Clinical practice review

Clinical Toxicology: Part I. Diagnosis and Management of Common Drug Overdosage

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ABSTRACT

Objective: *To review the diagnosis and management of drug overdosage in a two-part presentation.*

Data sources: *A review of articles reported on drug overdose and poisoning.*

Summary of review: *A patient who has taken an overdose of a common drug often presents with an alteration in neurological, cardiovascular and respiratory functions. The differential diagnosis includes, central nervous system injury and metabolic encephalopathies (e.g. hepatic failure, hyponatraemia, hypocapnia, hypoglycaemia). In general, measures to prevent absorption (e.g. emesis, gastric lavage) or increase excretion (e.g. diuresis, catharsis) of the drug, have not been shown consistently to reduce mortality associated with drug toxicity. However, in selected instances, adsorbents (activated charcoal, Fuller's earth), gastric lavage and haemodialysis or continuous renal replacement therapy are useful in the management of drug overdosage and specific antidotes can be recommended for individual poisons. Nevertheless, as the major hazards of an overdose are aspiration, hypoventilation, hypoxia, hypotension and cardiac arrhythmias, the most important aspects in the management of a poisoned patient is the maintenance of the patient's airway, ventilation and circulation, while the drug is excreted.*

The diagnosis and management of common drug overdoses (e.g sedative, hypnotic, psychoactive, neuroleptic, anticonvulsant, sympathomimetic, analgesic and cardiac drugs) as well as the alcohols are discussed in the first part of this presentation on clinical toxicology.

Conclusions: *In the critically ill overdosed patient, while activated charcoal, continuous renal replacement therapy and specific antidotes may be of benefit in selected cases, maintenance of the patient's airway, ventilation and circulation still remain the most important aspects of management.* (**Critical Care and Resuscitation 2002; 4: 192-215**)

Key words: Drug overdose, poison, coma,

Poisoning is an exposure to an amount of substance that is likely to produce untoward effects in an individual.[1] Only 20% of patients who have taken an overdosage are in any danger and, of these, most survive with non specific cardiovascular and respiratory support. Antibiotics, vitamins, oral contraceptives and simple antacids are generally nontoxic if taken as a large single acute ingestion.

At least 50% of patients who attempt suicide with a drug overdose take more than one drug, with ethyl alcohol usually being one of the agents. Approximately 25% of patients who are poisoned are less than 5 years of age, 50% are between the ages of 5 and 30, and the remaining 25% are more than 30 years old. The patients who are less than 5 years of age are usually accidental poisonings whereas those who are greater than 5 years old are usually suicidal poisonings. After the age of 5, females have twice the incidence of poisoning than

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males. The overall mortality associated with poisoning is approximately 0.5%.[2]

Clinical assessment

A clear history of poison ingestion is important (e.g. from patient, relatives or circumstances where the patient is found with a suicide note). Also what agent was ingested, how much and how long ago and if the patient has vomited since. Generally, signs of an overdose are often evident within the first 1 - 3 hr after ingestion, although some agents may have a delayed clinical onset (Table 1).

Table 1. Poisons that have a delayed effect

Drug	*Maximum time (in hours) until the first symptoms appear*
Ethylene glycol	6
Amanita (mushroom poisoning)	12
Salicylates	12
Arsenic	24
Paracetamol	36
Methyl alcohol	48
Paraquat	48
Thallium	96

The patient who has taken an overdose often exhibits varying clinical signs, with alteration in cardiovascular (e.g. hypotension), respiratory (e.g. reduced respiratory rate and airway reflexes), neurological (reduction in consciousness, tone, and corneal, lash, pupillary, and spinal reflexes) and thermal (e.g. hypothermia) functions, being the predominant effects. Other signs (e.g. pressure marks, bullae, limb muscle tenderness and oedema caused by rhabdomyolysis - due to muscle pressure, hypotension and/or seizures) may also be present.

Several clinical patterns may also be typical for different types of poisoning which can be a useful guide to the agent responsible, laboratory test needed and treatment required (Table 2).

The differential diagnosis of a drug overdosage includes, cerebral injury (e.g. trauma, haemorrhage, infarction, infection) and metabolic encephalopathies (e.g. hepatic failure, hyponatraemia, hypocapnia, hypoglycaemia) and psychosis.

Investigations

The investigations required in a patient suspected of drug overdosage include:

Specimen analysis. Specimens of urine, blood and gastric contents may be required for toxicological

Table 2. Common clinical patterns associated with poisoning

Clinical pattern	*Poisons*
Narcosis/sedative syndrome	
coma, reduced consciousness, purposeful response to pain, flaccidity, reduced reflexes	benzodiazepines, barbiturates, ethanol, tricyclics, phenothiazines, opiates, antihistamines, chloral hydrate
Anticholinergic syndrome	
coma, hyperreflexia, twitching, agitation, hallucinations, seizures, dilated pupils, tachycardia	anticholinergics, tricyclics, phenothiazines, antihistamines
Ventricular tachycardia/hypotensive syndrome	
coma, hypotension, ventricular tachycardia, ventricular fibrillation	tricyclics, chloral hydrate, quinidine, anticholinergics, antihistamines, phenothiazines
Sympathomimetic syndrome	
seizures, hypertonia, hyperreflexia, pyrexia, hypokalaemia, hyperglycaemia, metabolic acidosis	theophylline, MAOI*, phencyclidine, cocaine amphetamines (e.g., amphetamine, methamphetamine, para-methoxyamphetamine 3,4-methylenedioxyamphetamine 3,4-methylenedioxymethamphetamine)
Cholinergic syndrome	
bradycardia, diaphoresis, bronchorrhoea, diarrhoea, seizures, coma, pinpoint pupils	organophosphates

* MAOI = monoamine oxidase inhibitor

Table 3. Plasma therapeutic and toxic levels of some common drugs

	Therapeutic level		*Toxic level*		
Agent	μmol/L	(mg/L)	μmol/L	(mg/L)	Treatment
Amitriptyline	0.3 - 1.1	(0.09 - 0.35)	> 3.7	(1)	repeated charcoal
Carbamazepine	20 - 50	(4 - 12)	> 80	(20)	repeated charcoal
Ethylene glycol			> 10	(0.6)	haemodialysis
Isopropanol			> 10	(0.6)	haemodialysis
Imipramine	0.45 - 0.9	(0.14 - 0.28)	> 3.7	(1)	repeated charcoal
Iron	8 - 35		> 60		desferrioxamine
Lithium	600 - 1200		> 2 - 4 mmol/L		haemodialysis
Lignocaine	5 - 21	(1.2 - 5)	> 40	(10)	supportive
Meprobamate	20 - 80	(4 - 16)	> 120	(24)	repeated charcoal
			> 500	(100)	haemodialysis
Methanol			> 15	(0.5)	haemodialysis
Nortriptyline	0.2 - 0.6	(0.06 - 0.18)	> 3.7	(1)	repeated charcoal
Paracetamol	70 - 130	(10 - 20)	> 660	(100)	N- Acetylcysteine
Phenobarbitone	45 - 130	(9 - 26)	> 175	(35)	
		coma	> 250	(50)	repeated charcoal
barbitone			> 500	(100)	
all other barbiturates	10 - 20	(2-5)	> 40	(10)	
		coma	> 70	(18)	
Phenytoin	40 - 80	(10 - 20)	> 100	(25)	charcoal
Procainamide	7 - 20	(2 - 6)	> 33	(10)	charcoal
Quinidine	6 - 15	(2 - 5)	> 20	(7)	charcoal
Salicylate	1100 - 2200	(150 - 300)	> 2200	(300)	
			> 3600	(500)	repeated charcoal
			> 5500	(750)	haemodialysis
Theophylline	55 - 110	(10 - 20)	> 220	(40)	repeated charcoal

analysis. Therapeutic and toxic levels of some of the common drugs are listed in Table 3.

Other tests. These include plasma biochemical analysis (as hypokalaemia, hyperkalaemia, acidosis, osmolar gap, hyperglycaemia, rhabdomyolysis and renal failure may occur with drug overdosage), blood gas analysis (to detect the presence of acidosis, hypercapnia or hypoxia) and chest X-ray to (detect aspiration and placement of the nasogastric tube).

Treatment

As the major hazards of an overdose are aspiration, hypoventilation, hypoxia, hypotension and cardiac arrhythmias, the most important aspects in the management of a poisoned patient are the maintenance of the patient's airway, ventilation and circulation.[3] An intravenous cannula is inserted, and 500 mL of a 0.9% saline or colloid solution is infused if the patient is hypotensive. Up to 1000 mL of fluid is infused if the hypotension persists, thereafter right heart catheterisation is often used to monitor further therapy.

Prevention of further absorption of the drug

Emesis. Vomiting may be induced (if the patient is conscious) by simple pharyngeal stimulation (using a nasogastric tube). While apomorphine is a reliable emetic (which can be reversed by naloxone) and ipecacuanha (Ipecac syrup containing 0.12% alkaloids) 10 - 30 mL is an effective emetic (particularly in children),[4] there is no evidence that these agents improve the morbidity or mortality associated with drug overdosage.[5] Currently, these agents are rarely if ever used.[6,7]

Gastric lavage. This is performed using 0.9% saline and a 16 - 20 French gauge nasogastric tube (inserting the tube to a distance of 10 cm greater than the distance from the xiphisternum to the bridge of the nose or inserting it to the 55 cm mark at the tip of the nose in an adult), with the patient head down and right side uppermost.

When the patient's airway is assessed as 'protected' (i.e. has effective glottic reflexes or has an endotracheal tube in place), the stomach is completely aspirated and 50 mL of saline is instilled and aspirated. This is contin-

ued until the gastric aspirate is clear, which usually occurs after 500 mL of saline has been used.

Gastric lavage is usually performed if the quantity of drug is unknown and the agent has been ingested within the last 4 hours. Lavage is usually not indicated if benzodiazepines, phenytoin or antibiotics have been ingested, because the minimum lethal dosage with these agents is so high.

However, gastric lavage is becoming more and more selective, as controlled trials have not shown benefit from lavage in all patients.[8,9] It is usually indicated in adults if the patient has ingested an amount of the drug listed in Table 4 (or greater), within the time specified.

Table 4 Indications for gastric lavage

Drug	*Amount*	*Within the previous*
Aspirin	15 g	12 - 24 hr
Paracetamol	10 g	6 - 12 hr
Digoxin	5 mg	8 - 12 hr
Tricyclics	750 mg	12 - 24 hr
Methanol	25 mL	8 - 12 hr
Ethylene glycol	100 mL	8 - 12 hr
Phenobarbitone	1000 mg	8 - 24 hr
Dextropropoxyphene	325 mg	8 - 24 hr
Theophylline	2.5 gm	4 - 12 hr (8 - 24 hr sustained release)

Gastric lavage is contraindicated in patients who have ingested corrosives (e.g. acids or alkalis) or petroleum distillates (e.g. kerosene, petrol, eucalyptus oil), as it may cause perforation of the stomach or oesophagus (after ingestion of corrosives) and aspiration of as little as 1 mL of distillates can result in an overwhelming pneumonitis (distillates are almost nontoxic when ingested with only minor symptoms occurring with ingestion of 500 - 1000 mL). If ingestion and aspiration of a lipoid compound has occurred, large volume lung lavage may be used as this has been beneficial in cases of severe lipoid pneumonitis caused by paraffin oil[10] and coconut oil.[11]

While patients who have ingested eucalyptus oil are usually asymptomatic,[12] it may cause drowsiness, coma and seizures (and usually within the first 30 - 60 minutes). Nevertheless, management is conservative as the patient usually awakens within 24 - 48 hr.[13,14]

Adsorbents. The adsorbents commonly used include:

Activated charcoal

a. *Action.* Activated charcoal is a general all-purpose adsorbent, which is 'activated' to increase its adsorbent capacity. It is able to adsorb from 100 - 1000 mg of poison per gram, inhibiting the absorption of orally ingested compounds as well as increasing the systemic clearance of drugs through the gastrointestinal tract.[15-18] The mechanism for the latter may involve interruption of the enterohepatic recycling and/or promotion of drug movement from the systemic circulation into the gut lumen (i.e. gastrointestinal dialysis).[15,19] Variables that may alter the efficacy of charcoal therapy include the preparation and dose of charcoal used, toxins ingested, nature of the stomach contents, gastrointestinal pH and time from toxin ingestion to charcoal administration.[20]

b. *Indications.* Activated charcoal is effective in the treatment of salicylate, quinidine, quinine, chloroquine, dapsone, dextropropoxyphene, digoxin, meprobamate, barbiturates, carbamazepine, tricyclic antidepressants, phenothiazines and theophylline overdosage.[19] The increases in drug clearance with multiple doses of activated charcoal are detailed in Table 5.[16,21-24]

Activated charcoal is ineffective in the treatment of ferrous sulphate, cyanide, caustic alkalis, mineral acids, heavy metals, lithium, pesticides (i.e. malathion, DDT, carbonate) and alcohol (i.e. ethanol, methanol and isopropyl alcohol) overdosage.[21,25,26]

Apart from its use in the drug overdose patient, activated charcoal has been used to lower plasma cholesterol concentrations,[27] relie-ve uraemic pruritus,[28] remove uraemic toxins[29] and remove porphyrins (to reduce cutaneous photosensitivity in porphyria).[30]

c. *Dosage.* Activated charcoal is usually administered as an initial oral dose of 50 g suspended in 300 mL of water followed by 50 g in 300 mL of water 4-hourly or 25 mg in 150 mL of water 2-hourly, up to 200 g. More than 200 g may be administered if it is given with a cathartic (e.g. sorbitol) and it appears in the stools within 12 hr.

The initial dose is administered after gastric lavage is completed. Before each subsequent dose, the stomach is aspirated. Co-administration of sorbitol (100 g sorbitol per 50 g charcoal) or mannitol as a cathartic is common practice, although it reduces the capacity of drug absorption by charcoal,[31] and may cause intestinal pseudo-obstruction (particularly when used for anticholinergic drug overdosage) which may require surgical decompression.

d. *Side-effects.* Activated charcoal may cause constipation and charcoal impaction.[4,32] Massive

aspiration of activated charcoal has also been reported to cause bronchiolitis obliterans[33] and progressive respiratory failure.[33,34]

Fuller's earth (calcium montmorillonite)

Because only 5 - 10% of paraquat is absorbed in 24 hours, Fuller's earth is given as soon as possible after paraquat ingestion. It is administered as a 30% solution (i.e. 300 g suspended in 1 litre of water) followed by 200 mL of 20% mannitol. This is followed 2-hourly by a 15% solution (1000 mL of water with 150 g of Fuller's earth), followed by 200 mg of 20% mannitol, every 4 hours to induce a catharsis. This is repeated until the stools are seen to contain Fuller's earth.

Catharsis. To promote catharsis, 1 - 2 g/kg of sorbitol or mannitol (e.g. 300 - 500 mL of 20% mannitol) orally may be used. Polyethylene glycol (which is normally used for bowel preparation for colonoscopy or large bowel surgery) has also been used (2 litres per hour for adults orally or via a nasogastric tube until rectal effluent becomes clear - which is usually within 2 - 6 hours).[35] However, catharsis (or whole bowel irrigation) should only be considered when potentially toxic sustained-release or enteric-coated drugs have been ingested. Catharsis is contraindicated in patients with paralytic ileus or bowel obstruction.[36]

Table 5. The elimination half-life (in hours) with and without activated charcoal

	Normal	*Activated charcoal*
Carbamazepine	19 ± 6.9	8.6 ± 2.4
Dapsone	77 ± 23	12.7 ± 0.7
Digoxin	23.1 ± 1.7	17 ± 1.5
Phenobarbitone	110 ± 8	45 ± 6
Theophylline	10.2 ± 2.1	4.6 ± 1.27

Increasing elimination of adsorbed drug

Forced acid or alkaline diuresis. Forced acid diuresis has been used to treat overdosage of phencyclidine or amphetamine, and forced alkaline diuresis has been used to treat patients with barbiturate or salicylate overdosage. However, unless managed very carefully, forced diuretic therapies have the capacity to increase rather than decrease mortality due to hypokalaemia and fluid overload. Sedation for phencyclidine or amphetamine overdosage, and haemodialysis for salicylate overdosage and gastric charcoal administration for barbiturate overdosage are preferred to alkaline or acid diuresis.

Peritoneal dialysis. This has no place in the management of patients with poisoning.

Haemodialysis. This may be indicated for severe salicylate, phenobarbitone, lithium, isopropanol, methanol or ethylene glycol poisoning.

Haemoperfusion. This is largely an unproven form of therapy,[37] although it is often recommended for severe theophylline overdosage (particularly if severe and associated with vomiting),[38] methotrexate poisoning (particularly in association with renal failure),[39] disopyramide and camphor[40] overdosage. Charcoal filters are commonly used, although polystyrene resins (e.g. Amberlite XAD-4®) have been developed which have a high affinity for lipid-soluble compounds.[1] For most drugs, charcoal haemoperfusion is about twice as effective as haemodialysis, although only about half as effective as Amberlite XAD-4®.[1]

Specific therapy

Antidotes for the common poisons are listed in Table 6.[41]

COMMON DRUG OVERDOSAGES

Sedative and hypnotic drugs

Benzodiazepine, barbiturate and chloral hydrate

Overdosages of these agents commonly present with sedative and hypnotic features characteristic of the various stages of anaesthesia. While phenothiazines, and antihistamines also have sedative effects, an overdose of these agents may present with anticholinergic symptoms, arrhythmias and central nervous system (CNS) excitatory effects, similar to tricyclic overdosage.

Clinical features. Even with large doses, benzodiazepine overdosage usually does not progress to coma unless the patient has taken another sedative drug.

Barbiturate overdosage, however, often causes coma and because the patient often assumes a prolonged posture in one position, it can be associated with pressure neuropathy, skin blisters, pressure sores and rhabdomyolysis which may even manifest as a compartment syndrome.

Chloral preparations are all metabolised within minutes to trichloroethanol, causing profound respiratory depression as well as sensitising the myocardium to circulating catecholamines.[42] In up to 30% of cases with severe poisoning (particularly with respiratory acidosis) there are supraventricular and

Table 6. Indications and dose of the common poison antidotes

Antidotes	*indication*	*dose*
N-acetyl cysteine	Paracetamol	150 mg/kg i.v. in 15 min (10 g/70 kg)
	Carbon tetrachloride	50 mg/kg i.v. in 4 hr (3 g/70 kg) 100 mg/kg i.v. in 16 hr (7 g/70 kg)
Atropine	Organophosphates	1 - 2 mg i.v. repeated as necessary
Benztropine	Dystropic effects of butyrophenones phenothiazines and metoclopramide	1 - 2 mg i.v. repeated as necessary
Benzyl penicillin	*Amanita phalloides*	250 mg/kg i.v. daily
Calcium chloride	Calcium channel blockers fluorides, hyperkalaemia hypermagnesaemia	10 mL of 10% $CaCl_2$ i.v. over 5 - 10 min
Desferrioxamine	Iron	Gastric lavage with 2 g in 1 litre of water. After lavage leave 5 g in 50 mL of water in stomach. i.v. 5 -15 mg/kg/hr for no longer than 24 hr
Dicobalt edetate	Cyanide	600 mg i.v. over 1 minute followed by 300 mg i.v., if no response.
Dimercaprol	Arsenic, copper, gold, lead, mercury	2.5 - 5 mg/kg IM 4-hourly for two days then 2.5 mg/kg daily.
Ethanol	Methanol	50 gm i.v. followed by 10 - 12 g/hr to keep blood level at 1 - 2 g/L. If haemodialysis, then rate increased to 17-22 g/hr, or ethanol added to dialysate at a conc'n of 1 - 2 g/L; maintain for 4 days.
Physostigmine	Anticholinergic agents	1 mg i.v. (response is often unpredictable e.g., it may cause convulsions) and the effect only lasts for 30 mins
Folinic acid	Methotrexate	60 mg i.v. twice for first day then 15 mg 6-hourly for 5 - 7 days.
	methanol	30 mg i.v. 6-hourly for 2 days
Fuller's earth	Paraquat	1 litre of a 15% solution (i.e., 150 g suspended in 1 litre of water followed by 200 mL of 20% mannitol), 2-hourly until the stools are seen to contain Fuller's earth.
Pralidoxime	Organophosphates	1 g i.v. bolus followed by an infusion of 0.5 g/hr (i.e., 12 g/day)
Pyridoxine	Isoniazid	i.v. pyridoxine 1 gram/gram isoniazid ingested or 5 g i.v. each 15 minutes until seizures stopped
Glucagon	Beta blockers	3 - 10 mg i.v. followed by an infusion at 1 - 5 mg/hr
Sodium calcium edetate	Lead	50 - 75 mg/kg by i.v. infusion over 1 hr daily for 5 days (used in association with dimercaprol)
Sodium nitrate	Cyanide	300 mg i.v. over 3 minutes followed by 12.5 g of sodium thiosulphate (25 mL of 50%) i.v. over 10 minutes.

ventricular arrhythmias,[43-46] which are often terminated by correcting hypoxia or hypercapnia, although magnesium sulphate, amiodarone, lignocaine, phenytoin or beta-blockers may be required.

Treatment. Apart from gastric lavage and repeated oral charcoal (and occasionally mannitol catharsis and haemodialysis for severe barbiturate overdosage), treatment is largely supportive. The patient is intubated if there is a risk of aspiration and ventilated if respiratory failure occurs. Hypotension is treated with intravenous fluids and inotropic agents.

While flumazenil has been used to reverse the sedat-

ive effects of benzodiazepine overdosage, deaths (due to partial or ineffective reversal of respiratory depression),[47] convulsions (in patients a combined tricyclic and benzodiazepine overdosage),[48] and seizures with ventricular tachycardia (in patients with combined tricyclic[49] or chloral hydrate[50] and benzodiazepine overdosage) have been reported with its use. However, in one double-blind study of unconscious patients suspected of benzodiazepine overdose, intravenous flumazenil (0.1 mg every 30 s until full consciousness was regained or up to 2.5 mg) was a useful diagnostic tool in distinguishing pure benzodiazepine from mixed-drug intoxication or nondrug induced coma, and safe (if patients were monitored and flumazanil 1 mg readministered if respiratory insufficiency returned) even in patients with mixed benzodiazepine and tricyclic antidepressant overdosage.[51]

Antihistamines

The antihistamines include chlorpheniramine, cyclizine, cyproheptadine, dexchlorpheniramine, diphenhydramine, orphenadrine, pheniramine, and pyrilamine, and can be obtained either 'over the counter' or by prescription. In toxic doses, the antihistamines produce a mixture of CNS excitatory and depressant effects, usually due to their anticholinergic actions. They may also produce myocardial depression due to their quinidine like effects.[52]

Clinical features. These include drowsiness, dryness of the mouth, headache, nausea, tachycardia, agitation, tremors, ataxia, delirium, hallucinations, seizures, hyperthermia, coma, hypotension, pulmonary oedema and shock.

Treatment. Apart from gastric lavage and repeated oral charcoal, treatment is largely supportive. Physostigmine has been given to reverse the CNS effects although its use is controversial and often not recommended. Hypotension is managed using intravenous saline infusions, calcium chloride (10 mL of 10% intravenously over 5 min) and inotropic support. Right heart catheter monitoring may also be required.

Psychoactive drugs

Tricyclic antidepressants

Tricyclic antidepressants are a group of compounds that have a similar chemical structure to imipramine (e.g. clomipramine, desipramine, dibenzepin, opipramol, trimipramine), amitriptyline (e.g. butriptyline, dothiepin, nortriptyline, protriptyline) or doxepin. A typical therapeutic dose for any of these agents ranges from 75 - 200 mg/70 kg/day. Amounts greater than 1.0 - 1.5 g/70 kg are thought to be potentially lethal.[53] Amoxapine is structurally related to the tricyclic antidepressants and lacks cardiotoxicity, even in large overdoses. However, it may still cause seizures.[53,54]

The tricyclics are rapidly absorbed from the gastrointestinal tract (overdosages may have a slower absorption due to the anticholinergic effects of the drug) and avidly bind to tissue, producing a large volume of distribution, estimated at 10 - 50 L/kg. Hypoalbuminaemia and acidosis increase the amount of circulating free tricyclic antidepressant, whereas diseases associated with an elevation of 'acute phase reactants' may decrease the amount of free drug by 30%.[53] Increasing the blood pH from 7.38 to 7.5 decreases the amount of circulating free tricyclic antidepressant by 21%.[53]

Clinical features. The clinical features of a tricyclic overdose are due to:

1. *Antimuscarinic effects*, e.g. sinus tachycardia, mydriasis, ileus, dry mouth and urinary retention.
2. *CNS effects*, e.g. hallucinations, coma, coarse myoclonic jerks, seizures, extensor plantar reflexes, brisk tendon reflexes, nystagmus, choreoathetosis, dysarthria, ataxia, respiratory depression and neuroleptic malignant syndrome.
3. *Cardiac effects*, e.g. hypotension, ECG effects of widened QRS, right bundle branch block, prolonged QT_c and right axis deviation,[55] ventricular tachycardia, torsade de pointes and ventricular fibrillation.

   As the tricyclic antidepressants have a mixture of anticholinergic, antiadrenergic (i.e. inhibit uptake of noradrenaline at the nerve terminal) and quinidine-like effects, their resultant effect on the heart is complex.
4. *Metabolic effects*, e.g. hypothermia, hyperthermia, hypokalaemia, metabolic acidosis and rhabdomyolysis.

Treatment. This includes gastric lavage (even up to 12 - 24 hr after the overdosage) and repeated administration of activated charcoal. Oral (or nasogastric) mannitol (300 - 500 mL of 20%) may be used, although it may not induce a catharsis due to the anticholinergic gastrointestinal stasis caused by the drug.

1. *Monitoring.* As blood levels correlate poorly with cardiovascular or CNS toxicity, the ECG changes are often used to determine the degree of toxicity.[56,57] If, 6 hr after the overdosage, the maximal limb lead QRS complex is greater than 0.10 s, an R wave amplitude > 3 mm in aVR, and a terminal 40-msec QRS axis between 120° and 270° (this is usually associated with a tricyclic blood level of greater than 3.7 μmol/L or 1 mg/L),[53] then ECG monitoring for 24 hr is recommended because seizures or ventricular arrhythmias may occur (usually between

6 and 24 hr following the overdose).[53,56,57]

Because amoxapine does not prolong the QRS complex, the QRS width is not a useful guide for amoxapine CNS toxicity.[54]

2. *Acidosis.* Hyperventilation, to induce respiratory alkalosis, is used first to treat respiratory acidosis, metabolic acidosis and the ventricular arrhythmias associated with tricyclic antidepressant toxicity.[58-60] If ventricular arrhythmias persist, both hyperventilation and sodium bicarbonate are used to keep the plasma pH greater than 7.45.[53,61]
3. *CNS effects.* While coma associated with tricyclic antidepressant overdosage may be severe enough to require active airway and respiratory support, it usually only lasts for 24 - 48 hr. Seizure activity should be rapidly controlled with intravenous diazepam 5 - 10 mg followed by intravenous phenytoin 50 mg/min up to 1000 - 1500 mg/70 kg as a loading dose. Some have even recommended prophylactic phenytoin in patients with severe tricyclic overdosage,[53] because seizures often occur immediately before a cardiac arrest,[53] perhaps by increasing the cardiotoxicity of the drug with the onset of hypoxia and acidosis.

   The use of 1 mg of physostigmine intravenously is controversial. While it may control the CNS effects of agitation and seizures, it lasts for 30 - 60 min only and does not reverse the cardiac effects, because the latter are mediated by the quinidine rather than the anticholinergic effects of the tricyclic antidepressant. Physostigmine has also been associated with severe bradycardia and asystole.[53,62]
4. *Cardiovascular effects.* Hyperventilation and sodium bicarbonate (to keep the pH > 7.45) are generally accepted as the first line treatment for ventricular tachycardia, torsade de pointes or ventricular fibrillation. Defibrillation is also used for ventricular fibrillation. If ventricular tachycardia with hypotension exists, cardioversion (using low energies, e.g. 50 J) is required. Magnesium sulphate may be used to control ventricular tachycardia and torsade de pointes[63] and phenytoin may also be used to control ventricular tachycardia, although quinidine, disopyramide and procainamide are contraindicated[64] and lignocaine is probably of little use.[63] If cardiac arrest occurs then refractory asystole, pulseless electrical activity or ventricular fibrillation do not carry the same prognosis as that observed for acute myocardial infarction. A case of full recovery following tricyclic antidepressant overdosage and cardiac arrest with 5 hr of cardiopulmonary resuscitation has been reported.[53] If complete heart block or torsade de pointes with ventricular tachycardia occur, then adrenaline or cardiac pacing may be required. Hypotension is managed using intravenous saline infusions, calcium chloride (10 mL of 10% intravenously over 5 min) and inotropic support. Right heart catheter monitoring is also be required.

Monoamine oxidase inhibitors (MAOIs)

There are two main types of monoamine oxidase (MAO) enzymes: monomanine oxidase A (MAO-A) and monomanine oxidase B (MAO-B). While both types deaminate dopamine, tyramine, octamine and tryptamine, monomanine oxidase A preferentially deaminates 5-HT, adrenaline and noradrenaline, and monoamine oxidase B preferentially deaminates phenylethylamines, phenylethanolamines and O-tyramine. MAO-A is found mainly in the liver and gastrointestinal tract and acts as a defense against the systemic effects of ingested tyramine and other exogenous amines. MAO-B is responsible for all the MAO activity in platelets and 80% in the brain (MAO-B inhibition is considered essential for direct MAOI antidepressant effects).

Nonselective (and ireversable) inhibitors of monoamine oxidase

Tranylcypromine and phenelzine are nonselective MAOIs which are commonly used to treat depression.

Clinical features. These drugs, taken in excess, cause clinical features that include, excitement, agitat-ion, delirium, ataxia, pyrexia, tachycardia, hypertension, hypotension, diaphoresis, fixed and widely dilated pupils, generalised muscle rigidity with opisthotonos, trismus, metabolic acidosis, rhabdomyolysis and seizur-es. These effects may be exacerbated by sympatho-mimetic amines, pethidine and theophylline.[65,66]

Treatment. Apart from gastric lavage and repeated administration of activated charcoal, treatment is largely symptomatic. Propranolol may be used to control hypertension and tachycardias, although close haemo-dynamic control is necessary as severe hypotension may occur, particularly if hypovolaemia is present. Dantrolene sodium (2.5 mg/kg intravenously 6-hourly for 24 hr) has been used to treat muscle rigidity and hyperpyrexia.[66]

Reversible inhibitors of monoamine oxidase

The reversible inhibitors of monoamine oxidase A are a group of drugs (e.g. moclobemide, clorgyline) that selectively inhibit monoamine oxidase A (producing an antidepressant effect by inhibiting 5HT deamination) allowing metabolism of tyramine by monoamine oxidase B. Selegiline is a selective MAO-B inhibitor. These drugs taken singly in excess are remarkably free of side effects or clinical symptoms following over-dosage.[67]

Selective serotonin reuptake inhibitors (SSRIs)

The selective serotonin reuptake inhibitors are a group of drugs (e.g. fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram) that inhibit cerebral serotonin reuptake with little affinity for adrenergic, cholinergic, dopaminergic or antihistamine receptors. Fluoxetine is metabolised to norfluoxetine which also acts as a selective serotonin uptake inhibitor. The clinical effects of fluoxetine last for 7 - 10 days as the elimination half life for fluoxetine is 1 - 10 days and for norfluoxetine is 3 - 20 days,[68] although with prolonged administration the $5HT_{1A}$ receptor becomes down regulated.

The symptoms that develop after acute fluoxetine overdosage are minor consisting of sinus tachycardia, drowsiness, orolingual dyskinesia, restlessness (akathisia), tremor, nausea and vomiting.[69] Paroxetine has a half life of 24 hours and has no active metabolites.[70] Symptoms relating to paroxetine overdose are minor and are similar to that which develop following fluoxetine overdosage.[71]

Nefazodone is a non-selective serotonin reuptake inhibitor, noradrenaline reuptake inhibitor (SNaRIs) and $5\text{-}HT_2$-receptor blocker. The latter is thought to be the major action of the drug,[72] and chronic administration causes down regulation of both the β_1 adrenoreceptor and $5HT_{1A}$ receptor. Venlafaxine at low doses is is a non-selective serotonin reuptake inhibitor and at high doses is also a noradrenaline reuptake inhibitor with a weak inhibitory effect on dopamine reuptake.[73] Mirtazapine is a potent antagonist of central α_2-adrenergic receptors and an antagonist of serotonin $5HT_2$ and $5HT_3$ receptors (i.e. a noradrenergic and specific serotonergic antidepressant - NaSSA); reboxetine is a selective noradrenergic reuptake inhibitor (NaRI).[74]

The selective serotonin reuptake inhibitors should not be coadministered with MAOIs or L-tryptophan as this may cause the '*serotonin syndrome*' to develop which is characterised by,[75,76] a rapid onset of an acute confusional state (e.g. insomnia, confusion, restlessness, anxiety, agitation, delirium, hallucinations, seizures, coma), autonomic dysfunction (e.g. mydriasis, diaphoresis, tachycardia, hypertension, hypotension, diarrhoea, nausea, salivation, piloerection, flushing) and neuromuscular abnormalities (e.g. ataxia, dysarthria, restlessness, hypertonicity, hyperreflexia, myoclonus, oculogyric crisis, opisthotonus, nystagmus, hyperthermia, shivering, tremor, rigidity).

The diagnosis of the serotonin syndrome is a clinical one.[77] In severe cases there may be leucocytosis, rhabdomyolysis, renal failure, hepatic failure, acute respiratory distress syndrome and disseminated intravascular coagulation. The treatment includes, discontinuation of the causative agent, symptomatic control of temperature (which may require intubation and paralysis with a nondepolarising relaxant and artificial ventilation to reduce the muscular rigidity), acid-base and fluid and electrolyte maintenance. The syndrome typically resolves within 24 hours, although confusion may be prolonged. Serotonin antagonists including cyproheptadine,[78] chlorpromazine,[79] methysergide,[80] and propranolol[81] as well as benzodiazepines[81] have also been used to manage the agitation, although in some cases they may have no effect.[81]

Baclofen

Baclofen is a lipophilic analog of gamma-aminobutyric acid, which is often used clinically to control spasticity. Baclofen overdose (usually > 400 mg) may cause coma, respiratory depression, hyporeflexia, flaccidity, facial dystonia (twitching), hypotension, hypothermia, abdominal pain, bradycardia, supraventricular tachycardia (usually within 2 hours of ingestion)[82] due to its GABA and cholinergic effects.[83] It is usually treated conservatively (mechanical ventilation, intravenous fluid and inotropic agents may be required for 24 hours up to 4 days), although haemodialysis has been used (particularly in patients who have co existant renal failure) to reduce the length of coma.[84] Facial dystonia may be made worse by GABA enhancers (e.g benzodiazepines) which are contraindicated in baclofen overdose.[85]

In patients receiving baclofen chronically who have taken an acute overdosage, an abrupt baclofen withdrawal syndrome may develop manifesting in hallucinations, delirium, seizures, and high fever.[86]

Other antidepressants

Mianserin, trazodone and viloxazine are a group of miscellaneous antidepressants that have novel actions that are not yet completely understood. Overdoses of these agents also produce minor symptoms. Venlafaxine is a selective noradrenaline reuptake inhibitor.

Phenothiazine, butyrophenones and atypical neuroleptic agents

The phenothiazines include chlorpromazine, fluphenazine, perphenazine, prochlorperazine, promazine, promethazine, thioridazine, trifluoperazine and trimeprazine; the butyrophenones include haloperidol and droperidol; and the atypical neuroleptic agents (which have less sedative and extrapyramidal side-effects) include clozapine, rispiridone, olanzapine.

Clinical features. An overdose of any of these agents may present with clinical features that include dryness of mouth, drowsiness, hypotension, hypothermia, tachycardia, ataxia, fever, constipation, tremor, rigidity, seizures, coma, ventricular tachycardia, torsade de pointes and shock.[87]

Treatment. Apart from gastric lavage and repeated oral activated charcoal, treatment is largely supportive. Benztropine mesylate 1 - 2 mg may be administered to reverse the extrapyramidal effects of these agents. Hypotension is managed using intravenous saline infusions, calcium chloride (10 mL of 10% intravenously over 5 min) and inotropic support. Right heart catheter monitoring may also be required.

Lithium

Lithium (Li^+) is a monovalent cation with properties similar to other group IA alkali metals (e.g. sodium, potassium, rubidium, cesium) and is often used for the treatment of bi-polar disorders. It is usually prescribed as lithium carbonate (Li_2CO_3) which contains 27 mmol of Li^+ per gram. Lithium is rapidly absorbed by the gastrointestinal tract, reaching a peak serum concentration after 2 - 4 hr, and by 12 hr after ingestion 30 to 60% of the oral dose is excreted in the urine (the remainder is excreted over the next 14 days). About 80% of filtered Li^+ is reabsorbed by the proximal tubule, with a small amount being reabsorbed by the ascending loop of Henle.[88] In contrast to Na^+, the distal nephron reabsorbs very little of the filtered Li^+. The lithium ion crosses cell boundaries slowly with a distribution volume equalling total body water. A steady state is reached after 5 - 6 days of therapy.[89] The therapeutic range for serum lithium (measured 12 hr after the last dose) is 0.6 - 1.2 mmol/L.

Clinical features. While thyroid dysfunction (e.g. hypothyroidism, goitre), renal dysfunction (e.g. polyuria, nephrogenic diabetes insipidus, interstitial nephritis, renal tubular acidosis, acute renal failure), peripheral neuropathy, myopathy, hypothermia, hyperthermia and hyperglycaemia may occur with chronic lithium toxicity,[90] acute lithium toxicity usually presents with CNS or cardiac effects or, rarely, acute renal failure.

1. *CNS effects.* When the serum lithium level is greater than 1.5 mmol/L, apathy, sluggishness, tremor, blurred vision, ataxia, dysarthria, nausea, vomiting, muscle fasciculations, hyperreflexia, extensor plantar reflexes and confusion, often occur. When the blood level is above 3.0 mmol/L, seizures, coma, flaccid paralysis, cerebral oedema and death, may also occur. The acute neurologic effects of lithium toxicity may also persist, with ataxia, nystagmus, myoclonic jerks, dysarthria, tremor and rigidity, being the commonly observed neurological sequelae following severe toxicity.
2. *Cardiac effects.* These include refractory ventricular tachycardia, bradycardia and asystole.[91,92]
3. *Acute renal failure.* While chronic lithium intoxication can cause a variety of renal disorders, acute lithium intoxication can also cause acute renal failure.[93]

Treatment. Gastric lavage is performed and further therapy is dictated by the clinical condition and serum levels. Activated charcoal is ineffective (although resonium A, 150 mg in 24 hr has been used sucessfully to increase lithium clearence).[94] If the patient has a lithium level greater than 4 mmol/L or between 2 - 4 mmol/L with a deterioration in the clinical condition, in the presence of renal failure,[90,95,96] or if the extrapolated time required before the serum level reaches 0.6 mmol/L is greater than 36 hr (two serum lithium levels are taken 3 h apart and log serum values are plotted against time on log paper),[96] haemodialysis is indicated. Haemodialysis should be continued until the serum lithium level is below 1 mmol/L.[95,96] Due to the fact that lithium crosses cell boundaries slowly, when intermittent haemodialysis is used, it is often needed to be repeated to prevent the lithium levels from rising 6 - 8 hours after dialysis (i.e. 'lithium rebound').

Continuous haemodiafiltration (veno-venous or arterio-venous) has been found to be an effective alternative to haemodialysis as it can often be rapidly deployed within an intensive care environment (reducing the delay to initiate therapy), prevents postdialysis lithium rebound and, in one study with dialysate flow rates of 1 and 2 L/hr, reached lithium clearance rates of 48 ± 1.4 mL/min and 61.9 ± 2.3 mL/min[97] which were similar to the reported haemodialysis lithium clearance rates of 50 mL/min. [96]

If the patient is hypotensive or dehydrated, intravenous saline or dextrose solutions may be required. Intravenous sodium chloride 'loading' and diuretics, however, are of no value in increasing the excretion of the lithium ion and may cause life threatening complications (e.g. hypernatraemia, pulmonary oedema).[95] Ventricular tachycardia may be successfully treated with intravenous magnesium sulphate (5 - 20 mmol).[91]

Anticonvulsants (nonbarbiturate)

Phenytoin overdosage even if severe usually only causes mild clinical effects (e.g. ataxia, nystagmus, hyperreflexia, confusion, lethargy), with no cardiovascular instability[98] and only rarely causes coma.[99]

Carbamazepine overdosage may cause similar clinical effects to tricyclic overdosage (as they are structurally related) causing coma, hypotension, respiratory depression, cardiac arrhythmias, abnormal movements and seizures. While sinus tachycardia is usually present (particularly in younger patients),[100]

bradycardia and complete heart block may occur (particularly in elderly female patients).[100,101]

Sodium valproate overdosage is usually benign and rapidly reversible, although drowsiness, irritability, seizures, coma, and cardiorespiratory failure may occur when amounts of 200 mg/kg or more are ingested, requiring cardiovascular and respiratory support.[102] Hyperammonaemia, hypernatraemia, metabolic acidosis and hypocalcaemia,[103] bone marrow suppression and pancreatitis[104] and delayed (and reversible) cerebral oedema[105] have also been reported with sodium valproate intoxication.

Vigabatrin overdosage may cause vertigo, tremor, psycosis[106] and rarely coma (and is usually associated with an artifactually low plasma ALT level after 12 hr).[107]

Sympathomimetic 'designer' drugs

These include amphetamine, methamphetamine, para-methoxyamphetamine (PMA or 'death'), 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy'), cocaine, pencyclidine, and lysergic acid diethylamide (LSD).

Clinical features. In cases of sympathomimetic 'designer' drug toxicity, clinical features range from agitation, tremor, hyperventilation, diaphoresis, nausea, vomiting, abdominal pain, diarrhoea, headache, and tachycardia during mild to moderate toxicity, to delirium, hyperthermia, hyperpyrexia, cardiac arrhythmias, hypertension, hypotension, seizures, coma and cardiac arrest (which may even be the presenting feature), in cases of severe toxicity. The biochemical features include, hypokalaemia, hyperkalaemia, hyperglycaemia, hypoglycaemia, hypophosphataemia, hypomagnesaemia, hypercalcaemia, respiratory alkalosis, lactic acidosis and rhabdomyolysis. The latter may cause hyperphosphataemia, hypocalcaemia and renal failure. Severe toxicity may also cause hepatic necrosis and liver failure, due to a toxic metabolite, drug impurity or hyperpyrexia.

Treatment. This includes cardiovascular and respiratory resuscitation (which may require endotracheal intubation, mechanical ventilation, intravenous fluids, sedation and beta adrenergic blockade) and rapid reduction in core temperature as a core temperature of > 42°C is usually fatal. Management of cocaine 'body packers' (i.e. ingested latex baloons filled with cocaine) who develop symptoms of cocaine toxicity due to rupture of the packages, as well as intensive care medical management, may require surgery to remove the packages, particularly if mechanical bowel obstruction occurs.[108] Asymptomatic 'body packers' may be followed conservatively for 2 days after sorbitol purgation.

Analgesic drugs

Opioids

Clinical features. The clinical features of opioid toxicity are largely due to respiratory failure caused by hypoventilation, hypoxia, aspiration, pneumonia, and pulmonary oedema. Opioids may also produce hypothermia and convulsions (the latter are induced by metabolites of pethidine or dextropropoxyphene). Dextropropoxyphene can also cause severe hypotension, tachycardia, shock, and cardiac arrest, unrelated to hypoxia and venodilation.[109,110]

Treatment. This is largely symptomatic, with endotracheal intubation and mechanical ventilation to manage respiratory failure and right heart catheterisation, fluids and inotropic agents as required to manage cardiovascular failure.

Naloxone will reverse the respiratory depression, sedation, analgesia, miosis and nausea associated with opioid toxicity. However, it does not reverse seizures. While naloxone has an elimination half-life of 1 hour, it has only a short clinical effect of 10 - 30 min. Therefore, if opiate toxicity is to be treated with naloxone the initial dose of up to 2 mg may need to be followed by an infusion of up to 5 mg/hr.[111] However, naloxone treatment is not without hazard. It produces an acute withdrawal of opiates and may precipitate shock, seizures, arrhythmias,[112,113] hypertensive crisis,[114] pulmonary oedema[115] and intractable ventricular fibrillation.[116,117]

Salicylates

Salicylate toxicity uncouples oxidative phosphorylation and increases heat production, glycogenolysis (causing an initial hyperglycaemia), peripheral demand for glucose (causing late hypoglycaemia), liberation of free fatty acids and generation of ketones.[118]

Therapeutic plasma levels of salicylate are up to 300 mg/L (2200 μmol/L) and toxic signs of salicylate usually do not occur unless the plasma salicylate levels are greater than 500 mg/L (3600 μmol/L) 6 hours after ingestion. While absorption of salicylates in therapeutic doses is rapid and usually complete in 1 hour, large single doses of salicylates may delay gastric emptying resulting in continuing absorption for up to 24 hr after the ingestion.[119] The elimination half-life of salicylate increases with increasing dosage from 2.5 hr after 300 mg to 5 - 7 hr after 1000 mg and 15 - 30 hr after doses greater than 4000 mg.[120,121] Because only a small percentage of salicylate is not ionised at 7.4 (i.e. 0.004%), small changes in pH result in large changes in

nonionised salicylate, changing the amount able to enter tissues. A reduction in blood pH from 7.4 to 7.2 will increase the amount of nonionised salicylate from 0.004% to 0.008%.

Clinical features. These include nausea, vomiting, epigastric pain, agitation, tremor, tinnitus, deafness, hyperventilation, diaphoresis, pulmonary oedema, hypotension, shock, hypoprothrombinaemia, hypokalaemia, fever, hyperglycaemia, hypoglycaemia, respiratory alkalosis, metabolic acidosis (lactic, keto- and salicylic acids), coma, renal failure and hepatic failure. Severe salicylate toxicity may even mimic septic shock.[122]

Treatment. The initial treatment involves gastric lavage and oral activated charcoal. Intravenous glucose and vitamin K are also administered to guard against hypoglycaemia and hypoprothrombinaemia, respectively.[123] Therapy thereafter depends on plasma levels. For example:

1. *Mild toxicity* occurs at peak levels of salicylate less than 500 mg/L (3600 μmol/L) and usually requires no further treatment.

2. *Moderate toxicity* occurs at levels of 500 - 750 mg/L (3600 - 5500 μmol/L). While many recommend forced alkaline diuresis at these levels,[124] excretion of salicylate is at best only moderately promoted by keeping the urine pH greater than 7.5 (an effect which is not enhanced by the use of diuretics),[125] and pulmonary oedema, cerebral oedema, hypokalaemia and hyponatraemia may develop following the large volumes of fluid and sodium bicarbonate required.[125,126] Repeated oral activated charcoal decreases the half-life of salicylate from 24 - 30 hr to less than 4 hr,[127] and this, along with sodium bicarbonate and hyperventilation to correct metabolic and respiratory acidosis respectively, is recommended for moderate salicylate toxicity.[127,128]

3. *Severe toxicity* occurs with levels above 750 mg/L (5500 μmol/L). In such cases or if acidosis, impaired consciousness, pulmonary oedema or renal failure coexist, haemodialysis should be used.[129]

Paracetamol

Paracetamol absorption is rapid. Peak concentrations occur within 1 hr and the elimination half-life is 2 - 3 hr (increasing to 7.3 hr with overdosage[130,131] and up to 11 hr with an overdose of an extended release formulation).[132] Normally, 5% of paracetamol is excreted unchanged in the urine. Approximately 85% of the therapeutic dose is conjugated by the liver (55% with glucuronic acid and 30% with sulphate) to form inactive metabolites which are excreted in the urine.[133] Smaller amounts (5 - 8%) are oxidised by the cytochrome P_{450} mixed-function oxidase system to a reactive intermediate (N-acetyl-p-benzoquinoneimine) that is normally conjugated with hepatic glutathione and excreted in the urine.[134] With glutathione depletion, the N-acetyl-p-benzoquinoneimine is free to bind covalently to macromolecules in the liver cells and cause hepatic necrosis.

This is more likely to occur if:[135-137]

- excessive paracetamol has been ingested,
- the P_{450} mixed-function oxidase system has been induced by phenobarbitone or chronic alcohol ingestion (e.g alcohol-paracetamol syndrome where the alcoholic takes more than 4 g of paracetamol per 24 hr for pain relief) or,
- glutathione depletion exists (e.g. starvation).

The normal minimal threshold dose of paracetamol in an adult is 10 g before glutathione availability is exceeded and hepatic damage occurs,[138,139] although in malnourished patients and following starvation, hepatic damage may occur after ingestion of 4 - 10 g of paracetamol.[140] Acute ethanol administration may protect against paracetamol toxicity because there is competition for the same cytochrome P_{450} mixed-function oxidase enzyme.[135] Cimetidine, however, which also inhibits the P_{450} mixed-function oxidase enzyme, does not protect against paracetamol toxicity.[141]

Clinical features. On the first day after taking a hepatotoxic dose of paracetamol (i.e. more than 150 - 200 mg/kg), the patient may complain of nausea and vomiting. On the second day, abdominal pain and tenderness occurs. Without treatment, 60% of patients with a plasma paracetamol concentration above the 'treatment line' show signs of severe liver damage by the third to fifth day, (i.e. peak levels of plasma aspartate aminotransferase and alanine aminotransferase occur and are usually greater than 1000 U/L). Lactic acidosis develops by the third to the fifth day, although a transient hyperlactataemia may occur within the first 15 hours.[142]

The high anion gap acidosis may be caused by pyroglutamate accumulation (which can also be caused by flucloxacillin or vigabatrin).[143] Only 5% who develop severe hepatic necrosis, progress to hepatic failure, encephalopathy, gastrointestinal haemorrhage and death.[144] The remainder recover after 1 - 2 weeks. Acute renal failure, acute cardiac failure and pancreatitis are uncommon complications that usually, but not invariably, occur in association with hepatic failure.[145]

Treatment. Gastric lavage, oral activated charcoal and 500 mL 20% mannitol should be used in all patients who have ingested an hepatotoxic dose of paracetamol within the previous 4 hours. A paracetamol level is taken (preferably 4 hr after the overdose) to guide further treatment[146] (although, treatment based on serum levels of paracetamol after an overdose of an extended-release formulation may be invalid).[132]

To reduce the effect of the toxic metabolite of paracetamol (N-acetyl-p-benzoquinoneimine), N-acetylcysteine or L-methionine is administered to enhance and replenish glutathione stores by acting as a precursor for glutathione synthesis,[147,148] thereby having an indirect antioxidant effect. N-acetylcysteine may also have direct antioxidant effects by acting as a glutathione substitute or even enhancing nontoxic sulphate conjugation of paracetamol.[149] N-acetylcysteine also increases cyclic guanosine monophosphate levels causing vasodilation and inhibiting platelet aggregation, acts as a sulphydryl donor to regenerate endothelial-derived relaxing factor and reduces IL-8 and TNF-α production.[150] Because N-acetylcysteine is the only intravenous preparation available, it is the treatment of choice for paracetamol overdosage.[131,144]

If the blood paracetamol level is above the 'treatment' line of 200 mg/L (1300 μmol/L) or greater at 4 hr, 100 mg/L (660 μmol/L) or greater at 8 hr, 50 mg/L (330 μmol/L) or greater at 12 hr, or 30 mg/L (200 μ mol/L) or greater at 15 hr, then N-acetylcysteine is administered at 150 mg/kg (10 g/70 kg or 50 mL of a 20% solution) over 15 min followed by 50 mg/kg (3 g/70 kg or 15 mL of a 20% solution) in 4 hr, followed by 100 mg/kg (7 g/70 kg or 35 mL of a 20% solution) in 16 hr.

If the patient has been taking hepatic P_{450} mixed-function oxidase inducing drugs (e.g. chronic ethanol or barbiturate ingestion), glutathione depletion exists (e.g. malnourished) or following starvation (which reduces paracetamol conjugation with glucuronide),[140] then the paracetamol level at which treatment with N-acetylcysteine is considered is halved [i.e. 100 mg/L (660 μmol/L) or greater at 4 hr, 50 mg/L (330 μmol/L) or greater at 8 hr, 25 mg/L (165 μmol/L) or greater at 12 hr, or 15 mg/L (100 μmol/L) or greater at 15 hr].[151] If the patient has fulminant hepatic failure before N-acetylcysteine administration, then the last dose of 100 mg/kg/16 hr, is continued until the patient recovers from the encephalopathy.[152]

The paracetamol blood level 'treatment line' (Figure 1) is an exponential one and may be derived from the equation:

$$399 \times e^{(-0.1725 \times \text{hours})} \text{ mg/L}$$

or

$$2660 \times e^{(-0.1725 \times \text{hours})} \text{ μmol/L.}$$

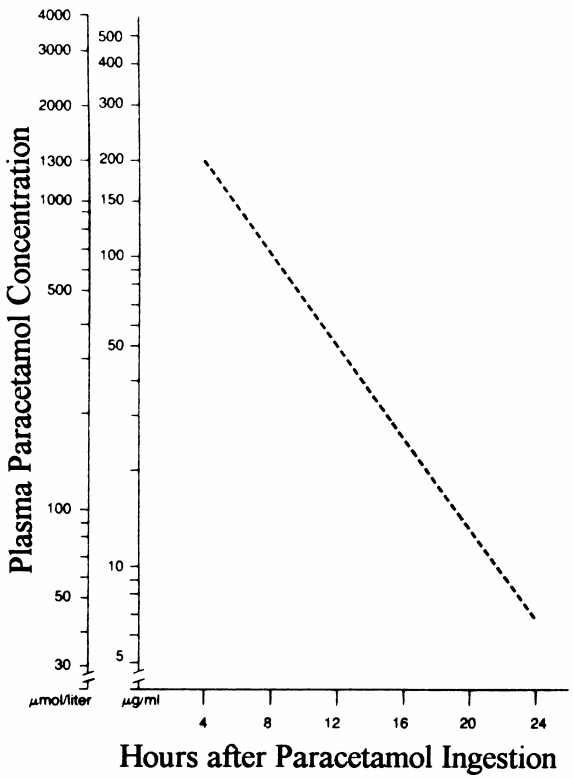

Figure 1. Nomogram 'treatment' line used to define risk (and therefore need for treatment), according to the plasma paracetamol concentration (Adapted from Smilkstein MJ, et al.. N Engl J Med 1988;319:1557-1562).

Oral methionine may be used as an alternative treatment (e.g. 2.5 g orally for 4 doses each separated by 4 hr to a total of 10 g),[136] although, activated charcoal should not be given as well as it will absorb the oral methionine.[153]

If the ingestion of paracetamol is greater than 10 g, or the quantity is unknown and it is likely that there will be a significant delay (i.e. > 8 hr after paracetamol taken) before the blood paracetamol levels are known, N-acetylcysteine is commenced and continued or stoped once the blood levels are known.[149]

Treatment within 8 - 10 hr of the paracetamol overdose with N-acetylcysteine is effective in preventing hepatic damage, whereas treatment delayed beyond this time becomes less effective.[149] While treatment after 15 hr may be of little benefit in reducing the severity of the liver damage,[131,144] administration of N-acetylcysteine 16 - 36 hr after the overdose,[149,154,155] and even after fulminant hepatic failure develops,[152] lowers the mortality. Liver function tests, blood glucose and prothrombin time should be monitored daily for 4 days or until the prothrombin time improves.[156]

N-acetylcysteine was initially introduced into clinical practice as a mucolytic agent for patients with COPD.[157] However, as well as an antidote for paracetamol poisoning, it has also been recommended to reduce the cardiotoxicity of doxorubicin, haemorr-hagic cystitis associated with ifosfamide/cyclophosph-amide metabolites, hepatotoxicity associated with chloroform, carbon tetrachloride and potassium permanganate,[158] and neurological sequelae of carbon monoxide poisoning.[159,160] It has also been used to reactivate vascular responsiveness to glyceryl trinitrate, and to treat a wide variety of conditions ranging from acute respiratory distress syndrome,[161] multiple organ dysfunction syndrome,[162,163] HIV infection,[164] acute hepatic failure,[152] amanita phylloides (mushroom poisoning),[165,166] shock,[167] myocardial 'stunning',[162,163] ischaemic reperfusion renal injury[168] and radiographic contrast agent induced reduction in renal function.[169] However, while there may be experimental evidence for its benefit in many of these conditions, it can only be routinely recommended for paracetamol overdosage.[170]

The side-effects of N-acetylcysteine include rash, pruritus, angio-oedema, hypotension and broncho-spasm,[171-174] which relate to its ability to release histamine.[171] The reaction occurs in 9% of patients,[175] is dose-dependent and usually develops 15 - 60 min after the commencement of the infusion.[175]

If despite N-acetylcysteine there is a rapid progress-ion to severe multiple organ failure including acute hepatic failure, acute renal failure, haemodynamic instability and encephalopathy, the only other therapy of proven benefit is emergency hepatic transplantation. One study concluded that liver transplantation should be strongly considered if the arterial blood lactate was greater than 3.5 mmol/L after early fluid resuscitation, and that the patient should be listed for liver transplantation if the arterial pH is below 7.3 with a blood lactate above 3.0 mmol/L after adequate fluid resuscitation or serum creatinine is greater than 0.3 mmol/L, INR greater than 6.5 and the patient has a grade 3 or greater, encephalopathy.[176]

Other non steroidal anti-inflammatory drugs

These agents are characterised by their analgesic, anti-inflammatory and antipyretic effects. They block cyclooxygenase activity and reduce cyclic endoperox-ides, PGE_2, PGF_2, PGI_2 and TXA_2.

Clinical features. Apart from salicylate and paracetamol intoxications, overdosage with non-steroidal anti-inflammatory agents seldom cause more than drowsiness and mild gastrointestinal effects (e.g. nausea, vomiting, gastric erosions, peptic ulceration, diarrhoea).[177,178] The major exceptions are:

1. *Benorylate.* This is an ester of aspirin and paracetamol. An overdose of this agent causes paracetamol toxicity.
2. *Mefenamic acid.* An overdose of mefenamic acid may cause coma and seizures.
3. *Phenylbutazone and oxybutazone.* An overdose of these agents may lead to severe gastric erosions haematemesis, coma, seizures, renal failure and hepatic failure.[179]
4. *Ibuprofen.* Ibuprofen is largely nontoxic and only rarely causes coma when taken in excess.[180]

Treatment. Apart from gastric lavage and repeated charcoal, treatment for NSAIDs overdosage is largely supportive.[120]

Cardiac drugs

Quinidine

Clinical features. The clinical features of quinidine overdosage include tinnitus, headache, nausea, diarr-hoea, nystagmus, hypotension (due to both peripheral vasodilation and negative inotropic effects), prolonged PR, QRS and QT intervals, ventricular tachycardia, torsade de pointes, drowsiness, coma, respiratory failure and seizures.

The cardiovascular features of hypotension, prolon-ged QRS, PR and QT intervals, ventricular tachycardia and torsade de pointes; and the central nervous system features of agitation, hallucinations, twitching, hyperreflexia, seizures, drowsiness and coma, may also be observed (to a greater or lesser extent) with procainamide, disopyramide, mexiletine, lignocaine, chloroquine, buflomedil, phenothiozine, tricyclic and antihistamine overdose (i.e. both the ventricular tachycardia/hypotensive syndrome and anticholinergic syndrome - table 2).

Treatment. Apart from gastric lavage and repeated oral activated charcoal, treatment is largely supportive. Hyperkalaemia and hypocalcaemia potentiate the effects of quinidine and therefore should be rapidly corrected. Hypotension is managed using standard therapy of intravenous fluids followed by intravenous calcium chloride (10 mL of 10% calcium chloride over 5 min) and inotropic support. Right heart catheter monitoring may also be required. Intra-aortic balloon pumping and cardiac pacing may be required for severe hypotension unresponsive to conventional therapy.[181,182]

Beta-adrenergic blockers

Clinical features. Overdosage of beta-adrenergic blockers may cause, 1 - 6 hours after ingestion, brady-cardia, hypotension, cardiogenic shock, pulmonary oedema, asystolic cardiac arrest, seizures and coma.

Bronchospasm is unusual.[183] If the patient remains symptomless for 12 hr then it is unlikely that a severe overdosage has occurred.

Treatment. This includes gastric lavage and repeated oral charcoal. Management of hypotension and bradycardia may require isoprenaline (doses up to 10 - 250 μg/min for 2 - 3 days may be required. In one report, undiluted isoprenaline i.e. 0.2 mg/mL was used for the first 12 hr).[184] Glucagon 4 - 10 mg as a bolus followed by an infusion at 2 - 5 mg/hr has also been beneficial,[183,185,186] as it activates adenylate cyclase by a different mechanism from that of the beta-adrenoceptor agonists. Phosphodiesterase inhibitors (which also act by a mechanism independent of adrenergic receptors) have also be used (e.g. aminophylline, milrinone, enoximone).[187] In resistant cases, cardiac pacing or intra-aortic balloon pumping may be required.

Isoprenaline rather than adrenaline is the adrenergic agent of choice as the alpha-vasoconstrictor effect of adrenaline is unblocked and therefore predominates; furthermore, the bradycardia usually persists when a beta-blocker overdosage is treated with adrenaline.

Calcium-channel blockers

Clinical features. Overdosage of verapamil, diltiazem or nifedipine may be associated with hypotension, sinus bradycardia or heart block. Severe verapamil overdosage (by increasing cellular uptake of potassium) may also be associated with hypokalaemia,[188] ileus and colonic perforation.[189]

Treatment. This includes gastric lavage and repeated oral charcoal. Hypotension and bradycardia often respond to intravenous calcium chloride (10 mL of a 10% solution or 6.8 mmol over 2 - 5 min), which may be followed by an infusion (e.g. 1.5 - 10 mL/hr of 10% calcium chloride or 1.0 - 6.8 mmol/hr, up to 40 mmol in 3 hr,[190] keeping the plasma ionised calcium between 1.5 - 2.0 mmol/L),[191] although isoprenaline, glucagon, adrenaline, noradrenaline cardiac pacing or intra-aortic balloon pumping may also be required.[192-195]

During shock, the myocardium uses glucose predominantly for fuel. However, as pancreatic beta cell antagonism occurs with severe calcium channel overdosage, hypoinsulinaemia and hyperglycaemia may occur reducing glucose entry and utilisation by myocardial cells. Glucose insulin and potassium infusions have been used to treat experimental myocardial depression associated with verapamil poisoning successfully,[196] and in one report, two patients with severe calcium-channel blocker poisoning (e.g. amilodipine and diltiazem) were successfully managed with hyperinsulinaemic-euglycaemic therapy (e.g. a continuous infusion of insulin 0.5 U/kg/hr or 35 U/70kg/hr and glucose).[197]

Clonidine

Clinical features. Clonidine acts primarily as a centrally acting α_2 adrenergic agonist, exerting its effects mainly through a reduction in central nervous system sympathetic outflow at the medullary vasomotor centre. Overdosage of clonidine causes sedation, somnolence, coma, hypotonia, miosis, bradycardia (caused by vagal dominance due to diminished sympathetic outflow), and either hypertension (which is usually short-lived and due to clonidine's partial α_2 adrenoreceptor agonist effect) or hypotension.[198] The average serum half-life of clonidine is 12 hours, although its toxic effects may last up to 48 hours.

Treatment. This includes gastric lavage and oral charcoal. Atropine may be used to treat severe bradycardia, although the response may be transient.[199] Naloxone has also been used with variable effect. Hypotension is treated with intravenous fluids and catecholamines if necessary. Hypertension may be treated with nitroprusside.[198] One report described the use of the α_2 adrenergic antgonist yohimbine (5.4 mg orally) as an antidote for clonidine overdose, reversing both the sedative, hypotensive and bradycardic effects within 1 hour of its administration[200] (clonidine has also been suggested as an antidote for yohimbine toxicity).[201]

Theophylline

Clinical features. In mild cases of theophylline toxicity, nausea, vomiting, abdominal pain, diarrhoea, headache, agitation, tremor, hyperventilation, and tachycardias are frequent and often seen with theophylline levels ranging from 20-30 mg/L (110 - 165 μmol/L). In severe overdosage (serum theophylline levels 40 - 60 mg/L, 220 - 330 μmol/L) cardiac arrhythmias, diaphoresis, hypotension, seizures, coma and cardiac arrest may follow (or may even be the presenting feature). The biochemical features include, hypokalaemia, hyperglycaemia, hypophosphataemia, hypomagnesaemia, hypercalcaemia, respiratory alkalosis, lactic acidosis, and rhabdomyolysis. The latter may cause hyperphosphataemia, hypocalcaemia and renal failure. Sustained release preparations may result in delayed peak effect (i.e. 12 - 24 hr after dose ingested).

Treatment. Plasma theophylline should be monitored 1 to 2-hourly until the theophylline level plateaus. Treatment includes gastric lavage, oral mannitol (300 - 500 mL of 20%) and repeated oral activated charcoal (50 g initially followed by 25 g 2-hourly).[202-205] Haemoperfusion is effective in removing systemic theophylline and is often recommended for patients with severe theophylline toxicity[206] (e.g. serum levels > 100 mg/L, i.e. > 550 μmol/L) who have intractable vomiting,[38] seizures or arrhythmias,[207] although there is no evidence so far that it reduces morbidity or mortality

in comparison with oral activated charcoal.[207-209] Supportive therapy is also required in patients with theophylline toxicity, for example:

1. *Cardiovascular.* Verapamil 5 - 10 mg[209] or, in the nonasthmatic, esmolol (500 μg/kg loading dose followed by 50 μg/kg/min)[210] may be useful in controlling supraventricular tachycardias. While propranolol has also been used and has the advantage of controlling the metabolic effects of hypokalaemia and hyperglycaemia, its use in asthmatics is not recommended.[211] While adenosine has been reported to slow the heart rate, abolish arrhythmias and increase left ventricular systolic pressure during experimental theophylline toxicity, its effect was short lived (due to its short half-life) and often resulted in rebound arrhythmias when the effect of adenosine wore off, indicating that a long acting adenosine analogue would probably be of more use in clinical practice.[212]

2. *Gastrointestinal.* Ranitidine (50 - 100 mg intravenously)[203] or metoclopramide (10 mg intravenously)[213] may be used to control intractable vomiting, thereby allowing oral activated charcoal to be used. Cimetidine and phenothiazines should be avoided, as the former interferes with theophylline clearance and the latter are epileptogenic. If vomiting cannot be controlled, then anaesthesia and mechanical ventilation may be required to allow activated charcoal to be used.[213]

3. *CNS.* Phenobarbitone 10 - 20 mg/kg (600 - 1200 mg/70 kg) intravenously is effective in controlling agitation and in suppressing seizures, and should be given prophylactically in patients with severe toxicity (i.e. theophylline level > 40 - 60 mg/L). Additional doses of 1.5 - 2.8 mg/kg (100 - 200 mg/70 kg) may be given every 20 min up to a desired effect. Phenytoin is ineffective in controlling theophylline seizures.[214] Morphine has also been used to control the agitation.[215] Some of the central nervous system excitatory effects (particularly tremor) may be reversed by pyridoxine supplementation.[216]

Alcohol and glycol

The various alcohols are metabolised by alcohol dehydrogenase and aldehyde dehydrogenase, some of which may liberate toxic metabolites (Table 7). The average lethal adult dose and blood levels are listed in Table 8.

Table 7. Catabolic enzymes and metabolic products of various alcohols

	Alcohol dehydrogenase	*Aldehyde dehydrogenase*
Methanol	formaldehyde	formate
Ethanol	acetaldehyde	acetate
Ethylene glycol	glycoaldehyde	glycolate
Isopropanol	acetone	
Paraldehyde	acetaldehyde	acetate

Table 8. Lethal doses and blood levels of alcohols

	Adult lethal		*Lethal blood levels*	
	MW	*dose (mL)*	*g/L*	*mosmol/kg*
Methanol	32	100	1.6	50
Ethanol	46	400	4.6	100
Ethylene glycol	62	100	3.1	50
Isopropanol	60	250	3.0	50
Paraldehyde	132	30	0.7	5

Ethanol

Ethyl alcohol is used as a solvent, an antiseptic and a beverage. The hepatocyte cytosolic alcohol dehydrogenase metabolises ethanol at a constant rate of 7 - 8 g/hr, converting ethanol to acetaldehyde and NAD to NADH, changing the cytosol redox state and increasing the lactate:pyruvate ratio.

Clinical features. In normal adults, mild to moderate intoxication, with ataxia, slurring of speech and drowsiness occurs with blood levels of 0.5 - 1.5 g/L. Moderate to severe intoxication occurs at blood levels of 1.5 - 3 g/L, stupor occurs at blood levels of 3 - 5 g/L and coma occurs with blood levels greater than 5 g/L. The fatal dose for an average adult is 400 mL of 100% alcohol (320 g) which may produce a blood level of 7.6 g/L. The blood level of ethanol in g/L may be calculated from the osmolar gap using the formulae 0.032 x (osmolar gap - 10).

Treatment. Treatment is largely supportive. While naloxone (1.2 mg) has been reported to reverse coma of acute ethanol intoxication in 16% of patients,[217] the ethanol-antagonising effects of naloxone have not been confirmed.[218,219]

Isopropanol

Isopropanol is about twice as toxic as ethanol. Supportive treatment only is required, because its metabolites are harmless. The blood level of isopropanol

in g/L may be calculated from the osmolar gap using the formulae 0.06 x (osmolar gap - 10).

Methanol (and formaldehyde)

Methyl alcohol is used as an antifreeze, fuel, solvent and a paint remover. Methanol is nontoxic, although its metabolite, formic acid, produces a profound metabolic acidosis, inhibits cytochrome oxidase and is injurious to retinal cells.[220] Normally, only 10% of methanol excreted in the urine. Ingestion (or rarely percutaneous absorption[221] or inhalational abuse[222]) of 4 mL of methanol may lead to blindness; 30 - 250 mL may be fatal. As formaldehyde poisoning may also produce excess formic acid, the clinical features of formaldehyde toxicity are the same as for methanol toxicity.[223]

Clinical features. The patient is often asymptomatic for 8 - 12 hours. This is followed by headache, disorientation, vertigo, nausea, vomiting, abdominal and back pain, blurring of vision, blindness after 24 - 72 hr (which may be permanent) with fixed dilated pupils, coma and death. The diagnosis is confirmed with a serum methanol level, increase in osmolar gap and metabolic acidosis. The blood level of methanol in g/L may be calculated from the osmolar gap using the formulae 0.046 x (osmolar gap - 10).

Treatment. Due to rapid absorption, gastric lavage is likely to be ineffective, repeated oral charcoal is also ineffective. Specific treatment requires:

1. *Haemodialysis*: this is instituted if greater than 30 mL of methanol have been ingested, or if a metabolic acidosis or ocular manifestations are present. Haemodialysis or continuous renal replacement therapy should be instituted if the serum methanol level is greater than 0.3 g/L and continued until the methanol level is less than 0.1 g/L,[224,225] although in chronic alcoholics, methanol levels of up to 1.6 g/L may occur without any signs of toxicity due to ethanol inhibition of formate production.[226] If formic acid can be measured, dialysis should be instituted if formate concentrations are 0.2 g/L or greater because ocular toxicity may occur at these levels.[227]
2. *Intravenous ethanol:* As alcohol dehydrogenase has 20 times the affinity for ethanol than methanol has, ethanol is administered to inhibit the metabolism of methanol, which is effective at a blood level of 1.5 g/L (i.e. 33 mmol/L, which will cause intoxication but not stupor). This is achieved by:
   a. Administering 1.14 mL/kg of 100% ethanol (i.e. 80 mL/70 kg) as a bolus. Ethanol weighs 0.7893 g/mL, therefore 1.5 g/L is equal to 1.9 mL/L. Because ethanol distributes throughout the total body water (TBW), a level of 1.5 g/L in a 70 kg man with a TBW of 42 L is achieved with 80 mL (i.e. 42 x 1.9) of 100% ethanol or 1.14 mL/kg of 100% ethanol).
   b. This is followed by 0.14 mL/kg/hr of 100% ethanol (i.e. 10 mL/70 kg/hr), as ethanol is metabolised at 8 g/kg/hr (or 10 mL/kg/hr). The ethanol infusion is increased to 0.2 mL/kg/hr (14 mL/70 kg/hr) during dialysis.
3. *4-methylpyrazole*: Instead of using ethanol, the oxidation of methanol may be prevented by the use of the alcohol dehydrogenase inhibitor, 4-methylpyrazole (see treatment of ethylene glycol poisoning), and currently is recommended as treatment of choice.[228]
4. *Folinic acid:* while folinic acid 30 - 60 mg may be used in an attempt to increase the metabolism of formic acid, in monkeys 50 mg/kg of folate was required (i.e. folate concentrations of 2000 times normal) to increase the formic acid metabolism by 50%.[229]
5. *Treatment of hyperkalaemia:* the patient's acid base, plasma potassium, osmolar gap and plasma methanol levels should be monitored 2- to 4-hourly. Hyperkalaemia is treated using standard therapy.

Ethylene glycol

Ethylene glycol is the major constituent of antifreeze. Although non toxic itself, it is converted to active metabolites by alcohol dehydrogenase that may cause metaboloic acidosis, shock, renal failure, hypocalcaemia, oxaluria and central nervous system damage. It has an elimination half-life of 3 hours when metabolised to glycolic acid which is converted to glyoxylic acid and oxalic acid. The oxalic acid combines with calcium and deposits as calcium oxylate crystals perivascularly in almost every tissue. Glyoxylic acid is converted to glycine or enters the citric acid cycle using thiamine as a cofactor. Oxalic acid combines with calcium and is excreted as calcium oxalate in the urine which may precipitate in the proximal tubules and cause acute renal failure. The latter may be prolonged.

Clinical features. There is often an asymptomatic period of 8 - 12 hr followed by headache, vomiting, tachypnoea, hypotension, visual blurring, nystagmus, stupor, seizures, and coma. Pulmonary oedema and cardiac arrhythmias may occur 12 - 24 hr after ingestion and acute renal failure may develop 48 hours after ingestion.[230,231] The biochemical findings include metabolic acidosis, osmolar gap, hypocalcaemia (due to calcium oxalate crystal formation), hyperoxaluria, and calcium oxalate crystals in the urine.[232] While the blood level of ethylene glycol in g/L may be calculated from the osmolar gap using the formulae 0.062 x (osmolar gap - 10), there have been reports of a normal osmolar gap in patients with ethylene glycol poisoning (due to

metabolism of ethylene glycol and low baseline level of osmolar gap).[233] The plasma lactate may be artificially elevated due to glycolate interference with analysers using lactate oxidase to assess plasma lactate levels. If lactate is also measured with an analyser using lactate dehydrogenase (unaffected by glycolate) then a lactate gap may be recorded.[234]

Treatment. This is recommended for patients with serum ethylene glycol levels of 0.2 g/L or greater[235] using an agent that inhibits alcohol dehydrogenase. This previously required an ethanol infusion which increased the elimination half-life to 17 hr when the blood ethanol levels were between 1.3-2 g/L (25 - 40 mmol/L)[236] and was administered along with haemodialysis and sodium bicarbonate as outlined for methanol toxicity. A diuresis was also often recommended to reduce renal oxalate deposition and acute renal failure.

Currently, however, the treatment of choice is the alcohol dehydrogenase inhibitor fomepizole (4-methylpyrazole which increases the ethylene glycol elimination half-life to 12 hr), 15 mg/kg in 250 mL of isotonic sodium chloride, administered intravenously over 45 min, followed by 10 mg/kg 12-hourly for three doses, then followed by 15 mg/kg 12-hourly until the plasma ethylene glycol is less than 0.2 g/L.[235,237-240] Haemodialysis may also be initiated after the loading dose, although fomepazole alone is probably sufficient therapy in patients with normal renal function and acid-base status.[241]

Fomepizole is easily administered has none of the adverse effects of ethanol[237] and has also been used successfully in methanol poisoning.[242,243]

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