



POISONS

INFORMATION CENTRE OF IRELAND

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Antidote List



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Availability requirements

The antidotes listed are considered useful in the treatment of acute human poisoning. Recently, there has been a move away from the older International Programme on Chemical Safety (IPCS) guidelines. The new availability requirements reflect those published by the College of Emergency Medicine, the National Poisons Information Service and Guy's and St. Thomas Poisons Unit in the UK. The decision on what quantities to be stocked should be based on the local epidemiology of poisoning.

- A** *required to be immediately available (within the Emergency Department).*
- B** *required to be available within 1 hour (within the hospital).*
- C** *These drugs are rarely used and can be held supra-regionally. It would be advisable to know in advance where you can obtain a supply.*

Each antidote has its own availability requirement listed and any slight deviation from the A, B and C classification is noted in each individual entry.

Supplier	Telephone
Baxter	(01) 2065502
Beacon Pharmaceuticals	+ 44 1892 600930
Braun	(01) 45543111
Cahill May Roberts	(01) 6305555
Clonmel Healthcare	1 800 262626
Department of Health (DOH) UK	+ 44 207 9725536
Georgelle	(01) 4513733
GlaxoSmithKline	(01) 4955000
IDIS	(01) 6319325
Lennox	(01) 4552201
Leo Laboratories	(01) 4908924
MSD	(01) 2998700
Medisource	(01) 2866366
Novartis	(01) 2601255
Pinewood Laboratories	(01) 4569123
Technopharm	(01) 6602988
UDG Masta	+44 113 2387510
Uniphar	(01) 4041700
United Drug	(01) 4598877
Waymade UK	+ 44 1268 531111

Acetylcysteine

Availability Requirement A

Indication 1: ***Paracetamol.***

Mode of action: Overdose with paracetamol causes saturation of the glucorinidation and sulfation pathways and increased metabolism by cytochrome P450. This causes increased production of the highly reactive metabolite N-acetyl-p-benzoquinoneimine (NAPQI) which rapidly exhausts the natural protective stores of glutathione in the liver. When these stores are sufficiently exhausted, NAPQI undergoes covalent binding with proteins and enzymes in the hepatocytes, causing cell death and zone 3 (centrilobular and distal acinar) degeneration of the liver. Acetylcysteine protects against liver damage in early paracetamol poisoning by production of cysteine, which acts as a glutathione precursor. It also acts by supplying additional thiol groups, which bind directly with NAPQI encouraging its reduction to acetaminophen without inhibiting its production. There have also been several putative mechanisms put forward for usage of NAC in late presentation paracetamol poisoning. These include improving hepatic microcirculation and increasing blood flow. It is also suggested that NAC may have some chemoprotective qualities that may be of value. It has been shown to scavenge oxygen-free radicals liberated by necrotic hepatic tissue and also to reduce cytokine concentrations preventing neutrophil migration into the hepatic parenchyma. In isolated hepatocytes, it can also restore the capacity of the intracellular proteolytic system to degrade toxic arylated proteins.

Indication 2: ***Carbon tetrachloride.***

Mode of action: Carbon tetrachloride causes marked cellular toxicity and produces cellular destruction throughout the body. The exact mechanism of carbon tetrachloride hepatotoxicity is unclear but is expected to be dependent on its metabolism. Acetylcysteine shows promise in preventing hepatic damage and appears to work by replenishing the supply of reduced glutathione in the hepatocytes.

Presentation: 10ml ampoules of 200mg/ml.

Supplier: United Drug.

Dosage: Initially 150mg/kg in 200mls of 5% dextrose by slow iv injection over 15 minutes, followed by 50mg/kg in 500mls of 5% dextrose over 4 hours, then 100mg/kg in 1000mls 5% dextrose over 16 hours.

Note: Most effective up to 10 hours post ingestion but may be used up to 36 hours p.i.

Activated charcoal

Availability Requirement A

Indication: **Most poisons.**

Mode of action: Activated charcoal is produced by the pyrolysis of various organic materials and treatment at high temperatures with a variety of activating agents. This ensures a very high adsorptive capacity for a wide range of compounds which are often encountered in accidental and deliberate poisonings. When administered orally, activated charcoal minimises the extent of systemic absorption of the poison in the gastrointestinal tract by adsorbing the toxin onto itself, thereby reducing or preventing systemic toxicity. Notable exceptions to this are the alcohols, caustics, cyanide, iron and lithium. Activated charcoal is contraindicated when corrosive agents have been

ingested. Single dose activated charcoal may be administered if a patient has ingested a potentially toxic amount of poison up to one hour following ingestion, it may also be considered more than one hour after ingestion, but there are insufficient data to support or exclude its use. Multiple dose activated charcoal appears to enhance gastrointestinal elimination of many drugs by preventing enterohepatic recirculation from bile and also by binding drugs, which diffuse from the circulation into the gut lumen (interrupting entero-enteric circulation). Activated charcoal is not absorbed by the gastrointestinal tract or subject to any metabolic process and is eliminated in the faeces. Charcoal should be administered with caution when agents that decrease gut motility have been ingested (e.g. anticholinergic drugs) and the monitoring of bowel sounds is advised. A laxative may be given concurrently to accelerate removal of the activated charcoal-toxin complex but should be used with caution and only intermittently during multiple dose activated charcoal therapy since profuse and protracted diarrhoea may lead to fluid and electrolyte imbalance. Gastrointestinal obstruction associated with MDAC therapy has been reported.

Presentation: 50g

Supplier: Technopharm

Dosage: Adult Single dose: 50g orally.

Multiple dose: 50g orally every 4 hours until it appears in the stool.

Child Single dose: 10-15g orally.

Multiple dose: 10-15g orally, repeated every 4 hours until it appears in the stool.

Note: The position statements of the American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists may be of some interest.

Single dose activated charcoal: *Clinical Toxicology, 35(7), 721-741 (1997)*

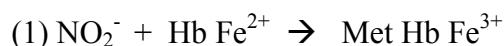
Multiple dose activated charcoal: *Clinical Toxicology, 37(6), 731-751 (1999)*

Amyl nitrite

No availability Requirement (see note)

Indication: **Cyanide**

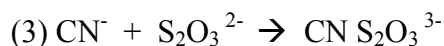
Mode of action: Cyanide exerts its toxicity by combining with the cytochrome oxidase enzymes containing iron in the ferric state, to which cyanide has a great affinity and subsequently interrupting cellular respiration. In the presence of nitrites, haemoglobin is converted to methaemoglobin (1).



This complex has a higher binding affinity for cyanide than the cytochrome oxidase complex and removes cyanide from the cytochrome oxidase forming cyano-methaemoglobin (2) regenerating cytochrome function.



The resultant cyano-methaemoglobin in the presence of sulphate donors (sodium thiosulphate) is converted by rhodanase to thiocyanate (3), which is renally excreted, and methaemoglobin.



The methaemoglobin is then reduced via methaemoglobin reductase to haemoglobin. Nitrite and thiosulphate are administered sequentially in cyanide poisoning, as their combined effects are synergistic compared to either agent alone. Cyanide is also directly converted to thiocyanate by direct complexation with thiosulphate in the presence of the enzyme rhodanase.

Presentation: 12 x 0.3 mls ampoules

Supplier: Georgelle

Dosage: An ampoule should be broken and inhaled by the patient for 30 seconds every minute, using a new ampoule every three minutes. It can be broken into gauze and held next to the nose and mouth of spontaneously breathing patients. The broken ampoule can be placed inside the resuscitation bag or into the inner lip of the face mask for patients requiring assisted ventilation.

Note: Amyl nitrite will produce 5% MetHb and has been considered to have minimal antidotal efficacy with the potential for causing significant hypotension. However some patients may have significant benefit when amyl nitrite is used as a first aid measure. Use must be stopped when sodium nitrite is administered intravenously. We no longer recommend that it be available.

Atropine

Availability Requirement A

Indication: **Organophosphate and carbamate insecticides.**

Mode of action: Atropine competitively inhibits the action of acetylcholine at the muscarinic sites on post-synaptic parasympathetic receptors and penetrates the central nervous system and exerts the same effect on cholinergic post-synaptic receptors. This will decrease tracheobronchial secretions, bronchoconstriction, intestinal secretions and motility as well as antagonising vagal stimulation and some CNS effects. It has no effect on skeletal muscle weakness or paralysis and because it is rapidly cleared by the body, it has no effect on the actual rate of restoration of inhibited acetyl cholinesterase. The end-point to atropinisation is clearing of the secretions from the tracheobronchial tree; pupillary dilation is an early response not a therapeutic end-point.

Presentation: 500 ug/5mls

Supplier: United Drug

Dosage: Adult: 2 mg IV Paediatric: 0.05 mg/Kg IV

Note: Repeat doses may be administered every 10-30 minutes as needed to achieve and maintain full atropinisation, indicated by complete clearing of rales and drying of pulmonary secretions.

Benzylpenicillin**Availability Requirement C**

Indication: **Amatoxin poisoning.**

Mode of action: It is thought to provide a hepatoprotective effect by inhibiting the entry of amatoxins into the liver cells. Animal experiments have shown that high doses of benzylpenicillin reduced or inhibited the liver uptake of amatoxins in rodents. Its true efficacy is hard to assess as in most human cases it is administered as part of a polydrug therapy.

Presentation: 600mg vial X 25

Supplier: Clonmel

Dosage: The suggested dose for benzyl penicillin is 600mg/kg body weight (1 million units/kg) on the first day and 300mg/kg body weight (500,000 units/kg) on the second and third days. Penicillin therapy should be terminated on day 3.

Note: Benzylpenicillin and Silibinin should not be used in combination.

Calcium gluconate**Availability Requirement A**

Indication 1; **Hydrofluoric acid**

Mode of action: Hydrofluoric acid is a relatively weak acid, which is poorly dissociated in solution and rapidly penetrates skin, nail and deep tissue layers. Once absorbed hydrofluoric acid slowly dissociates and the fluoride ion proceeds to affect tissue integrity and metabolism in three ways; liquefaction necrosis, decalcification and destruction of bone and the production of the insoluble salts (magnesium fluoride and calcium fluoride). It is the complexation of fluoride with calcium and magnesium which causes cellular necrosis and the liberation of potassium ions with the potential to disrupt all metabolic pathways resulting in systemic acidosis, hyperkalaemia, hypocalcaemia and hypomagnesaemia. It is also proposed that the fluoride ion binds to metal-containing enzymes, thereby inactivating them and that it is directly toxic to the CNS.

Dosage: Calcium gluconate gel can be used on burns less than 5% of body surface or exposures to concentrations of less than 20% hydrofluoric acid. A 2.5% gel can be made from calcium gluconate powder with 150mls of a water soluble lubricant such as KY jelly. This should be massaged well into the affected area and covered with an occlusive dressing such as a latex glove. The application should be repeated until cessation of pain.

Otherwise administer 0.1 to 0.2 mls/kg i.v. (10%) up to 10mls/dose immediately and repeating the dosage as required.

Note: Administering large amounts of calcium gluconate can result in decreased tissue perfusion and tissue necrosis. Patients with intravenous treatment failure or exposure to high concentration, particularly to digits, may require continuous intra-arterial calcium infusion. Contact the National Poisons Information Centre for details.

Indication 2: **Calcium channel blockers (CCB)**

Mode of action: Calcium channel blockers function by binding to the L-type voltage dependent, slow calcium channels found in cell membranes. This decreases the flow of calcium into the cell. This action leads to an inhibition of the 0 phase depolarisation in cardiac pacemaker cells and the phase 2 plateau of Purkinje cells, cardiac myocytes and vascular smooth muscle cells. However, CCBs do not alter receptor-operated channels, the release of calcium from intracellular stores or serum calcium concentration. When calcium (calcium gluconate or calcium chloride) is administered IV, theoretically it will create a large enough concentration gradient to partially overcome the channel blockade, thereby driving calcium into the cells.

Dosage: *Adults* – 3g in a 10% solution (i.e. 30 ml) repeated every 10-20 mins for 3-4 doses or by infusion of 0.6-1.2ml/kg/hour.
Children – 0.5ml/kg repeated every 10-20 mins for 3-4 doses.

Note: Calcium chloride contains three times as much calcium as calcium gluconate and is probably more effective.

Indication 3: **Oxalates**

Mode of action: Once absorbed, oxalates bind to calcium forming insoluble calcium oxalate crystals which precipitate in the renal tubules causing tubular necrosis. This may precipitate hypocalcaemia and neurological symptoms including muscle cramps (especially of the jaw and extremities), tetany, convulsions, stupor and coma.

Dosage: 0.1 to 0.2 mls/kg i.v. (10%) up to 10mls/dose

Presentation: 10%, 10 X 10mls ampoules

Supplier: Georgelle

Cholestyramine

Availability Requirement B

Indication: Cholestyramine is effective in reducing the half-life and increasing the total clearance of oral anti-coagulant such as warfarin and the long-acting anti-coagulants used as pesticides.

Mode of action: Cholestyramine is a strongly basic anion-exchange resin which is not absorbed in the gut. It reduces the absorption of anti-coagulants. Cholestyramine may also reduce enterohepatic recirculation of anticoagulants by forming a non-adsorbable complex with bile acids in the intestine thereby inhibiting their re-uptake. It has also been used in one animal study to prevent enteral resorption of bile acids and decrease hepatic cirrhosis in carbon tetrachloride poisoned rats.

Presentation: 4g sachets.

Supplier: United Drug.

Dosage: Adults: 4g three times daily orally.

Children 6-12 years: $\frac{\text{Child's weight in kg} \times \text{adult dose}}{70}$

70

Children under 6: No dosage established.

Cyanokit**Availability Requirement (see note)**

Indication: Cyanide toxicity

Mode of action: Hydroxocobalamin is the hydroxylated active form of vitamin B12. It is used in the treatment of cyanide poisoning because of its ability to tightly bind cyanide ions. Each hydroxocobalamin molecule can bind one cyanide ion by substituting the hydroxo ligand linked to the trivalent cobalt ion to form cyanocobalamin. Cyanocobalamin is a stable, non toxic compound that is excreted in the urine.

Presentation: Each vial contains 2.5 g of hydroxocobalamin. After reconstitution with 100 ml of diluent, each ml of the reconstituted solution contains 25 mg of hydroxocobalamin.

Supplier: Swedish Orphan Biovitrum Ltd. (can be ordered through United Drug)

Dosage: Cyanokit is administered as an intravenous infusion over 15 minutes.

Adults: The initial dose of Cyanokit is 5 g.

Paediatric patients: In infants to adolescents, the initial dose of Cyanokit is 70 mg/kg body weight not exceeding 5 g.

A second dose can be given, if necessary, over 15 minutes to 2 hours.

Notes: Cyanokit should not be given in the same IV line (cannula) as other drugs. Because of its deep red colour, hydroxocobalamin has the potential to interfere with determination of laboratory parameters (e.g. clinical chemistry, haematology, coagulation, and urine parameters).

Note: The NPIC is currently not making any recommendation on the availability of cyanokit.

Cyproheptadine**Availability Requirement B**

Indication: **Serotonin syndrome**

Mode of action: The serotonin syndrome (serotonin toxicity) results from excessive stimulation of the serotonin-5-hydroxytryptamine (5HT)-1a and possibly 5HT-2 receptors in the central nervous system (CNS). It can be characterised as a clinical triad of mental-status changes, autonomic dysfunction and neuromuscular hyperactivity, although all these findings may not be present in all cases. Mental-status changes occur in 40% of patients, with neuromuscular features in 50% of patients and autonomic instability in 50% of patients. Agitation, delirium, coma, diaphoresis, mydriasis, gastrointestinal symptoms, tremor, trismus, tachycardia and blood pressure fluctuation are commonly observed features. Myoclonus may also occur and be severe enough to mimic seizure activity. In severe cases hyperthermia, seizures, rhabdomyolysis, coagulopathies and renal failure may develop. The syndrome usually resolves within 24 hours. There is no diagnostic test available and a diagnosis of serotonin syndrome is made on clinical presentation, exposure to an agent (or agents) likely to produce serotonin excess in the CNS and exclusion of differential diagnoses (anticholinergic poisoning, malignant hyperthermia and

neuroleptic malignant syndrome). Cyproheptadine is a first generation, histamine-1 receptor blocking drug with non-specific antagonist properties at 5HT-1a and 5HT-2 receptors. Animal studies have shown that it prevents the onset of experimentally induced serotonin syndrome effectively. Cyproheptadine has also been reported to be beneficial in human cases, although its efficacy has not been rigorously established. Treatment may require 12-32mg in a 24-hour period, a dose which binds 85-95% of serotonin receptors. This dosage may cause sedation but this is one of the goals of therapy and should not deter from its use. Caution should be exercised in hyperthermic patients as this may be exacerbated.

Presentation: 4mg tablets.

Supplier: MSD

Dosage: Initially: 12mg p.o. and then 2mg every 2 hours if symptoms continue.
Maintenance: 8mg every six hours.

Note: Cyproheptadine is only available in oral form, but tablets may be crushed and administered by nasogastric tube.

Dantrolene

Availability Requirement B

Indication: Used in the treatment of hyperthermia associated with muscle rigidity and fulminant hyper-metabolism of skeletal muscle, which occurs with neuroleptic malignant syndrome (NMS), malignant hyperthermia and overdose of several agents including monoamine oxidase inhibitors (MAOIs), cocaine and amphetamines.

Mode of action: Dantrolene acts directly on skeletal muscle to reduce the contractile response. This is achieved by dissociation of the excitation-contraction coupling probably by interfering with the release of calcium from the sarcoplasmic reticulum and thereby lowering intracellular levels. It diminishes the force of electrically induced twitches without altering muscle action potential and reduces reflex more than voluntary contraction.

Presentation: 20mg X 12 vials

Supplier: United Drug

Dosage: 1mg per kg body weight by rapid intravenous injection, repeated as required to a total dose of 10mg per kg. The average effective dose is about 2.5 mg per kg.

Desferrioxamine

Availability Requirement B

Indication: Iron

Mode of action: Desferrioxamine is a specific chelator of iron in the ferric state produced from the bacteria *Streptomyces pilosus*. It is believed to work by binding free circulating iron in the plasma to form the octahedral iron complex ferrioxamine. It has also been hypothesised that it can enter the cells, binding iron in the cytoplasm and preventing it from interfering with mitochondrial enzyme systems and mitochondrial membranes. Ferrioxamine is water-soluble and is rapidly excreted unchanged in the urine. Iron in ferritin and haemosiderin from hepatic and splenic stores is minimally affected and iron in haemoglobin and the cytochromes remaining

unaffected. A dose of 100mg desferrioxamine will chelate approximately 9mg elemental iron.

Presentation: 500mg vials X 10

Supplier: CMR

Dosage: Up to 15mg/Kg/hour by slow i.v. infusion in 5% dextrose or 0.9% saline not exceeding 80mg/Kg in 24 hours.

Note: Rapid infusion rates increase the risk of hypotension. Infusion of desferrioxamine at 15mg/kg per hour for longer than 24 hours appears to be of little value and may lead to increased risk of pulmonary oedema. Haemodialysis may be required if the patient is in renal failure.

Diazepam

Availability Requirement A

Indication: **Toxin induced muscular twitching and convulsions.**

Mode of action: Diazepam is a benzodiazepine. Gamma-amino butyric acid (GABA) is the major inhibitory neurotransmitter in the CNS and it is believed that benzodiazepines enhance or facilitate its action by causing it to bind more tightly to its receptor. Activation of the GABA receptor results in the opening of the chloride channel allowing the flow of chloride ions into the neuron. This results in hyperpolarisation of the neuron with decreased neuronal excitability, thus reducing the effects of subsequent depolarising excitatory transmitters. There is also evidence that benzodiazepines may act at GABA-independent receptors.

Presentation: 5mg/ml, 10 x 2mls.

Supplier: Uniphar

Dosage: Convulsions/twitching – 0.1-0.3 mg/kg body weight i.v.
Chloroquine – 2mg/kg body weight i.v. over 30 mins in combination with assisted ventilation.

Dicobalt edetate

Availability Requirement B (see note 1)

Indication: **Cyanide toxicity.**

Mode of action: Dicobalt edetate is a chelating agent used in the treatment of severe cyanide poisoning. It forms relatively non-toxic stable ion-complexes (cobalto-cyanides, cobalti-cyanides) with cyanide, which are then excreted in urine. Cobalt ions are toxic and the use of dicobalt edetate, in the absence of cyanide will lead to serious cobalt toxicity. It should never be used as a precautionary measure. Animal experiments suggest that glucose protects against cobalt toxicity and it is recommended that it be administered after the dicobalt edetate.

Presentation: 300mg/20mls X 6 vials

Supplier: Cahill May Roberts

Dosage: 300mg by intravenous injection over about 1 minute, repeated if the dose is inadequate, a further dose of 300 mg may be given 5 minutes later if required. Follow each injection with 50mls of 50% dextrose intravenously.

Note 1: Only one of the three cyanide treatment options (Dicobalt edetate / hydroxocobalamine / sodium nitrite-sodium thiosulphate) is required to be available

Note 2: If symptoms of cobalt toxicity occur (nausea, vomiting, urticarial rash, chest pain, bronchospasm, hypotension, convulsions, tachycardia, ventricular arrhythmias and periorbital oedema), stop administration of the drug and institute supportive measures immediately.

Digoxin-Specific Antibody fragments Availability Requirement A

Indication: **Digoxin and Digitoxin toxicity.**

Mode of action: Digoxin specific antibody fragments are derived from antibodies produced in sheep immunised to digoxin. They have a greater affinity for digoxin than the tissue-binding sites (Na-K-ATPase enzyme). The Fab fragments bind the intravascular free digoxin and then diffuse into the interstitial space, binding free digoxin there. This establishes a concentration gradient which encourages dissociation of tissue-bound digoxin. The digoxin-antibody complex is then rapidly excreted in the urine. Administration is by intravenous infusion over 30 minutes. If cardiac arrest is imminent the dose may be given as a bolus. It is important to note that most laboratories are not equipped to determine free serum digoxin levels. Once the antibody fragments have been administered serum levels will be no longer clinically useful as the level will represent both free and bound digoxin. Because of this it is important to monitor the cardiac status of the patient for at least 24 hours after administration for signs of recurrent toxicity. The onset of response for Digifab is usually within 1 hour with complete reversal of effects within 6 hours. Each vial will bind approximately 0.5mg of digoxin or digitoxin.

Presentation: Each vial contains 40mg of digoxin specific antibodies.

Supplier: Beacon Pharmaceuticals, UK.

Dosage: **a) If the dose of digoxin ingested is known then:**

<p><i>Adults:</i> (and children > 20kgs) $\text{Number of vials} = \frac{\text{ingested dose (mg)} \times 0.8}{0.5}$</p>
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b) If the serum concentration is known:

Digoxin	Number of vials = $\frac{\text{digoxin concentration (ng/ml)} \times \text{body weight (kg)}}{100}$
Digitoxin	Number of vials = $\frac{\text{digitoxin concentration (ng/ml)} \times \text{body weight (kg)}}{1000}$
This calculation should be rounded up to the nearest vial (better too much than too little)	
<i>Infants and children <20kgs:</i>	
<u>Acute toxicity:</u>	
Dose of digifab (mg) = 0.40 X serum digoxin level (ng/ml) X Body weight (kgs)	

Chronic toxicity:

One vial is usually sufficient.

c) If the dose ingested and serum level are both unknown.

Adults:

(and children > 20kgs)

20 vials can be administered. This can be done either as single dose, or commencing with 10 vials to be followed by the remainder if required.

Infants and children <20kgs:

Clinical judgement should be used, using an estimate of the likely dose ingested. It is important to be wary of fluid overload.

Note: Caution should be exercised when using high serum levels to calculate Digifab doses as digoxin assay kits are not designed to measure concentrations greater than 5 ng/ml (6.4nmol/L).

Dimercaprol

Availability Requirement C

Indication: **Dimercaprol is a chelating agent used in the treatment of acute poisoning by arsenic, gold and inorganic mercury. It is also used in conjunction with sodium calcium edetate in acute lead poisoning.**

Mode of action: Dimercaprol is a dithiol chelating agent (i.e. its chemical structure contains two sulfhydryl groups). These sulfhydryl groups bind with some heavy metals thereby preventing or reversing the binding of metallic cations to body ligands such as the essential sulfhydryl-containing enzymes. The dimercaprol-metal complex formed is readily excreted by the kidney. The aim of treatment is to provide an excess of dimercaprol in body fluids until the excretion of the metal is complete as the chelate may dissociate (at acidic pH) or undergo oxidation in vivo. Alkalinisation of the urine may protect the kidney during therapy by stabilising the dimercaprol-metal complex. Dimercaprol is much more effective when given shortly after exposure to the metal as it is more effective in preventing inhibition of sulfhydryl enzymes than in reactivating them.

Presentation: 50mg/ml in Arachis oil, 12 x 2mls

Supplier: Waymade (UK)

Dosage: 2.5-3mg/kg body weight by deep intramuscular injection every 4 hours for 2 days, 2-4 times daily on the third day and then 1-2 times daily for 10 days or until recovery.

Note: This product is contra-indicated in patients with a hypersensitivity to peanuts as it contains an arachis oil solvent.

Ethanol**Availability Requirement A (see note)**

Indication: **Ethylene glycol and methanol poisoning.**

Mode of action: Methanol is metabolised to the toxic metabolite formaldehyde and then formic acid by the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase respectively. It is the formic acid which accounts for the majority of the anion gap acidosis and ocular toxicity associated with methanol intoxication. Ethylene glycol (EG) is metabolised by the same enzymes to glycoaldehyde and glycolic acid. Further metabolism sees the formation of glyoxylic acid, oxalic acid and formic acid. The formation of these acids causes a profound anion gap acidosis with calcium oxalate crystals precipitating in the renal cortex. This results in decreased glomerular filtration, renal insufficiency and hypocalcaemia. Ethanol is a competitive antagonist for ADH and possesses a far greater affinity for the enzyme than either methanol or EG. This prevents further formation of toxic metabolites and the toxic alcohol can be excreted unchanged in the urine. However, it does not affect the presence of toxic metabolites already present. Administration of ethanol significantly prolongs the half-lives of both methanol and EG and in most cases haemodialysis is recommended to remove the toxic alcohol.

Presentation: 10 X 5mls*Supplier:* Georgelle*Dosage:* An ethanol concentration of 100-150mg% is required to completely saturate the ADH enzyme. A loading dose of ethanol is normally given while awaiting laboratory results in order to achieve this.*Loading dose:*7.5mls/kg of 10% ethanol in water i.v. Over 30 mins. *OR*1 ml/kg of 100% ethanol (suitably diluted) orally over 15-30 mins. *OR*

2.0 mls/kg of 40% ethanol (spirits i.e. vodka, whiskey) diluted and given orally over 15-30 mins.

Indications for continued ethanol therapy are:

- * Ethylene glycol level >200mg/L or Methanol level >200mg/L
- * Acidosis
- * Increased osmolar gap (>10mOsm/kg H₂O)
- * Calcium oxalate crystals in urine (for EG)
- * Increased blood formate levels (>10mg/L) (for methanol)

Dosage for continued ethanol therapy.

The amounts below are just a guide and should be adjusted to maintain the blood ethanol level between 100-150mg%. Dextrose should be added to i.v. solutions and the blood sugar should be monitored as ethanol can induce hypoglycaemia.

	5% ethanol (oral or iv)	10% ethanol (oral or iv)	40% ethanol (oral only)
Non-drinker / child	1.65ml/kg/hour	0.825ml/kg/hour	0.2ml/kg/hour
Average adult	2.76ml/kg/hour	1.38ml/kg/hour	0.3ml/kg/hour
Chronic drinker	3.9ml/kg/hour	1.95ml/kg/hour	0.4ml/kg/hour

Note: Either ethanol or Fomepizole should be available immediately.

The National Poisons Information Centre should be contacted in all cases where ingestion of ethylene glycol and methanol is suspected. Haemodialysis is an important facet of treatment and may be indicated following discussion.

Flumazenil**Availability Requirement A**

Indication: **Benzodiazepine overdose**

Mode of action: Flumazenil is a competitive inhibitor of drugs which act via the benzodiazepine receptors, specifically blocking their central effects. It should only be considered in severe cases of overdose (e.g. those requiring ventilation or those not responding to supportive care). It is not routinely recommended in benzodiazepine overdose for many reasons. Benzodiazepines, when taken alone are relatively safe in overdose. Flumazenil may precipitate convulsions in the presence of pro-convulsant drugs such as tricyclic antidepressants. It may cause arrhythmias in the presence of cardiotoxic drugs such as calcium channel blockers, beta-blockers and chloral hydrate. It can also cause the precipitation of convulsions in epileptics and withdrawal syndrome or convulsions in those addicted to benzodiazepines. The half-life of flumazenil (52 minutes) is much shorter than that of most benzodiazepines and therefore re-sedation is very likely, which may necessitate setting up an infusion of flumazenil.

Presentation: 500 ug per 5 mls x 5 ampoules.

Supplier: Uniphar

Dosage: *Adults:* Initially 0.2mg i.v. over 30 seconds. If there is no response within 30 seconds, then a second dose of 0.3mg can be administered over 30 seconds. Further doses of 0.5mg can be given over 30 seconds, at 60 second intervals, to a total dose of 3mg. If there is still no response, it is unlikely flumazenil will reverse the CNS/resp depression. The infusion rate is 0.1-0.5mg/hr; individually adjusted to maintain the desired response.

Children: A dose has not been recommended in children, the following has reversed coma in an overdose situation: 10mcg/kg i.v. not more

Folinic acid**Availability Requirement B**

Indication: **Folic acid antagonist (e.g. Methotrexate, trimethoprim) and methanol toxicity.**

Mode of action: Folic acid antagonists competitively inhibit dihydrofolate reductase, preventing the formation of tetrahydrofolate. Folinic acid is a reduced form of folic acid, which is readily converted to other reduced folic acid derivatives (e.g., tetrahydrofolate). It does not require reduction by dihydrofolate reductase as does folic acid, and is not affected by blockage of this enzyme. This allows purine and thymidine synthesis, and thus enabling DNA, RNA and protein synthesis to occur. Methanol toxicity is currently thought to develop as a result of reduced formate metabolism secondary to reduced folate levels. Leucovorin and folic acid have been shown to enhance the metabolism of formate, oxidising it to carbon dioxide.

Presentation: 3mg/1ml X 5vials, 15mg/2ml X 5 vials, 15 mg tablets

Supplier: United Drug

Dosage: **Methotrexate toxicity**

Where the dose of methotrexate ingested is known; give an equivalent or greater dose of folinic acid (orally or i.v. 6 hourly until the methotrexate level is $<5 \times 10^{-8}$ M. Where the dose of methotrexate is unknown, give $100\text{mg}/\text{m}^2$ of body surface area (orally or i.v.) 6 hourly until the methotrexate level falls below 5×10^{-8} M.

Methanol toxicity

1 mg/kg body weight (oral/i.v.) every 6 hours.

Fomepizole (4-MP)

Availability Requirement B (see note 1)

Indication: Ethylene glycol and methanol intoxication (although it is not licensed for use in methanol poisoning).

Mode of action: 4-MP is a competitive inhibitor of alcohol dehydrogenase. Alcohol dehydrogenase catalyses the initial steps in the metabolism of ethylene glycol and methanol to their toxic metabolites (see ethanol for more details). 4MP is an alternative to ethanol therapy due to its lack of adverse effects, minimal CNS depressant effects and slower and reproducible rate of elimination.

Presentation: (i) Antizol 1g/ml (1.5ml vial) which is an exempt (unauthorised) product, therefore the product name must be specified by the prescriber on the prescription or patient notes.
(ii) Fomepizole EUSA 5mg/ml (20ml vial) - authorised product

Supplier: (i) IDIS (UK)
(ii) Allphar (Ireland) and Masta (UK).

Dosage: Adult: Loading dose 15 mg/kg should be administered, followed by doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours until the ethylene glycol concentration is less than 200 mg/l (or methanol level $< 250\text{mg}/\text{l}$) and the patient is asymptomatic with a normal arterial pH. Do not give undiluted or by bolus injection. Dilute Antizol with at least 100 mL of sterile 0.9% sodium chloride injection or dextrose 5% injection. Fomepizole EUSA must be diluted in 100-250mls of 0.9% sodium chloride solution or 5% glucose solution for intravenous use.
Child: Safety and effectiveness in children have not been established.

(**N.B.** 4-MP is dialysable and the frequency of dosage should be increased to every 4 hours during haemodialysis. Please contact the National Poisons Information Centre for in-depth details on how to alter the timing of the dosage schedule in these instances.)

Note 1: Either ethanol or Fomepizole should be available immediately.

Note 2: 4MP is excreted via kidneys and toxic reactions may be increased in patients with renal impairment.

Glucagon**Availability Requirement A**

Indication: **Beta-blocker toxicity, calcium channel blocker toxicity, hypoglycaemic toxicity.**

Mode of action: Glucagon is a pancreatic polypeptide hormone that stimulates adenylyl cyclase to produce cyclic adenosine monophosphate (cAMP) at a site distinct from the beta-receptor. This produces effects in the heart similar to those of beta-agonists resulting in increased myocardial contractility and heart rate. Glucagon also decreases vascular resistance, which improves cardiac output. It also mobilises glucose by activating hepatic glycogenolysis. This is limited however on there being adequate stores of hepatic glycogen. A carbohydrate meal should be provided once the patient has responded sufficiently to replenish these stores. Supplemental potassium may be necessary for treated patients as glucagon reduces serum potassium.

Presentation: 1 mg GlucaGen® Hypokit

Supplier: Uniphar

Dosage: **Beta-blocker and calcium channel blocker toxicity**

Adults: 2-10mg i.v. bolus repeated as required
or
1-10mg/hour by i.v. infusion depending on response.
Children: 50-150 mcg/kg i.v. Bolus.
or
Up to 50 mcg/kg/hour by i.v. infusion.

Hypoglycaemic toxicity

Adults: 1-2mg i.m.
Children: 1mg in children >25kg, 0.5mg if <25kg

Note: The diluent supplied with the hypokit should not be used to reconstitute large quantities (>2mg) of glucagon as it contains phenol. Sterile water should be used.

Mesna**Availability Requirement B (see note 1)**

Indication: **Reduction of urothelial toxicity in antineoplastic therapy.**

Mode of action: Cyclophosphamide and its analogue ifosfamide induce haemorrhagic cystitis in about 5-10% of patients via urotoxic metabolites such as acrolein. Mesna is administered to neutralise these toxic metabolites. Mesna undergoes hepatic metabolism to mesna disulphide (dimesna) which is reduced back to free mesna in the kidney. This free mesna provides sulphhydryl (thiol) groups that inactivate the toxic metabolites of cyclophosphamide and ifosfamide. These inactivated compounds are then excreted renally. The aim of mesna therapy is to ensure adequate levels of mesna in the urine for the duration that the toxic antineoplastic metabolites are also present. Mesna has no effect on the concentration of either cyclophosphamide or its metabolites in plasma.

Presentation: 100mg/ml 400mg, 600mg tablets
400mg, 600mg tablets

Supplier: Baxter.

Dosage: **Intravenous preparation**

Adults: Doses are dependent on the amount of cyclophosphamide taken. The dose for intravenous mesna should be 20% weight for weight the dose of cyclophosphamide taken, administered three times at four hourly intervals (e.g. If 4 g of cyclophosphamide taken, give 800 mg mesna at 0, 4 and 8 hours).

Children or high-risk patients: Doses of up to 40% of the cyclophosphamide dose four times at three hourly intervals may be given (ie. 160% w/w total dose).

Oral preparation

All patients: Mesna takes up to 2 hours to appear in the urine when administered orally but excretion is more prolonged. Availability in the urine is only 50% of that for an equivalent intravenous dose, so doses given must be doubled. It is usually given in a flavoured drink.

Note 1: Only required if using cyclophosphamide.

Note 2: Urinary output should be maintained and the urine monitored for haematuria and proteinuria throughout treatment but frequent bladder emptying should be avoided.

Methionine

No Availability Requirement (see note)

Indication: **Paracetamol poisoning.**

Mode of action: Methionine is an amino-acid which is an essential part of the human diet. It is also used as an alternative to N-acetylcysteine in paracetamol poisoning to prevent hepatic damage. Methionine acts as a glutathione precursor and replenishes glutathione stores which have been depleted as a consequence of paracetamol poisoning. It will protect against paracetamol-induced liver and renal toxicity provided it has been administered within 8-10 hours of an overdose. The hepatocytes have to be intact in order to convert methionine to cysteine for glutathione synthesis. It has limited use in patients who are comatose or vomiting as it is administered orally and administration of activated charcoal will impair the absorption of methionine. It should not be used in patient with acidosis and may aggravate hepatic encephalopathy in patients with liver damage.

Presentation: 500mg tablets.

Supplier: IDIS

Dose: Adult and children <6 yrs: 2.5 grams initially followed by three further doses of 2.5g every 4 hours.
Child < 6 yrs: 1 gram initially followed by three further doses of 1g

Note: Methionine is no longer considered essential because of its short time span of efficacy. It can only be administered if the patient presents within 10 hours of ingestion. It is also problematic as it frequently causes vomiting and has to be administered orally.

Methylene Blue (Methylthioninium chloride)**Availability Requirement A**

Indication: **Treatment of methaemoglobinaemia (nitrates, nitrites, aniline, dapsone, benzocaine, lignocaine, nitrobenzene, sulphonamides.**

Mode of action: Methylene blue is reduced by NADPH and methaemoglobin reductase to leukomethylene blue. Leukomethylene blue then reacts with the oxidised methaemoglobin (Fe³⁺) to produce haemoglobin (Fe²⁺) and methylene blue. The onset of action is quite rapid with maximum effect usually seen within 30 minutes. Methylene blue is ineffective in patients with Glucose-6-Phosphate dehydrogenase deficiency and may cause haemolytic anaemia in these patients.

Presentation: 50mg/5ml ampoule x 5.

Supplier: Georgelle.

Dosage: Adults and children 1-2mg/kg i.v. over 5 minutes. Do not exceed total dose of 7mg/kg since methylene blue itself can cause methaemoglobinaemia and large doses can cause or exacerbate Heinz body haemolytic anaemia

Note: Methaemoglobin levels should be measured 1-2 hours after administration to assess efficacy of therapy. Cyanosis is a poor guide as methylene blue may result in a blue/grey discoloration of the skin. Accidental subcutaneous injection will produce tissue necrosis.

Naloxone**Availability Requirement A**

Indication: **Treatment of opioid overdose.**

Mode of action: Naloxone is a specific antagonist that acts competitively at opioid receptors. It is an effective antagonist of opioids with agonist or mixed agonist-antagonist activity. It usually has a rapid onset of action which occurs within 2 minutes when given intravenously. The plasma half life is approximately one hour. Naloxone can precipitate symptoms of withdrawal if given too quickly or in too high a dose to an opioid dependent patient.

Presentation: 400mcg/1ml x 10 ampoules.

Supplier: United Drug.

Dosage: Adult: Start with an initial bolus dose of 0.4mg i.v., increased every 2 to 3 minutes to a maximum bolus of 2mg. (total maximum dose 10mg). Repeat as required to maintain response.
Child: 0.01mg/kg bolus i.v., increased every 2 to 3 minutes to a maximum bolus dose 0.1mg/kg. Repeat as required.

IV INFUSION REGIME: Bolus dose giving adequate response x 0.66 = the hourly rate of naloxone likely to be necessary. The rate may be adjusted depending on response. Dilute in 5% dextrose or 0.9% saline to provide adequate fluid maintenance for the patient.

Note: Naloxone may be given intravenously, subcutaneously or intramuscularly. Intravenously is the preferred route in the treatment of acute poisoning as this gives the most rapid response. The IM or SC routes may be preferred for the maintenance doses since the duration of action is longer. But it must be noted that the onset of

action also takes longer. These routes may also be used where intravenous access is impractical. Naloxone has also been given via endotracheal tube in a case of acute opioid poisoning where intravenous access was unobtainable.

Octreotide**Availability Requirement B**

Indication: **Refractory hypoglycaemia induced by sulphonylureas and quinine.**

Mode of action: The conventional approach to sulphonylurea (SUA) overdose involves frequent measurements of blood glucose with administration of hypertonic glucose to correct hypoglycaemia. Hypertonic glucose rapidly corrects hypoglycaemia but then acts as a powerful stimulus for SUA sensitized pancreatic beta-cells. This increases insulin secretion, exacerbating hyperinsulinaemia and results in recurrent hypoglycaemia. Glucagon has also been used in emergencies but only produces transient effects on glycaemia and also stimulates endogenous insulin release. These effects are particularly important in non-diabetic patients, non-insulin-dependent diabetics and patients not previously exposed to SUAs. Diazoxide has been used to prevent such insulin release and rebound hypoglycaemia but its efficacy appears limited and its use may cause significant side effects. Octreotide is a synthetic analogue of the hormone somatostatin which inhibits the secretion of several hormones, including insulin. The use of octreotide for SUA-induced hypoglycaemia remains unlicensed, but several authors report its success in both adults and children. It has advantages insofar as it reduces the need for administration of hypertonic dextrose. This may be critical in patients with renal impairment or cardiac dysfunction. It may also obviate the need to insert a central line. The drug octreotide is well tolerated with minimal side-effects. Quinine may also induce hyperinsulinaemia in patients with metabolic stresses such as malnutrition, concurrent malaria or alcohol consumption. It is a rare complication but octreotide has also been shown to inhibit insulin release and correct hypoglycaemia in these cases.

Presentation: 50ug per ml, 5 x 1ml vials.

Supplier: Novartis

Dose: Adults: 50ug subcutaneously or IV every 12 hours.
Children: 1 ug/kg subcutaneously or IV every 12 hours.

Penicillamine**Availability Requirement C**

Indication: **Lead, copper and arsenic poisoning**

Mode of action: Penicillamine is a chelation agent for certain heavy metals such as copper, lead and mercury. It forms stable water soluble complexes with the metals that are readily excreted by the kidney. It is administered orally but is less effective than other agents in the treatment of severe lead poisoning. It is however used as an adjunctive treatment following initial therapy with another agent or may be used as sole therapy in asymptomatic patients with moderately elevated blood concentrations of lead.

Presentation: 125, 250mg tablets X 100

Supplier: United Drug.

Dosage: Adults: 1-2g daily in divided doses before meals.
Children: 20mg/kg daily in divided doses.

Phentolamine**Availability Requirement A**

Indication 1: **Hypertension caused by alpha-adrenergic poisoning.**

Mode of action: Phentolamine is an alpha-blocker (alpha-adrenergic antagonist) which has a broad affinity for both the alpha1 and alpha2 subtypes of receptor. Blockade of alpha1 adrenoreceptors inhibits the vasoconstriction induced by endogenous catecholamines. Both arteriolar and venous vasodilation occur resulting in a fall in blood pressure due to decreased peripheral resistance.

Indication 2: **Cocaine toxicity**

Mode of action: Cocaine causes vasoconstriction of the coronary arteries. It also binds to the sodium channel of the cardiac muscle further increasing the risk of arrhythmias. When cocaine is co-ingested with alcohol a toxic metabolite, cocaethylene, is produced which has even more severe effects on the heart. Alpha-blockers have been shown to alleviate cocaine induced coronary vasoconstriction. For this reason, Phentolamine, is recommended in the treatment of cocaine induced myocardial ischaemia.

Presentation: 10mg/ml X 5 ampoules.

Supplier: United Drug.

Dosage: Adults – 2-5mg IV bolus, repeated if necessary.
Children – 0.05 to 0.1 milligram/kilogram (2.5 milligrams maximum) intravenously every 5 minutes until hypertension is controlled, then every 2 to 4 hours as needed.

Phytomenadione (Vitamin K)**Availability Requirement B**

Indication: **Used in the treatment of anticoagulant poisoning**

Mode of action: Anti-coagulants inhibit hepatic synthesis of the vitamin dependant coagulation factors (II, VII, IX and X) and anticoagulant proteins. These clotting factors are produced as inactive proteins which must be activated by a carboxylase enzyme before clotting can occur. Vitamin K is a cofactor in this enzyme system which is reduced to vitamin K epoxide and then regenerated to its active form by a reductase enzyme. Anticoagulants inhibit this reductase enzyme thereby preventing reactivation of vitamin K and competitively blocking the clotting process. Administration of phytomenadione (vitamin K) overcomes this block.

Presentation: 10mg/1ml x 10. 10mg tablets

Supplier: Uniphar.

Dosage:
Patients not on anticoagulant therapy

If no active bleed – Adults: 10-20mg orally, Children: 250ug/kg body weight orally.

If an active bleed – Same doses except given by slow intravenous injection.

Daily doses will be necessary until the prothrombin time returns to normal.

Patients on anticoagulant therapy

If no active bleed and INR between 5 and 9 then vitamin K 2.5mg orally.

If no active bleed and INR > 9 then vitamin K 5mg orally

If there is active bleeding give fresh frozen plasma and vitamin K 1mg by slow IV infusion. Further treatment should be titrated according to repeat INR and the presence of active bleeding.

The INR should be assessed at least every 24 hours in the above patients on anticoagulant therapy.

Note: Treatment with vitamin K may be required for weeks or months. Intravenous vitamin K has been associated with fatal anaphylaxis in the literature so the oral for is preferred where possible.

Polyethylene glycol

Availability Requirement B

Indication: **Whole bowel irrigation (WBI)**

Mode of action: Polyethylene glycol electrolyte solution (PEG-ES) is an osmotically balanced solution used for WBI. PEG-ES cleanses of the bowel by means of fluid overload, inducing a liquid stool within a short period of time. The concentration of electrolytes in the solution causes no net absorption or secretion of ions; thus no significant changes in water or electrolyte balance occur. WBI is a treatment option for potentially toxic ingestion of sustained release or enteric coated drugs. It is also of use for the removal of ingested packets of illicit drug or agents not absorbed by charcoal. It should be continued until the rectal effluent becomes clear. WBI is contraindicated in the presence of ileus, obstruction, bowel perforation, clinically significant gastrointestinal haemorrhage, haemodynamic instability, uncontrollable intractable vomiting, coma, seizures and an unprotected compromised airway or if the patient is obtunded.

Presentation: 4 sachets of white granular powder, each to be reconstituted to 1 litre.

Supplier: Uniphar

Dosage: Children <6 years: 0.5 Litre/hour 6-12 years: 1 Litres/hour
Adults: 1.5-2.0 Litres/hour

The American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists have published a position statement on Whole Bowel Irrigation.

Clinical Toxicology 1997; 35(7): 753-762.

Pralidoxime

Availability Requirement C

Indication: **Organophosphorus (OP) insecticides.**

Mode of action: The predominant toxicological effects of organophosphate (OP) insecticides are due to the inhibition of acetylcholinesterase (AC-ase). The phosphate radical moiety of the OP binds to the active serine-containing site of the AC-ase

(phosphorylation) and inhibits it from functioning. This results in accumulation of acetylcholine at the neuronal synapse. This accumulation initially stimulates and subsequently paralyzes cholinergic synaptic transmission in the CNS, somatic nerves, autonomic ganglia, parasympathetic nerve endings and some sympathetic nerve endings. Pralidoxime restores AC-ase activity by removing the bulky phosphate moiety from the phosphorylated AC-ase. This returns the stereochemistry of the AC-ase to normal, allowing it to accept acetylcholine molecules, restoring enzymatic destruction of acetylcholine at the neuromuscular junction and relieving muscular paralysis. The efficacy of pralidoxime in treating different organophosphate compounds varies widely as it depends on the nature of the phosphoryl group.

Presentation: 20% w/v, 5 x 5ml ampoules.

Supplier: Department of Health, United Kingdom.

Dosage: 30mg/kg IV over 5-10 minutes, repeated in serious cases at 4-6 hourly intervals. It may be given as an IV infusion at a rate of 8mg/kg/hour in either 5% dextrose or 0.9% NaCl after two bolus injections 30mg/kg have been given 4 hours apart.

Note: Concomitant use of atropine or glycopyrrolate with pralidoxime is necessary to directly counteract parasympathetic effects (e.g. bradycardia).

Procyclidine

Availability Requirement A

Indication: **Dystonia caused by antipsychotic drugs and Metoclopramide.**

Mode of action: Parkinsonian symptoms can be relieved by either potentiation of the dopaminergic system or blockade of acetylcholine by antimuscarinic agents. Procyclidine is a synthetic tertiary amine with antimuscarinic actions. It competitively inhibits the excitatory effects of acetylcholine at muscarinic receptors of the autonomic effector sites innervated by parasympathetic nerves. It also blocks the effects of acetylcholine on smooth muscle lacking cholinergic innervation.

Presentation: 5mg/ml, 5 x 2mls or 5mg tablets

Supplier: Pinewood (inj) GlaxoSmithKline (tablets)

Dosage: The oral, intravenous and intramuscular dose for adults is 5-10 mg and elderly patients should be given 5mg initially. Children under 2 years should be given 500ug to 2mg, children 2-10 years can be given 2-5mg. Severe reactions can usually be abolished within a few minutes with intravenous or intramuscular administration. Subsequent oral doses may be required for 2-3 days.

Protamine Sulphate

Availability Requirement A

Indication: **Heparin poisoning**

Mode of Action: Protamine is used to neutralise the anticoagulant action of heparin in the treatment of haemorrhage from heparin overdose. Heparin is an electronegative molecule that binds with anti-thrombin III (AT III), altering its stereochemistry and

thereby catalysing the subsequent inactivation of thrombin. Protamine is a basic electropositive protein which has a greater affinity for heparin than AT III and is able to cause a dissociation of the heparin-AT III complex, in favour of the stable and inactive heparin-protamine complex. Approx. 1mg of protamine will neutralise about 100 units of heparin. Doses administered should always be underestimated as excessive doses of protamine have an anticoagulant effect.

Presentation: 10mg/ml, 1 x 5 ml vial.

Supplier: Leo Laboratories.

Dosage: Not to exceed 50 mg in a 10-minute period

If given within a few minutes of heparin administration then:
1mg per 100 units of heparin administered.

If more than 1 hour since the heparin injection then:
0.5 - 0.75mg per 100 units of heparin administered.

If more than 2 hours since the heparin injection then:
0.25 – 0.375mg per 100 units of heparin administered.

Prussian blue

Availability Requirement C

Indication: **Thallium poisoning.**

Mode of action: Thallium has a similar sized ionic radius to that of potassium and is known to exchange with potassium in the body. This inhibits many enzyme systems and interferes with oxidative phosphorylation. Thallium has also been shown to have a high affinity for sulphhydryl groups in the mitochondrial membranes. Prussian blue is a non-adsorbable lattice of potassium ferric ferrocyanide. Its mechanism of action is the release of potassium ions to mobilise intracellular thallium with the absorption of thallium onto the insoluble crystal lattice in the gut. Neither this complex nor Prussian blue is systemically absorbed. The half-life of thallium is multiphasic and complex and prussian blue is recommended until the thallium level is <10ug/L in blood and urine.

Presentation: 25g powder.

Supplier: Lennox Laboratories.

Dosage: 250mg/kg/day orally in divided doses via a fine bore nasogastric tube.

Note: Mannitol may be given with the prussian blue to prevent or delay the onset of paralytic ileus, which is common in thallium poisoning.

Pyridoxine

Availability Requirement A

Indication: **Isoniazid, Gyromitrin, Hydrazine and ethylene glycol toxicity.**

Mode of action: Pyridoxine is a vital component in cellular metabolism and the utilisation of amino acids. It also serves as a cofactor in more than 40 enzyme systems. Isoniazid (a hydrazine compound) affects the availability of pyridoxine in the body in several ways according to its different metabolites. It will bind with pyridoxine directly to form an isonicotinylhydrazide complex which is excreted

directly in the urine. It is also metabolised to hydrazones which inhibit the enzyme (pyridoxine phosphokinase) that converts pyridoxine to its active form, pyridoxal 5' phosphate. Other isoniazid metabolites (hydrazides) inactivate available pyridoxal 5' phosphate directly. This leads to decreased GABA synthesis and subsequently increased cerebral excitability and seizures. Isoniazid can also increase the transamination of existing GABA, giving a decrease in GABA and loss of its inhibitory effects. Gyromitrin is hydrolysed to monomethylhydrazine and its toxicological mechanism is similar. Pyridoxine (in conjunction with Thiamine) is also recommended by some sources for the treatment of ethylene glycol poisoning to promote the biotransformation of glyoxylate to non-toxic glycine, although clinical evidence for its use is lacking.

Presentation: 100mg/2mls x 5

Supplier: IDIS

Dosage: ***Isoniazid poisoning***

Adults: 1g pyridoxine IV for every gram of isoniazid ingested to a maximum of 5g (where the dose of ingested isoniazid is unknown give 5g of pyridoxine).

Children: 70mg/kg, to a maximum of 5g.

Give at a rate of 0.5g/minute as a 5-10% solution in 5% dextrose (no information on use with saline). If convulsions are controlled before the full dose is given, administer the remaining pyridoxine as a slow IV infusion over 1-2 hours. Repeat if necessary.

Gyromitrin/Hydrazine poisoning

The recommended dose in literature is 25mg/kg body weight given as an infusion over 15-30 minutes. Repeat doses may be administered for recurring neurological signs to a maximum daily total of 15-20 grams.

Note: Convulsions need to be controlled with both diazepam and pyridoxine as they act synergistically. If a parenteral preparation of pyridoxine is unavailable, then tablets may be crushed and given orally or via a nasogastric tube as a slurry at the same dose.

For Ethylene glycol poisoning

100mg/day IV.

Silibinin

Availability Requirement C

Indication: **Amatoxin poisoning.**

Mode of action: Silibinin is derived from the milk thistle plant *Silybum marinarum*. It is thought to provide a hepato-protective effect by inhibiting the entry of amatoxins into the liver cells. It is also proposed that silibinin stimulates cellular biosynthesis.

Presentation: Rubber stoppered vial containing the equivalent of 350mg silibinin. The contents of 1 vial (350mg silibinin) should be dissolved in 35mls infusion solution (5% glucose or 0.9% saline).

Supplier: Madaus AG, D51101 Koln, Germany. Tel 0049 221 89980

Dosage: Adult: The recommended daily dose is 20mg/kg distributed over 4 infusions, each of 2 hours duration (5mg/kg per infusion). The infusion

should be repeated every 4 hours so that a total of 4 infusions are administered in 24 hours. There is no limit to the duration of treatment.
Children: Not indicated.

Note: Benzylpenicillin and Silibinin should not be used in combination.

Sodium bicarbonate**Availability Requirement A**

Indication 1: Salicylate (aspirin) toxicity

Drugs which are weak acids (e.g. salicylates) exist in a state of equilibrium between their ionised and un-ionised form. The ratio between the ionised form of a drug and its un-ionised form is shifted by altering the systemic pH because of the relationship between pH and pKa. Ionised drugs penetrate the cell membrane poorly. By increasing the systemic pH with sodium bicarbonate more of the salicylate is trapped in its ionised form in the extra-cellular fluid resulting in enhanced renal excretion. In the presence of alkaline urine renal excretion of salicylate ions is enhanced (10-20 fold with an increase from pH 5 to 8). Therefore sodium bicarbonate should be administered to correct any acidosis (arterial pH should not rise above 7.6) and to alkalinise the urine (optimum pH 7.5-8.5). It is very difficult to produce an alkaline pH if the patient is hypokalaemic as hydrogen ions tend to be excreted with the bicarbonate instead of potassium. Therefore the potassium should be kept at the upper end of normal (>4.5mEq/L).

Dosage: Adult: 1 litre of 1.26% sodium bicarbonate (isotonic) + 40 mmol potassium IV over 4 hours and/or 50 ml boluses of 8.4% sodium bicarbonate IV (ideally via a central line) if peak salicylate level > 500mg/L (3.6mmol/L).

Child: 1 ml/kg 8.4% sodium bicarbonate + 1mmol/kg potassium diluted in 10ml/kg saline infused at 2-3 ml/kg/hr if peak salicylate level > 350mg/L (2.5mmol/L).

Indication 2: Tricyclic antidepressant toxicity.

The administration of sodium bicarbonate in tricyclic antidepressant (TCAD) poisoning has been shown to have beneficial effects but the mechanism of these effects is a subject of much debate. It is not surprising that it has a therapeutic effect in acidotic patients, although it has also been found to be beneficial in the absence of acidosis and even in a patient with preceding alkalosis. Alkalinisation may cause increased protein binding of TCADs in serum, thereby decreasing the amount of free drug. Although the small decrease in free drug concentration would not be expected to elicit such a beneficial clinical response. Animal experiments have suggested that increasing the extracellular sodium ion concentration may cause the beneficial effects by partially reversing the fast sodium channel blockade and facilitating uncoupling of the TCA drug from the sodium channel by altering its binding properties. Other experimental work suggests that sodium bicarbonate ameliorates conduction delays converting wide complex tachycardia to normal sinus rhythm and improving contractility.

Dosage: The initial dose is 1-2 mmol/kg (1 ml of 8.4% contains 1mmol of both sodium and bicarbonate) i.e. 1-2ml/kg of 8.4% IV (ideally via a central line) over 15

minutes. A continuous IV infusion of 500-1000 ml of 1.26% may be given if indicated to adults. 1L of 1.26% sodium bicarbonate can be infused over 4 hours. The infusion rate should be titrated to match the individual. The arterial blood pH must be closely monitored to maintain it between 7.45-7.55. Subsequent bicarbonate therapy should be guided by arterial blood gas measurements. Potassium should be maintained at the upper end of normal.

Presentation: 8.4% x 100mls

Supplier: Braun

Sodium calcium edetate**Availability Requirement C**

Indication: **Lead toxicity.**

Mode of action: Calcium disodium edetate (CDE) is a chelating agent used in the treatment of acute and chronic lead poisoning and lead encephalopathy. The EDTA moiety of CDE preferentially binds with divalent and trivalent metals such as lead, with the resultant displacement of the calcium molecule. This does not cause any significant changes in the serum or total calcium concentration although depletion of endogenous metals (zinc, iron and manganese) is a concern with chronic therapy. Some authors recommend the use of zinc and iron supplements after therapy. The chelate which is formed with lead is a stable, water soluble ring-compound that is readily excreted in urine. Following CDE administration, urinary lead excretion is increased 20-50 fold. 50% of the chelate is excreted in the urine in 1 hour and more than 95% in 24 hours. The lead which is extracted is primarily removed from the soft tissue. The removal of lead from the skeletal system occurs more slowly with restoration of equilibrium with the soft tissue compartments. It is important to monitor the renal function during CDE administration as lead may be displaced from the chelate in the kidneys during excretion and lead intoxication can cause kidney damage independent of chelation.

Presentation: 200mg/ml, 6 x 5mls.

Supplier: Medisource

Dosage: 30-40mg/kg by IV infusion in 5% dextrose or 0.9% saline twice daily for up to for up to 5 days, repeated if necessary after 48 hours for a maximum of another 5 days.

Sodium nitrite**Availability Requirement A (see note 1)**

Indication: **Cyanide / Acrylonitrile**

Mode of action: In the presence of nitrites haemoglobin is converted to methaemoglobin, which has a higher binding affinity for cyanide than cytochrome oxidase. (See amyl nitrite)

Presentation: 300mg/10mls ampoules X 10

Supplier: Georgelle

Dosage: Adults: 10mls of a 3% solution (300mg) intravenously over 5-20 minutes followed by sodium thiosulphate.
Children: 0.15-0.33 mls/kg of a 3% solution (max 10mls) over 5-20 minutes followed by sodium thiosulphate.

Note 1: Only one of the three cyanide treatment options (Dicobalt edetate / hydroxocobalamine / sodium nitrite-sodium thiosulphate) is required to be available

Note 2: Use of amyl nitrite must be stopped when sodium nitrite is administered. Careful frequent blood pressure monitoring must accompany the sodium nitrite injection, and the rate slowed if hypotension occurs. Some authors suggest diluting the sodium nitrite in 50-100mls of normal saline, beginning the infusion slowly and increasing to as rapid as possible without a decrease in blood pressure. Also, if methaemoglobinaemia becomes excessive (>40%) the effect of the antidote is negated as oxygen transport to the tissue is significantly impaired.

Sodium thiosulphate**Availability Requirement A (see note)**

Indication: **Cyanide / Acrylonitrile**

Mode of action: Sodium thiosulphate acts as a substrate for the enzyme rhodanase, which catalyses the conversion of cyanide to the relatively non-toxic thiocyanate. It also provides sulphate donors for the conversion of cyano-methaemoglobin to thiocyanate and methaemoglobin. (See amyl nitrite)

Presentation: 25% USP 50mls vials

Supplier: IDIS.

Dosage: Adults – 50mls of 25% solution (12.5g) i.v. over 10 minutes
Children – 1.6mls/kg (400mg/kg) of 25% solution to a max of 50mls.

Note: Only one of the three cyanide treatment options (Dicobalt edetate or hydroxocobalamine or sodium nitrite-sodium thiosulphate) is required to be available

Starch**Availability Requirement A**

Indication: **Iodine**

Mode of action: Starch reduces iodine to the relatively harmless iodide.

Presentation: 500g powder

Supplier: Medisource.

Dosage: 15g starch in 500mls water orally.