipate, respectively.[111]

The affinity of ethanol for alcohol dehydrogenase is significantly greater than the affinity of alcohol dehydrogenase for methanol or ethylene glycol.[112] Therefore, ethanol competitively acts to remove alcohol dehydrogenase from the normal metabolic disposition of methanol and ethylene glycol; thereby preventing the formation of the toxic metabolites, formic acid or glycolic acid, respectively.

7.3 Administration Guidelines

In patients with alcoholism, methanol or ethylene glycol is often ingested as an alternative to ethanol. The metabolism of ethanol is modified in patients with alcoholism versus those without, so different ethanol administration guidelines are suggested depending upon patient history.

In patients without alcoholism, an intravenous loading dose of ethanol 600 mg/kg (or 7.6 ml/kg of a 10% parenteral ethanol formulation) followed by a maintenance dose of 66 mg/kg/h (0.83 ml/kg/h of a 10% parenteral solution) is recommended.[106,110,113] For those patients who require haemodialysis (section 7.6), ethanol 169 mg/kg/h (2.13 ml/kg/h of a 10% parenteral solution) can be given after the loading dose.[106,110,113] The type of haemodialysis filter used may alter the quantity of ethanol required. To optimally saturate alcohol dehydrogenase, serum ethanol concentrations should be maintained at 1000 to 1500 mg/L.

Because of the higher rate of ethanol metabolism in patients with chronic alcoholism, the amount of ethanol required in these patients is greater than that for those who do not abuse ethanol.[113] In patients with chronic alcoholism, the same loading dose as those without alcoholism may be used, but the maintenance dosages for patients not receiving dialysis and those who are receiving dialysis increase to 154 mg/kg/h (1.96 ml/kg/h of a 10% parenteral solution) and 257 mg/kg/h (or 3.26 ml/kg/h of a 10% parenteral solution), respectively. In those patients whose baseline serum ethanol concentration is greater than 1000 mg/L, no loading dose is required.[110] In all patients, serial serum ethanol concentrations should be measured to ensure that they are maintained at or above 1000 mg/L.[111]

The oral route of ethanol administration has been used; however, ethanol concentrations of less than 20% are preferred, because of the gastric irritation (gastritis and vomiting) that may occur with higher concentrations. The oral ethanol loading dose is 600 mg/kg, followed by 125 to 150 mg/kg/h.[114] Since ethanol is removed effectively by haemodialysis, patients undergoing this procedure require 237 mg/kg/h (approximately 250 mg/kg/h) administered orally or through a nasogastric tube, on an hourly basis. In calculating both oral and parenteral doses, it must be remembered that ethanol has a specific gravity of approximately 0.8. Therefore, 95% ethanol is approximately 76g/100ml, *not* 95g/100ml.

7.4 Adverse Effects

The adverse effects associated with ethanol are well known. CNS depression, respiratory depression and gastritis are commonly reported. As a result of the short duration of ethanol administration during the management of these ingestions, adverse effects should be of limited duration. However, careful monitoring in an intensive care setting is required especially in children.

7.5 Precautions and Contraindications

Serum methanol concentrations are not the sole indicators for continued therapy, since toxicity is the result of the metabolites, not the parent compound. Other monitoring parameters should include serum electrolytes, glucose, arterial pH, hydration status and osmolar gap.[111]

Advantages of oral ethanol administration include easy access by mouth or nasogastric tube and the use of more concentrated solutions, thereby requiring less fluid administration. However, the risk of gastritis, aspiration and vomiting is greater with oral ethanol administration. Frequent administration requires increased nursing time that potentially results in missed doses.[110]

Advantages of intravenous administration include the ability to rapidly titrate maintenance infusions and the reduced tendency towards gastritis, vomiting or aspiration. Disadvantages include the potential for fluid overload, resulting from the administration of dilute solutions (especially loading doses), and the need for a central venous catheter because of the hyperosmolality of the solution.[110] The osmolality of 10% ethanol in 5% dextrose in water is approximately 2000 mOsm/kg water.[110]

7.6 Other Considerations

Methanol and ethylene glycol are both rapidly absorbed through the gastrointestinal tract. Therefore, gastric decontamination efforts may not be efficacious unless they are performed in a timely fashion after the ingestion.

Other treatments that can be initiated in patients with methanol or ethylene glycol toxicity include bicarbonate solutions, to prevent severe metabolic acidosis, and haemodialysis, to remove the alcohols and their toxic metabolites. Controversy exists regarding the degree of acidosis at which bicarbonate solutions should be administered. Further discussion of this issue is beyond the scope of this article.

Haemodialysis is indicated in conjunction with ethanol infusion in the presence of a serum methanol concentration greater than 500 mg/L,[115] visual disturbances, or a severe acidosis that does not respond to intravenous bicarbonate.[105] Once haemodialysis is instituted, the dose of ethanol should be increased 2- to 3-fold (as outlined in section 7.3) in order to maintain adequate serum ethanol concentrations.

Since folic acid is a vitamin cofactor in the conversion of formic acid to carbon dioxide and water, it has been used as adjunctive therapy in the treatment of methanol poisoning. Intravenous dosages of 50 to 100mg every 4 hours for 24 hours have been suggested.[111,116] The alternative regimen of intravenous calcium folinate (folinic acid; leucovorin calcium) 1 to 2 mg/kg every 4 to 6 hours has also been used.[105]

In patients with ethylene glycol poisoning, daily administration of pyridoxine 100mg and thiamine 100mg may be useful as adjunctive therapies, since these vitamins act as cofactors in the conversion of glyoxylic acid to the nontoxic substances glycine and α-hydroxy-β-ketoadipate.

4-Methylpyrazole (4-MP) is a potent alcohol dehydrogenase inhibitor that has been used experimentally in the treatment of ethylene glycol and methanol ingestions. Compared with ethanol, the slower elimination rate and better safety profile of 4-MP have made it superior to ethanol in the treatment of these poisonings.[117,118] It has been suggested that 4-MP may replace current recommendations for ethanol administration in patients with methanol ingestions.[119]

In summary, methanol and ethylene glycol produce toxicity through similar oxidative pathways within the liver. Ethanol is used as an antidote to compete with methanol or ethylene glycol for alcohol dehydrogenase. This results in reduced formation of the toxic metabolites generated by these agents. Haemodialysis is a nonpharmacological method of quickly removing the parent compound and its metabolites. 4-MP is a newer agent that shows promise in the treatment of methanol ingestions. The prognosis of patients who have ingested either methanol or ethylene glycol depends upon the quantity ingested, degree of acidosis and underlying vitamin deficiencies.

8. Hydroxocobalamin

8.1 Indication

Although not approved by the FDA, hydroxocobalamin can be administered to patients with cyanide toxicity, and is used for this indication in Europe. There are 3 situations in which cyanide toxicity usually presents. The first may be iatrogenic, such as with sodium nitroprusside; this may be particularly true for patients with impaired hepatic or renal function. A second source of cyanide toxicity is exposure to inhaled combustion products; although carbon monoxide is the immediate concern in patients with smoke inhalation, a combination of

carbon monoxide and cyanide poisoning is usually present. The final scenario by which toxic cyanide concentrations may be encountered is by deliberate or accidental oral ingestion.

Clinical manifestations of severe cyanide toxicity include metabolic acidosis, seizures and deep coma. A clinical hint of cyanide poisoning is the scent of bitter almonds from vomitus or gastric lavage contents, although many individuals are genetically incapable of detecting the odour.[120]

8.2 Mechanism of Action

Cyanide is a potent, rapidly acting toxin that inhibits oxygen use at the cellular level. The hepatic enzyme rhodanese converts normally ingested quantities of cyanide into thiocyanate, which is renally eliminated. The affinity of cyanide for the ferric form of iron in cytochrome oxidase (a respiratory enzyme) inhibits cellular respiration, which causes significant tissue hypoxia and, ultimately, death. Manifestations of cyanide poisoning result when the amount of cyanide present can no longer be handled by the rhodanese enzyme.[92] The mechanism of action of hydroxocobalamin is through its combination with cyanide in the blood to form cyanocobalamin (vitamin B_{12}), which can then be excreted in the urine.[121]

8.3 Administration Guidelines

The usual recommended dose of hydroxocobalamin is 50 mg/kg. Using the hydroxocobalamin solution that is available in the US, this would amount to 4 to 5L, rendering the US pharmaceutical formulation impractical for use.[66] However, hydroxocobalamin is available as a more concentrated solution in other countries, and was formerly an investigational agent in the US, so lesser fluid volumes may be used. A single dose of 5g may be sufficient in most patients.[122]

8.4 Adverse Effects

Adverse reactions to hydroxocobalamin are primarily constitutional, uncommon and self-limiting. Hypertension, diarrhoea and itching may occur. A reddish discoloration of the skin, mucous membranes and urine is common among patients receiving hydroxocobalamin, while anaphylaxis is a rare effect.

8.5 Precautions and Contraindications

Hydroxocobalamin is contraindicated in patients with hypersensitivity to the agent.

8.6 Other Considerations

As mentioned previously, patients receiving high-dosage sodium nitroprusside have the potential to develop cyanide or thiocyanate toxicity. Continuous infusions of hydroxocobalamin (25 mg/h) have been occasionally used as prophylaxis against sodium nitroprusside–induced cyanide toxicity. Hydroxocobalamin infusions should be continued for 10 hours beyond the discontinuation of sodium nitroprusside infusions, since the half-life of cyanide in red blood cells is 10 hours. Hydroxocobalamin has been deemed safe and effective in the prevention and treatment of sodium nitroprusside–induced toxicity.[123] However, the use of hydroxocobalamin in this situation is not considered to be routine practice.

Sodium nitrite, an agent that is commonly employed in patients with cyanide toxicity, has been associated with hypotension and methaemoglobinaemia (rare), which could further complicate combined cyanide and carbon monoxide poisoning. Hydroxocobalamin may have some benefit over sodium nitrite in patients with cyanide toxicity as a result of its better safety profile.[124]

There appears to be a discrepancy in table I concerning hydroxocobalamin and the cyanide antidote kit. In table I, 928 cyanide antidote kits were reported as being used over the 12-year period compared with 3130 reports of hydroxocobalamin use. Since the cyanide antidote kit is the only FDA-approved cyanide antidote in the US, it seems unlikely that it was administered almost 4 times less frequently than hydroxocobalamin. However, this is a reflection of the inaccuracy of the reporting system. US poison centres are perhaps more likely to be contacted regarding the use of hydroxocobalamin

in cyanide poisoning than the cyanide antidote kit, simply because of unfamiliarity with its use.

Primary care of the patient requires removal of the toxic source. Pharmacologically, the cyanide antidote kit (section 16) and hyperbaric oxygen are the preferred methods of treating cyanide toxicity.[125] Limited reports in the French literature[126] suggest that hydroxocobalamin is a reasonable alternative for use in cyanide intoxication.

9. Physostigmine

9.1 Indication

The anticholinergic toxidrome is common among poisoning exposures. There are many medications, available over the counter and via prescription, that may produce toxic anticholinergic effects. Anticholinergic symptoms result from a combination of central and peripheral components. Symptomatology includes tachycardia, fever, disorientation, mydriasis, decreased bowel sounds and urinary retention. Anticholinergic poisoning is often caused by antihistamines such as diphenhydramine and by ingestion of members of the plant species *Datura*.

Physostigmine is a cholinergic agent that is primarily reserved for the treatment of life-threatening anticholinergic poisoning.[43,111] Physostigmine has also been used to reverse the postoperative pharmacological effects of paralytic agents. However, routine postoperative use of physostigmine is not recommended, because other agents have shown more selective peripheral blocking activity.[127] Limited work has been performed on the prophylactic use of physostigmine against organophosphate intoxication.[128] Further studies in these indications are needed before widespread use can be recommended.

9.2 Mechanism of Action

Anticholinergic agents competitively antagonise acetylcholine. Most commonly affected are the cardiac muscle, smooth muscle and exocrine glands.[129]

Physostigmine is a lipophilic, tertiary amine that crosses the blood-brain barrier to reverse the central and peripheral effects of anticholinergic agents. Essentially, physostigmine inhibits acetylcholinesterase, thereby preventing the breakdown of acetylcholine and permitting the accumulation of acetylcholine at the neuromuscular junction.[127] As a result of either the large amounts of acetylcholine present at the postsynaptic muscle fibre[130] or altered acetylcholine ion-channel function,[131] acetylcholine binds to postsynaptic receptors to reverse anticholinergic effects.

Neostigmine and pyridostigmine are quaternary amine anticholinergic agents that are unable to cross the blood-brain barrier and therefore act only peripherally to antagonise the effects of anticholinergic agents.[132] Therefore, physostigmine is preferred, since it treats both CNS and peripheral toxicity.

9.3 Administration Guidelines

Physostigmine has been used (but is not recommended) to diagnose anticholinergic intoxication. In adults, physostigmine is usually administered as a single dose of 1 to 2mg intravenously over 5 to 10 minutes (the slow administration rate is strongly emphasised).[111] Reversal of symptomatology occurs quickly if the poisoning is solely the result of an anticholinergic substance. Because of the short duration of action of physostigmine, repeated doses of 1 to 2mg may be administered every 30 minutes until symptoms resolve.[133] The maximum single recommended dose of physostigmine is 2mg.[111] Paediatric patients may receive 0.02 mg/kg to a maximum of 0.5mg over several minutes.[111]

Anticholinergic toxicity should not be excluded if a negative physostigmine challenge is observed.[133] If anticholinergic agents are not the cause of clinical manifestations, physostigmine may precipitate cholinergic effects. Physostigmine should always be administered slowly and never administered as a bolus.

9.4 Adverse Effects

The use of physostigmine is limited by its adverse effect profile. Clinical features of physostigmine toxicity typically include signs of excessive

parasympathetic activity, such as bradycardia, hypotension and diaphoresis. Physostigmine use in patients with TCA overdoses has resulted in asystole.[134] Seizure activity has been reported with rapid intravenous physostigmine administration.[43]

9.5 Precautions and Contraindications

Absolute contraindications to physostigmine use include TCA overdose in patients with cardiac manifestations or mechanical obstruction of either the genitourinary tract or gastrointestinal tract.[111] Some of the relative contraindications of physostigmine therapy include diabetes mellitus, coronary artery disease, cardiac arrhythmia, asthma and glaucoma.[111,133]

Physostigmine prolongs the paralytic effects of suxamethonium chloride (succinylcholine) from 5 minutes to approximately 45 minutes.[43] Caution is required in patients receiving these agents concomitantly.

9.6 Other Considerations

Caution should be exercised in patients who are sensitive to sulfites, as physostigmine is available in a 0.1% sulfite concentration. Sulfites have been associated with anaphylaxis and other effects, such as vomiting, abdominal pain and wheezing. However, it has not been recommended that physostigmine should be withheld from treating life-threatening anticholinergic toxicity when clearly indicated.[135]

In summary, the use of physostigmine is fairly limited, as a result of its narrow therapeutic index. Removal of the pharmacological source of toxicity, together with supportive measures, is the treatment of choice in patients with anticholinergic intoxication. Only for the severe or life-threatening anticholinergic toxidrome is physostigmine possibly indicated. Careful patient selection, by consideration of potential toxicities and absolute or relative contraindications, should precede the decision to administer physostigmine.

10. Pralidoxime Chloride

10.1 Indication

Pralidoxime chloride (pyridine-2-aldoxime methochloride; 2-PAM) is an agent that is often used in conjunction with atropine for the treatment of organophosphate intoxication. The features of organophosphate poisoning, the intermediate syndrome and delayed neuropathy have been described.[56-58,60] Since pralidoxime chloride is not effective in resolving respiratory depression, atropine is always required as the initial agent to block the effects of acetylcholine accumulation. The value of pralidoxime chloride lies in its ability to reverse the nicotinic and CNS effects of these agents. Pralidoxime chloride is indicated in most forms of organophosphate toxicity, since it may protect the patient from chronic neurotoxicity. It is also indicated for the control of overdose by anticholinesterases used in the treatment of myasthenia gravis.[136]

10.2 Mechanism of Action

Acetylcholine is converted to choline and acetic acid via the acetylcholinesterase enzyme at neuronal endplates. Organophosphate agents phosphorylate acetylcholinesterase to block this reaction, resulting in an accumulation of acetylcholine. The acetylcholinesterase catalytic site may be restored, although this process has negligible significance. Another process, labelled the 'aging' process, is a nonenzymatic time-dependent loss of 1 alkyl residue attached to the phosphorus atom (which was added to acetylcholinesterase), resulting in a stable form of inactivated phosphorylated acetylcholinesterase.

Pralidoxime chloride is classified as a cholinesterase or oxime reactivator that acts to reverse organophosphate toxicity by regenerating acetylcholinesterase, which has been inhibited by the organophosphate. To exert its activity, pralidoxime chloride must act on phosphorylated acetylcholinesterase before the very stable 'aging' process occurs; it is only at that stage that pralidoxime chloride can restore the catalytic site of acetylcholinesterase.[64]

For this reason, pralidoxime chloride is most effective when administered within the first 24 to 36 hours of organophosphate ester ingestion. It should be remembered that organophosphate esters are irreversible inhibitors of acetylcholinesterase, while carbamates produce a reversible inhibition of acetylcholinesterase; therefore, pralidoxime chloride is not recommended in patients with carbamate poisoning.

Although the agent is most successful when administered less than 48 hours after exposure, patients presenting as late as 2 to 6 days after exposure have shown some improvement.[137] Proposed methods by which pralidoxime chloride may be beneficial in this situation include: (i) use in parathion poisoning, whereby the 'aging' process is slowed; (ii) exposure to large amounts of organophosphate, when there is slower absorption; (iii) redistribution of organophosphate from fat stores into the vascular compartment; and (iv) other unidentified actions of the drug.[66]

10.3 Administration Guidelines

The usual dose for adults is 1 to 2g, infused over 15 to 30 minutes. If amelioration of muscle weakness symptoms is not observed within 1 hour, a second infusion if 1 to 2g is indicated. The corresponding dose in children is 20 to 40 mg/kg.[136] Further doses of pralidoxime chloride should be titrated according to effect. In adults, the maximally recommended dose is 12g in 24 hours.[66] In some patients, pralidoxime chloride administration is necessary for up to 22 days, particularly in the treatment of poisoning with a very lipophilic organophosphate.[138]

As mentioned in section 10.2, pralidoxime chloride may be effective in patients presenting 2 to 6 days after exposure.[137] Atropinisation is required in all patients treated for organophosphate ester toxicity (section 10.1); pralidoxime chloride as a single agent is considered insufficient therapy.

10.4 Adverse Effects

Pralidoxime chloride is relatively well tolerated, although blood pressure fluctuations may occur.[62] Nausea, vomiting, dizziness and disturbances of consciousness have been reported and are the result of hydrogen cyanide, a metabolic degradation product of oxime therapy.[137] Blurred vision, tachycardia and muscular weakness may also occur after the use of pralidoxime chloride. However, it is often unclear whether the adverse effect is related to the poison, atropine or pralidoxime chloride. Biochemical signs of mild hepatic toxicity have been observed in patients receiving oxime therapy; values normalised once oxime therapy was discontinued.[139]

10.5 Precautions and Contraindications

Rapid administration of pralidoxime chloride (over 200 mg/min) can result in temporary worsening of cholinergic manifestations, including tachycardia, muscle rigidity and laryngospasm.[136] The agent is also known to accentuate the effects of atropine, so patients should be monitored closely for adverse effects.

80 to 90% of pralidoxime chloride is eliminated unchanged in the urine; therefore, the dosage should be reduced in patients with renal dysfunction. Special precautions should be taken in patients with myasthenia gravis, since pralidoxime chloride may precipitate a myasthenic crisis.

Pralidoxime chloride should be administered with caution in patients with carbamate poisoning since it may increase acetylcholinesterase inactivation.[61] Also, it should not be administered prophylactically since it may mask symptoms of organophosphate toxicity. Pralidoxime chloride is not effective in the treatment of poisonings caused by phosphorus or inorganic phosphates, or by organophosphates that do not possess anticholinesterase activity.[136]

10.6 Other Considerations

Controversy exists regarding the issue of using pralidoxime chloride in patients with carbamate poisoning. Its use in carbamate poisonings has produced mixed results, but is not recommended.[62] Atropine has been shown to be superior to pralidoxime chloride in the treatment of carbamate

toxicity and is considered to be the antidote of choice in this situation (section 3). Pralidoxime chloride should only be used when: (i) atropine therapy has failed; (ii) a mixed organophosphate and carbamate toxicity is present; or (iii) a patients shows profound toxicity caused by unidentified cholinesterase inhibitors.[140]

In summary, pralidoxime chloride can be administered adjunctively with atropine for the treatment of moderate to severe organophosphate poisonings. Adverse effects associated with pralidoxime chloride administration are often difficult to distinguish from atropinic effects or those of the organophosphate poisoning itself. The use of pralidoxime chloride in carbamate poisonings is generally not recommended.

11. Digoxin-Specific Antigen Binding Fragments (Digoxin Immune Fab)

11.1 Indication

The most widely used Fab product is digoxin immune Fab. It is indicated in the treatment of severe, life-threatening digitalis glycoside toxicity, including that caused by digoxin, digitoxin, foxglove (*Digitalis* species) and oleander (*Nerium oleander*). In overdose situations, it is used very selectively to treat ventricular arrhythmias, progressive bradycardia (with or without heart block) or hyperkalaemia.[141]

Digoxin is used in the treatment of supraventricular tachyarrhythmias and in the management of congestive heart failure to increase myocardial contractility and decrease conduction through the atrioventricular node.

11.2 Mechanism of Action

Digoxin immune Fab has 2 major mechanisms of action.[142] First, the toxicodynamic effect involves the extracellular binding of Fab to digoxin to form a Fab-digitalis complex, yielding a form of digoxin that is unavailable for receptor binding in the body. Total serum digoxin concentrations, which include the Fab-digitalis complex will increase, while free digoxin concentrations decrease to almost zero within a few minutes of administration of digoxin immune Fab.[143] The second action of digoxin immune Fab is based on its toxicokinetic properties. In patients with normal renal function, the half-lives of digoxin and digitoxin are 1.6 and almost 7 days, respectively.[144] On the other hand, the elimination half-life of the Fab-digitalis complex is approximately 10 to 20 hours.[145] Therefore, elimination is more rapid when digoxin is part of the Fab-digitalis complex than as the free drug, thus further decreasing the duration of intoxication.

11.3 Administration Guidelines

The quantity of digoxin immune Fab (Digibind®) required is a function of either the dose of digoxin ingested or the steady-state serum digoxin concentration. Digibind® contains 40mg digoxin immune Fab and neutralises 0.6mg digoxin or digitoxin. The Digibind® regimen may be calculated using the following formulae.[111] First, the digoxin body load is calculated:

(Eq 1a) Body load of digoxin (mg) = digoxin dose ingested (mg) × 0.8

or

(Eq 1b) Body load of digoxin (mg) = steady-state serum digoxin concentration (μg/L) × 5.6L (volume of distribution of digoxin) × bodyweight (kg)/1000

If the source of digitalis is in the form of digitoxin, substitute 0.56L (instead of 5.6L) for the volume of distribution in equation 1b. Then, the Digibind® dose is calculated:

(Eq 2) Digibind® dose (mg) = 64 × body load digoxin (mg)

In equation 2, the body load of digoxin is multiplied by 64 since 64mg of digoxin immune Fab will neutralise 1mg digoxin. Another formulation of digoxin immune Fab (Digidot®) is used in other parts of the world; 80mg of digoxin immune Fab in Digidot® neutralises 1mg of either digoxin or digitoxin so 80 should be substituted for 64 in equation 2 when using Digidot®.

11.4 Adverse Effects

Digoxin immune Fab is a relatively well tolerated agent. In a cooperative surveillance study of 717 patients, only 7% of patients had an adverse effect that was potentially related to Fab administration.[146] Allergic responses were reported in 0.8% of patients. Those with a history of allergy or asthma experienced this effect more often than those without such a history. Recrudescent toxicity occurred in 2.8% of patients treated with digoxin immune Fab, mostly as a result of patients receiving an insufficient Fab dose. Of 129 patients who were restarted on digoxin after Fab treatment, 1.6% developed a rapid ventricular response to atrial fibrillation. Noncardiovascular adverse effects were rarely reported, and were attributed to underlying disease or concomitant therapies.[146]

11.5 Precautions and Contraindications

To date, there are no absolute contraindications to digoxin immune Fab administration. However, caution should be exercised in individuals who have previously experienced an allergic reaction to ovine proteins.

Administration of digoxin immune Fab may result in severe hypokalaemia. Serial serum potassium levels should be measured in order to monitor patient status.[142]

Complete withdrawal of inotropic support in patients with severely impaired cardiac impairment may result in declining cardiac function. Other inotropic agents such as dobutamine, dopamine or vasodilators may be instituted.

11.6 Other Considerations

Serum digoxin concentrations should be measured a minimum of 6 hours after the overdose, or the last dose of digoxin in the case of overdosage. Serum concentrations drawn before this time may be artificially elevated, since at least 6 hours is required for digoxin tissue distribution. Elevated digoxin serum concentrations drawn before this 6-hour period should not be used to determine the need for digoxin immune Fab administration.

Digoxin immune Fab interferes with the laboratory measurement of total serum digoxin concentrations, producing an apparent significant elevation of the digoxin concentration. Unless *free* digoxin concentrations can be measured, total serum digoxin concentrations are unreliable and wasteful after digoxin immune Fab is administered.[111]

Although digoxin immune Fab is produced from sheep serum, skin testing is not routinely required before administration. Allergic reactions are rare, but the potential for anaphylaxis should be considered.

Higher mortality rates from digoxin toxicity have been associated with patients who exhibit a combination of 5 prognostic indicators:

- patients over 55 years of age
- male sex
- history of cardiac disease
- high degree atrioventricular block
- serum potassium levels above 5.5 mmol/L.

Recent literature suggests patients who display these characteristics should be treated with digoxin immune Fab earlier in the course of the toxic effect (before overt signs of serious toxicity occur) to reduce the likelihood of a fatal result.[142,147]

Cost should be considered when assessing the need for digoxin immune Fab. As can be calculated from table II, the average wholesale cost of digoxin immune Fab is $US401.99 per ampoule.[16] However, overall healthcare costs may potentially be diminished, since treatment may reduce length of stay in hospital.[148]

In summary, digoxin immune Fab is well tolerated and efficacious in the treatment of digitalis poisoning. Because of the extremely high cost, its use is commonly reserved for patients with a severe, life-threatening ingestion. However, recent literature encourages the use of digoxin immune Fab earlier in the treatment of some patients with digoxin ingestion.

12. Pyridoxine

12.1 Indication

Tuberculosis is becoming a more prevalent disease, as a result of the rapid increase in the number of patients with HIV and other immunocompromised states. Isoniazid is recommended in the treatment and prophylaxis of mycobacterial tubercular disease.[149,150] As a result of the greater access to isoniazid, poisoning from acute and chronic ingestions have become more common.

The primary antidotal use of pyridoxine is in the treatment of isoniazid ingestion. Pyridoxine has also been administered in other toxicologically emergent situations. It has been effectively used in the treatment of toxicity related to hydrazine derivatives, such as asymmetrical 1,1-demethylhydrazine (UDMH),[151] an industrial compound primarily used in aeronautics and astronautics. The treatment of *Gyromitra* mushroom poisoning is another toxicological indication for pyridoxine. *Gyromitra* mushrooms contain a pyridoxine antagonist, monomethylhydrazine. Poisoning may occur from ingestion or cooking of the mushroom.[43] As previously mentioned, pyridoxine may be further used as adjunctive therapy in patients with ethylene glycol poisoning (see section 7.6).

12.2 Mechanism of Action

The active form of pyridoxine, pyridoxal-5-phosphate, is a cofactor for glutamic acid decarboxylase and GABA transaminase, which are enzymes involved in the synthesis of the neuroinhibitory transmitter GABA. In patients with acute isoniazid toxicity, isoniazid binds with pyridoxal-5-phosphate to form a nontoxic metabolite that is readily eliminated in the urine.[152] Active pyridoxal-5-phosphate is depleted, resulting in a reduction in GABA levels, which causes increased CNS excitability and seizures. Pyridoxine restores pyridoxal-5-phosphate levels, which increases GABA formation[153] and thus decreases seizure activity.

12.3 Administration Guidelines

The usual pyridoxine dose is 1g per gram of isoniazid ingested,[153-155] given intravenously over 15 to 30 minutes. If the quantity of isoniazid ingested is unknown, 5g of pyridoxine may be administered every 30 minutes until seizure activity is resolved.[156]

As stated in section 7.6, daily administration of pyridoxine 100mg may serve as adjunctive therapy in ethylene glycol poisonings, because it acts as a cofactor in the conversion of glyoxylic acid to the nontoxic substance glycine.

12.4 Adverse Effects

It was once believed that excess ingestion of pyridoxine would be eliminated in the urine without adverse symptomatology. However, more recent literature brings to the forefront some of the toxic manifestations associated with excessive pyridoxine administration.[157,158]

One of the more significant clinical features involves a sensory neuropathy that resembles isoniazid toxicity. This neuropathy generally begins with a sensory loss in a glove and stocking manner, originating in the lower extremities. Accompanying these symptoms are ataxia and distal limb impairment of position and vibration sense.[158] Others have reported bone pain, muscle weakness, numbness and fasciculation.[159] Reversal of symptoms usually occurs upon suspension of pyridoxine therapy. Distinguishing the peripheral neuropathy attributed to isoniazid from that of pyridoxine can only be determined by discontinuing one of the agents.

12.5 Precautions and Contraindications

In patients with isoniazid-related seizure activity that is refractory to pyridoxine, other anticonvulsants may be used, including diazepam and phenobarbital. In patients who are slow acetylators, phenytoin should be administered cautiously, since isoniazid inhibits the metabolism of phenytoin and serious phenytoin toxicity may develop.[160]

12.6 Other Considerations

Although isoniazid is not a common cause of poisoning, its use has been on the increase as a result of the growing annual incidence of tuberculosis. In combination with supportive measures, pyridoxine is a pharmacological antidote that is readily available for treatment of isoniazid ingestions. Haemodialysis may be useful in patients with severe toxicity. It should be noted that excessively high doses of pyridoxine therapy may produce a peripheral neuropathy similar to that associated with isoniazid.

13. Dimercaprol (British Anti-Lewisite; BAL)

13.1 Indication

Lead toxicity is a serious health concern in the US and a leading cause of toxic illness in children.[161] Similar to other heavy metals, lead suppresses cellular respiration by inhibiting sulfhydryl-containing enzymes that are critical for physiological processes.[61] Signs and symptoms associated with lead toxicity involve most major organ systems, including the cardiovascular and haematological systems, and the CNS. Dimercaprol (British antilewisite; BAL; 2-3 dimercaptopropranol) has shown efficacy in the chelation treatment of lead toxicity.

13.2 Mechanism of Action

Dimercaprol was originally manufactured in the 1940s as an antidote for lewisite, an arsenical chemical warfare gas.[162] Today, it is primarily used in the treatment of lead or arsenic poisoning. Dimercaprol contains 2 sulfhydryl groups, which form a stable nontoxic chelate complex in the presence of heavy metals including lead, arsenic, mercury or gold. These hydrophilic chelates are then eliminated in the urine.

13.3 Administration Guidelines

In patients with lead poisoning, dimercaprol must be coadministered with sodium calcium edetate [edetate calcium disodium; calcium ethylenediamminetetra-acetate (EDTA)] to maximise efficacy and minimise toxicity. Children with blood lead levels greater than 690 μg/L require intensive care monitoring.[163] The combination may also be used in children with lead encephalopathy or protracted vomiting who require parenteral therapy, even if blood lead levels are lower than 700 μg/L. Although not an approved use, many clinicians use oral chelation with succimer (section 17) instead of parenteral chelation with dimercaprol and/or sodium calcium edetate.

The usual dosage of dimercaprol depends upon the type and severity of the poisoning. A common administration schedule is 3 to 5 mg/kg every 4 hours by deep intramuscular injection for 2 days, then 2.5 to 3 mg/kg every 6 hours for 2 days, followed by 2.5 to 3 mg/kg every 12 hours for 7 more days.[66] Five to 7 days after discontinuing therapy, the blood lead level will rebound because of a redistribution of lead from soft tissues and bone into the blood (section 13.6). A second course of therapy with dimercaprol plus sodium calcium edetate is indicated for patients with blood lead levels greater than 700 μg/L.[162]

13.4 Adverse Effects

Adverse effects of dimercaprol include hyperpyrexia, tachycardia and hypertension. Intramuscular injections of dimercaprol are extremely painful. Injection sites should be documented (mapped) and rotated with each dose. Before administration, 2ml of 2% procaine injected into the site may afford some pain relief. Patients should be informed of the unpleasant breath odour that accompanies dimercaprol administration.

13.5 Precautions and Contraindications

As a result of its lipophilic properties, dimercaprol is formulated in peanut oil. Therefore, dimercaprol should not be administered to patients with an allergy to peanuts or peanut products.[162] It must never be administered intravenously, as the oil formulation will produce immediate and disastrous pulmonary complications.

It is important to note that coadministration of iron to patients receiving dimercaprol will result in the formation of a toxic dimercaprol-iron chelate. Consequently, the concomitant use of dimercaprol and iron is contraindicated. This is unfortunate, since many patients with lead poisoning often have low iron stores that require replacement. Iron therapy may be started immediately after the cessation of dimercaprol therapy. Furthermore, dimercaprol is not recommended in the treatment of iron poisoning, as a result of formation of the toxic chelate. For similar reasons, dimercaprol should not be used in patients with cadmium or selenium poisonings.

Dimercaprol is contraindicated in patients with hepatic insufficiency, unless toxicity manifests as arsenic-induced jaundice. The drug should be administered very cautiously in patients with renal insufficiency. Alkalinising the urine may protect against further renal damage by dimercaprol, since the dimercaprol-metal complex degrades in acidic environments.[164]

Caution should be exercised in patients with underlying hypertension, as increases in blood pressure are commonly reported. Patients with glucose-6-phosphate dehydrogenase deficiency should be monitored closely for haemolysis. Dimercaprol is also contraindicated in patients with alkyl mercury poisoning, since it may increase brain mercury levels, thus intensifying the neurological effects.[165]

Dimercaprol is classified as 'pregnancy category C' and should not be used in pregnant women unless the benefits of therapy outweigh the risks of serious morbidity or possible fatal outcome.

13.6 Other Considerations

Dimercaprol is available as a 10% preparation in oil that can be stored at room temperature, but away from light. Ampoules may contain a small sediment that develops during the sterilisation process; this does not indicate deterioration. A precipitate may also form if the agent is refrigerated, but this may dissolve at room temperature.

There has been some controversy regarding the treatment of lead poisoning with chelating agents. Blood lead levels represent the lead burden in 2 separate compartments. The soft tissue compartment constitutes about 5 to 30% of total body lead, with a half-life of 40 days. On the other hand, the total lead burden in the skeletal compartment eventually increases to 90 to 95%, with a half-life of 1 to 5 years. Therefore, chelating agents are more likely to be useful in patients with acute lead poisoning, since most of the lead is located in the blood or soft tissues, and is more accessible to the chelating agent.

Patients with chronic low-level lead intoxication have more lead stored in the bony compartment, making extraction of the lead very difficult. When chelating agents are administered, lead is removed from the blood, and to some extent, the soft tissues. Upon discontinuation of the chelating agent, the lead in the bony compartment redistributes to the blood and soft tissue compartments. This is the explanation for the acute rebound effects that have been noted when chelating agent therapy is discontinued.

The single most important factor in lead intoxication is elimination of further exposure to lead. No patient, particularly a child, should be permitted to return to the lead-contaminated environment after completion of chelation therapy.

Most of the information that has been documented on the use of chelating agents for chronic ingestion in the literature is based on anecdotal case reports. There has been some question over whether patient improvement is a result of the chelation therapy or the fact that the patient has been removed from the source of his/her lead intoxication. For this reason, the rationale of using chelating agents in these situations is unclear.[166] With the advent of succimer, the use of dimercaprol to treat lead poisoning is decreasing.

14. Penicillamine

14.1 Indication

Penicillamine is a chelating agent that has been employed as a treatment modality in lead poisoning. However, like dimercaprol, it is largely being

replaced in the US by succimer (section 17). Penicillamine has also been used successfully in the treatment of other heavy metal poisonings including mercury, iron, arsenic and cadmium.

14.2 Mechanism of Action

Penicillamine is a chelating agent similar to dimercaprol. The d-isomer is the only form used clinically since the l-isomer and racemic mixture have been associated with a higher incidence of adverse effects.[167]

The agent acts by reversing sulfhydryl binding of the heavy metal to proteins in the blood. Although the mechanism is not completely understood, it has been proposed that penicillamine chelation may result from: (i) a simple bond between the lead atom and the single sulfhydryl group of penicillamine; (ii) trapping of lead into the penicillamine ring structure; or (iii) binding of a single lead atom between 2 penicillamine molecules. A 30-fold increase in urinary lead and γ-aminolaevulinic acid excretion occurs after penicillamine administration.

14.3 Administration Guidelines

The dosage of penicillamine depends on the type and severity of the poisoning. In paediatric patients, penicillamine therapy can be initiated at 10 mg/kg/day as a single daily dose. After 1 week, the dosage may be increased to 20 mg/kg/day in 2 divided doses. In the third week, dosages average 30 mg/kg/day, given once or twice daily.[168] The goal of therapy is to reach a blood lead level below 150 μg/L.[168] Depending on blood lead levels and adverse effects of penicillamine, therapy may be continued for 4 to 12 weeks. Adult dosages range from 15 to 40 mg/kg/day to a maximum of 500mg 4 times daily.

14.4 Adverse Effects

There are many reports of adverse effects with penicillamine administration.[167] Most commonly, it has been associated with gastrointestinal complaints, and a metallic or bitter taste. An unusual effect is an asparagus-like odour from the urine.

Penicillamine has also been associated with many serious adverse effects, including hypersensitivity reactions, blood dyscrasias, nephrotic syndrome and various autoimmune responses. The high incidence of adverse effects often limits the duration of use of this agent.

14.5 Precautions and Contraindications

Penicillamine is contraindicated during pregnancy and breastfeeding, and in patients with renal insufficiency or a history of allergy to penicillamine. Caution should be exercised in patients with a penicillin allergy because of possible cross-sensitivity reactions,[162] although this effect has been minimised by the newer synthetic production of the agent.

Penicillamine therapy should be discontinued immediately upon the development of any of the following: (i) increasing serum lead levels (i.e. continued exposure to lead); (ii) unexplained generalised urticarial rash; (iii) platelet count less than 100 000 cells/mm^3; (iv) white blood cell count less than 3000 cells/mm^3; or (v) abnormal urinalysis, defined as more than 1+ of proteinuria, more than 10 red blood cells per high-powered microscope field, or more than 10 white blood cells per high-powered microscope field.[168]

14.6 Other Considerations

Penicillamine is no longer considered to be the drug of choice in the management of lead poisoning in children. Succimer therapy has largely replaced penicillamine in these situations.

Antacids, food and ferrous sulfate decrease the amount of penicillamine absorbed. Ideally, penicillamine should be administered on an empty stomach, 2 hours before or 3 hours after meals.

Penicillamine may enhance the elimination of essential vitamins and minerals such as pyridoxine, zinc and iron.[168] Replacement of these nutrients is necessary to maintain the patient's nutritional status. In addition to enhancing penicillamine absorption, administration times should be separated

from meals by several hours to prevent penicillamine chelation of these vitamins or minerals and enhance their absorption.

Iron deficiency may increase lead absorption and retention.[169] Depending on a child's haematological, iron and lead status, simply treating iron deficiency may enable the child to be more responsive to lead chelation therapy.[170] Children with blood lead levels lower than 300 μg/L often achieve blood lead levels below which chelation therapy is required following iron repletion.[163] In view of the poor safety profile of penicillamine, it may be prudent to consider iron replacement before initiating chelation or penicillamine therapy particularly for those children in whom the administration of chelation therapy may be questionable.

From a pharmacoeconomic standpoint, Glotzer and colleagues[161] designed a decision model that evaluated the impact of various chelation therapies on the total healthcare expenditure on drug therapy, testing, follow-up and remedial education. The study authors concluded that if the estimated 1.4% of preschoolers in the US with blood lead levels 250 to 390 μg/L were treated with some form of chelation therapy, 45 000 cases of reading disability would be prevented, and overall costs, including those of remedial education, would be reduced by more than $US900 million annually.

In summary, the primary treatment of plumbism is removal of the environmental source of toxicity. At one time, penicillamine was considered to be the oral agent of choice in the treatment of lead toxicity. However, as a result of the comparatively poorer efficacy profile and increased incidence of untoward effects with penicillamine, succimer is the agent of choice when oral therapy is indicated.

15. Methylene Blue (Methylthioninium Chloride)

15.1 Indication

Methylene blue (methylthioninium chloride) is indicated as an antidote for symptomatic patients with drug-induced methaemoglobinaemia. Generally, most patients remain asymptomatic until 30% of haemoglobin is present as methaemoglobin. High levels of methaemoglobin may cause circulatory failure, seizures and death.[171] Dapsone, nitrites, nitrates, sulphonamides, primaquine, local anaesthetics and phenazopyridine are common agents that are associated with methaemoglobinaemia. A common source of toxic methaemoglobinaemia in infants is contaminated well water from agricultural run-off of fertilisers.

15.2 Mechanism of Action

The reduction of methaemoglobin in erythrocytes is controlled by the nicotine adenine dinucleotide phosphate (NADP) [95%] and reduced nicotine adenine dinucleotide phosphate (NADPH) [5%] methaemoglobin reductase systems as a normal physiological function of the human body.[172] To a much lesser extent, glutathione, sulfhydryl, ascorbic acid (vitamin C) and catalase are also involved in these processes.[173] The NADPH methaemoglobin reductase system is the primary site of methylene blue activity.

Methylene blue functions by accepting an electron from NADPH to form leukomethylene blue. Then, in a nonenzymatic manner, leukomethylene blue provides an electron to reduce methaemoglobin to haemoglobin.[173] More specifically, methylene blue potentiates the effects of NADPH, acting as a cofactor in the NADPH system to reduce iron from the ferric to the ferrous (Fe^{++}) form, which ultimately results in the conversion of methaemoglobin to haemoglobin. It is important to realise that some patients may have hereditary deficiencies in the NADPH reductase system, which may render methylene blue therapy ineffective.

15.3 Administration Guidelines

The usual dosage of methylene blue for patients with drug-induced methaemoglobinaemia is 1 to 2 mg/kg administered intravenously over 5 minutes. Disappearance of cyanosis should occur within 1 hour of injection. If symptoms are not improved within the hour, a second dose is recommended.

15.4 Adverse Effects

Adverse reactions are minimal, but include dizziness, headache and mental confusion. Methylene blue may also impart a blue-green colour to the urine and stools. A bluish discoloration of the skin may be noted, which can be difficult to distinguish from cyanosis. Other reported toxic manifestations in neonates include hyperbilirubinaemia, Heinz body haemolytic anaemia and desquamation of the skin.[174]

Cumulative methylene blue dosages over 4 mg/kg may exacerbate methaemoglobinaemia and produce an acute haemolytic state. Doses above 7 mg/kg have been associated with precordial pain, tremors and dyspnoea.[175]

15.5 Precautions and Contraindications

Methylene blue should be used with caution in patients with glucose-6-phosphatase deficiency, since it may precipitate haemolytic anaemia in these patients.[61] Another relative contraindication is NADPH methaemoglobin reductase deficiency, as this interferes with the mechanism of methylene blue.

Methylene blue is contraindicated in patients with methaemoglobinaemia associated with nitrite treatment of cyanide poisoning. It may cause the release of cyanide from the cyanomethaemoglobin complex, resulting in toxic free cyanide concentrations.[164]

15.6 Other Considerations

The development of methaemoglobinaemia in patients exposed to local anaesthetic agents is not often considered when prescribing these agents. Practitioners who routinely use benzocaine (which is particularly prone to cause methaemoglobinaemia) for common procedures such as intubation or endoscopy should be aware of the potential toxicities of this drug, particularly since many of the signs of acute methaemoglobinaemia can be masked by the general anaesthetic agents that are often administered concomitantly.[171]

While severe methaemoglobinaemia may result in a false overestimation of oxygen saturation, as measured by pulse oximetry, the use of methylene blue in treating methaemoglobinaemia may cause false underestimations. These issues should be considered during patient monitoring.[173]

In summary, methaemoglobinaemia is not commonly reported as an adverse effect of pharmacological therapy. However, the serious nature of methaemoglobinaemia warrants careful consideration. Methylene blue is a relatively nontoxic agent used in the treatment of drug-induced methaemoglobinaemia. Healthcare professionals who prescribe, administer, dispense or handle pharmacological agents such as those described above should be aware of this potential toxicity.

16. Cyanide Antidote Kit

16.1 Indication

Cyanide toxicity may be induced by inhalation, ingestion or iatrogenic causes (section 8.1). In the US, the standards of therapy include supportive modalities, the cyanide antidote kit and hyperbaric oxygen. As mentioned in section 8.1, hydroxocobalamin is an agent that is used in Europe for cyanide poisonings, although it is not approved in the US. The Cyanide Antidote Kit contains 3 ingredients: amyl nitrite, sodium nitrite and sodium thiosulfate. It is indicated in patients with symptomatic or suspected cyanide poisoning as well as hydrogen sulfide toxicity.[111]

16.2 Mechanism of Action

The activity relationship among the 3 pharmacological entities in the cyanide antidote kit in reducing cyanide toxicity is intriguing. Cyanide interferes with normal cellular aerobic metabolism by binding to the ferric iron of cytochrome oxidase (section 8.2). Amyl nitrite and sodium nitrite act to induce methaemoglobinaemia (only rarely can this reach dangerous levels). Methaemoglobin has a greater affinity for cyanide than the ferric iron of cytochrome oxidase, thereby enhancing normal aerobic metabolism. Sodium thiosulfate then pro-

vides a sulphur substrate for the enzyme rhodanese to form thiocyanate, which is renally eliminated.[111]

16.3 Administration Guidelines

In adults, the following guidelines are recommended for administration of the cyanide antidote kit. Initially, a patient who has been poisoned with cyanide should be given inhaled amyl nitrite for 30 seconds per minute. This should be a temporary measure until sodium nitrite 300mg can be prepared and administered intravenously over 15 to 20 minutes. Sodium thiosulfate 12.5g can then be given as a single intravenous dose. Paediatric patients may be given 0.19 to 0.39 ml/kg of a sodium nitrite 3% solution and 0.95 to 1.95 ml/kg of a sodium thiosulfate 25% solution, based on their haemoglobin level (calculated doses based on a haemoglobin range of 7 to 14 g/dl). Should symptoms reappear in any patient, sodium nitrite and sodium thiosulfate may be readministered at half of the original dose.[111,176]

16.4 Adverse Effects

Sodium nitrite has the propensity to cause severe hypotension. Blood pressure should be carefully monitored.

Methaemoglobinaemia is a sequela of sodium nitrite administration. The desirable therapeutic methaemoglobin concentration to treat cyanide toxicity is 25%,[177] although this concentration is rarely achieved. However, the clinical response to the adverse effects of methaemoglobinaemia (section 15.1) should guide sodium nitrite administration, rather than serum concentrations.[178]

16.5 Precautions and Contraindications

Cyanide poisoning occurs in individuals who experience smoke inhalation during fires; carbon monoxide is a by-product of combustion of all fires. Thus, the production of significant methaemoglobinaemia from nitrite administration, while unlikely, may further compromise the delivery of oxygen in patients with carbon monoxide poisoning. These risks are diminished if hyperbaric oxygen is available, which may be beneficial in the management of either carbon monoxide or cyanide toxicity. The use of nitrites, particularly in this group of patients, requires careful monitoring of serum carboxyhaemoglobin and methaemoglobin levels, if they can be made available quickly. Controversy exists over whether the nitrite portion of the cyanide antidote kit should be withheld in these patients.[179,180]

16.6 Other Considerations

The efficacy of amyl nitrite in patients with cyanide inhalation has been questioned because of its relatively low production of methaemoglobin. However, it may be used as a temporary measure while preparing intravenous sodium nitrite.[111]

Dose adjustments may be necessary in patients with anaemia, as a result of the potential development of profound methaemoglobinaemia. Caution should be exercised in this patient population.

The combination of carbon monoxide and cyanide poisoning commonly presents in patients exposed to fires. Frequently, treatment of burns and carbon monoxide poisoning takes precedence, as a result of the nonspecificity of clinical and laboratory findings initially associated with cyanide toxicity. All victims of smoke inhalation should be carefully evaluated for signs and symptoms of cyanide toxicity.

17. Succimer

17.1 Indication

Succimer (2,3-dimercaptosuccinic acid; DMSA) is not one of the foremost used antidotes in the US in table I, since it was only recently introduced. However, it is an agent for which increased use is anticipated. This dimercaprol analogue was approved by the FDA in 1990 for the treatment of lead poisoning in children with blood lead levels above 450 μg/L. Succimer has also shown efficacy in the treatment of arsenic and mercury poisonings.[181]

17.2 Mechanism of Action

Succimer is a heavy metal–chelating agent that forms water-soluble compounds to increase the urinary excretion of lead, mercury and arsenic. As may be anticipated with discontinuing any chelating agent, rebound increases in serum lead levels generally occur as a result of the redistribution of lead from bone and soft tissues to blood (section 13.6). Rebound associated with succimer may occur to a greater degree than with penicillamine therapy.[168]

17.3 Administration Guidelines

The usual dosage range for succimer in children is 10 mg/kg or 350 mg/m^2 orally every 8 hours for 5 days, followed by 10 mg/kg or 350 mg/m^2 orally every 12 hours for an additional 14 days. A course of therapy should last a total of 19 days.[182]

Mortensen and Walson[162] outline a clinical approach to the treatment of children with lead toxicity. Briefly, their recommendations include chelation treatment, usually with succimer, for any child with a blood lead level greater than 400 μg/L. Treating patients with blood lead levels between 250 and 390 μg/L is considered controversial. However, chelation therapy is not recommended for those children with blood lead levels below 250 μg/L. Additional issues pertaining to this controversy are discussed in section 14.6.

17.4 Adverse Effects

The most commonly reported adverse effects include gastrointestinal symptoms (12 to 20.9%), abdominal cramps (5.2 to 15.7%), drowsiness or dizziness (1 to 12.7%) and rash or pruritus (2.6 to 11.2%).[182] Although there have been reports of elevated hepatic enzyme levels during succimer administration (4.2 to 10.4%), the significance of this finding has not yet been established.[168] Mild to moderate neutropenia has also been reported with this agent; however, a causal relationship has not been established.

Patients should be informed that they may experience an unpleasant metallic taste, digestive adverse effects and 'flu-like symptoms while receiving this agent. Additionally, they may notice a sulphurous odour from their urine or on their breath. Termination or withholding of succimer therapy should be considered in patients with an absolute neutrophil count lower than 1200 cells/mm^3. Since succimer is eliminated renally, patients with renal failure should be monitored more closely for toxicity.

17.5 Precautions and Contraindications

The only contraindication to succimer use is a history of allergy to the drug. Succimer has been classified as 'pregnancy category C' and should not be used in pregnant women unless the benefits of therapy outweigh the risks.

17.6 Other Considerations

As mentioned in section 14.3, target blood lead levels are less than 150 μg/L.[168] It may be necessary to extend treatment beyond 19 days if blood lead levels remains elevated. However, the safety of uninterrupted therapy with succimer beyond 3 weeks has not been established. Succimer therapy may be repeated if rebound levels become seriously elevated. However, 2 weeks should elapse between courses of therapy, unless the blood lead levels warrant more rapid retreatment.[181]

Before administering succimer, children should be tested for iron deficiency. Frequently, children with lead toxicity have a low iron status, which may adversely affect therapy. Iron replacement therapy can be administered with succimer.[169] Additionally, adequate hydration is necessary in all patients, since the chelates are primarily excreted in the urine. Patients who have received sodium calcium edetate with or without dimercaprol may use succimer for future treatment after a 4-week interval.[182] To gain maximal effect, it is of utmost importance that the treatment of lead toxicity includes removal of the source of lead exposure. Chelation therapy is not a substitute for preventing exposure to lead and no agent should be used prophylactically.

Other chelating agents have been associated with increased excretion of trace minerals such as iron, calcium, copper or zinc. However, studies have shown that succimer chelation with heavy metals is fairly specific for lead and does not significantly affect trace mineral excretion at recommended doses.[183] Therefore, succimer therapy does not require trace element monitoring.[181] This is a major therapeutic advantage over other agents, since its specificity permits correction of lead-induced anaemia with rapid iron supplementation, which would otherwise be more difficult as a result of iron chelation.[184]

In 1985, studies conducted by Graziano et al.[185] suggested that the optimal dosage in adults is 30 mg/kg/day for 5 days. In clinical practice, it is being extensively used in adults with even moderately elevated lead levels.

Patients should be instructed to drink plenty of fluids while receiving this medication to ensure adequate renal elimination of the chelated lead. For ease of administration, the capsules may be opened and sprinkled on soft food or administered with fruit juice to mask the unpleasant sulphurous odour.[92]

Unithiol (2,3-dimercapto-1-propane sulfonate sodium; DMPS) is another oral chelator, used in the management of lead, mercury or arsenic poisoning,[186] that is potentially less toxic than other chelators. At present, its status remains investigational in the US. It has been used in Europe for several years, primarily as an antidote for mercury poisoning. Further study is needed establish its role in plumbism.

Although succimer is solely approved in the treatment of children with lead intoxication, research is being conducted into its use in other situations. A limited number of patients have received succimer for the treatment of other heavy metal toxicities (primarily mercury and arsenic) with some symptomatic improvement. Further study in this area is required before making definite recommendations.

Before succimer, penicillamine was the only oral heavy metal chelator. Succimer offers the advantage of fewer adverse effects than penicillamine. Sodium calcium edetate and dimercaprol are agents that are presently available for parenteral use, but are also associated with a poorer adverse-effect profile.

It is anticipated that succimer will become the agent of choice in the treatment of lead poisoning. Its 2 major benefits over existing therapies are that: (i) it is available as an oral agent, so that patients may be treated on an outpatient basis (this has substantial financial implications); and (ii) it appears to be associated with fewer adverse effects over other therapies. Further studies are required to determine the long term effects of succimer before establishing any definitive guidelines.

18. Conclusions

It is important for all healthcare professionals to understand the role of pharmacological antagonists, or antidotes, in the management of poisoned patients. They should be used prudently, since they may have inherent pharmacological or toxicological properties, which could further compromise a toxic patient. These agents can be extraordinarily expensive and their injudicious use has significant financial implications. However, they can be highly beneficial when used properly, by reducing morbidity and mortality, eliminating the use of invasive procedures and reducing total healthcare costs. Furthermore, it is essential to realise that situations in which their use is required are rather uncommon, and that most poisoned patients will recover if their treatment regimen merely includes supportive care and the use of basic gastrointestinal decontamination techniques.

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