ABC of Poisoning

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MISCELLANEOUS DRUGS

Quinine and other antimalarial drugs
H₁ and H₂ blocking drugs
Non-barbiturate anticonvulsants
Hypoglycaemic agents

Other articles in this series have concentrated on the problems with drugs that are commonly taken in overdose or which have a defined pattern of toxicity. The list could be very long because it is safe to assume that almost all drugs will sooner or later be taken or given in overdose. In many cases, however, there will be no serious toxicity and in others the rareness of the event does not justify inclusion. Poisons information services are available not only to help with the more severe cases of common poisonings but also to provide data on unusual problems. This article highlights some further problems which are both complicated and common enough to cause concern.

Quinine

Overdose of quinine and other antimalarials is comparatively rare, but the effects can be dramatic and serious. Although world wide quinine is used primarily for treating chloroquine resistant malaria, in the United Kingdom it is more commonly prescribed for the relief of nocturnal cramps. It has recently been found as an adulterant in illicit heroin, is present in small amounts in tonic water, and was once used as an abortifacient.

Most patients who have taken an overdose of quinine present with signs of cinchonism (headache, vertigo, tinnitus, deafness, nausea, and vomiting). Other signs and symptoms of severe toxicity include hypotension, convulsions, coma, and cardiac arrhythmias. The most dramatic features of quinine poisoning, however, are the visual disturbances. These include sudden loss of vision, which may occur up to 24 hours after the overdose—so that the patient may go to sleep with few complaints and wake with blurred vision. The initial sign is usually dilated pupils with loss of visual acuity. Retinal changes do not usually appear for one to three days, by which time the vision may be improving. The ophthalmoscopic changes include retinal oedema, disc pallor, and narrowing of the vessels.

Most patients recover their sight even after total loss of vision, although some may be severely handicapped by restricted peripheral visual fields. There is considerable controversy over the mechanisms by which quinine causes blindness. One theory is that it is caused by retinal arteriolar constriction, and this was the rationale for using vasodilator therapy and stellate ganglion blockade. Another suggestion is that there is a direct effect on the retinal cells themselves.

Treatment of quinine poisoning

The stomach should be emptied after any overdose of quinine. Because quinine has anticholinergic effects gastric emptying may be delayed and considerable amounts of drug may therefore be removed beyond the usual four hours. The mainstay of treatment is full supportive care. Stellate ganglion block has been used most often to try to prevent serious visual damage but only rarely has it produced a dramatic improvement in vision. This procedure is no longer routinely recommended and if used should be performed only by someone well practised in performing regional blocks. It may have to be repeated several times over a few days with a long acting anaesthetic and, to be effective, should produce Horner's syndrome.

Horner's syndrome indicates successful blockade

Ptosis
Miosis
Enophthalmos
Anhidrosis

Complications of stellate ganglion block

Intra-arterial injection (vertebral artery)	
Intrathecal injection	
Pneumothorax	
Nerve paralysis:	Brachial plexus
	Phrenic
	Recurrent laryngeal
	Vagus

Various ways of eliminating quinine have been tried. Forced acid diuresis increases quinine clearance but the amount removed is unlikely to be clinically important. Similarly, haemodialysis, peritoneal dialysis, and haemoperfusion do not appreciably increase clearance, though haemoperfusion may improve the clinical condition of the poisoned patient.

Although 70-80% of people who take quinine overdoses develop symptoms, death is unusual, occurring in about 2% of cases in one series. The only serious long term effect is visual impairment, usually peripheral visual field constriction with optic atrophy. Even without treatment, there is usually at least partial visual recovery, and so far there have been no reports of permanent total blindness.

Other antimalarial drugs

Commonly used antimalarial drugs

Approved name	Proprietary name
Quinine	—
Chloroquine	Avloclor, Nivaquine, Malarivon
Pyrimethamine	Daraprim
Proguanil	Paludrine
Primaquine	—
Pyrimethamine } Sulfadoxine }	Fansidar
Pyrimethamine } Dapsone }	Maloprim

Overdose with other antimalarial drugs is very rare. Of these, chloroquine is the most frequently reported and most serious, with a mortality of up to 20%. Toxic signs and symptoms include nausea, vomiting, drowsiness, coma, convulsions, visual problems, and cardiac arrhythmias. Death occurs early, at one to six hours, and is due to cardiorespiratory arrest. The lethal dose may be as low as 50 mg chloroquine base/kg—that is, about 24 tablets in adults.

Nausea, vomiting, and abdominal discomfort are the usual symptoms after overdose with other antimalarial drugs. Rare complications include haematuria, renal failure, ataxia, motor neuropathy, and optic atrophy. Severe methaemoglobinaemia and haemolytic anaemia may occur after a large overdose of dapsone or primaquine. Concentrations of methaemoglobinaemia above 10% produce cyanosis. Shortness of breath, headaches and fatigue usually occur with concentrations above 30-35%. Death occurs with concentrations of about 70%. Methaemoglobin is reduced spontaneously to haemoglobin through the action of two reductase enzymes, one of which is activated by methylene blue. This can be given in a dose of 1-2 mg/kg and repeated later if necessary. In patients with glucose-6-phosphate dehydrogenase deficiency methylene blue can cause haemolysis, and oral ascorbic acid should be used instead.

Histamine blocking drugs

Examples of uses of histamine blocking drugs

H₁ blockers for:

Allergies	clemastine, chlorpheniramine
"Colds"	brompheniramine, diphenhydramine
Sedation	promethazine
Motion sickness	cyclizine
Parkinsonism	orphenadrine

H₂ blockers for:

Peptic ulceration	cimetidine, ranitidine
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H₁ blocking drugs

Assessing the toxicity of H₁ blocking drugs is complicated not only by their wide range of actions and uses but also by their frequent inclusion in over the counter cold remedies. Thus in overdose they produce a mixture of effects varying according to the drug, the dose, the patient, and the presence or absence of other drugs. Some, such as promethazine and diphenhydramine, have a dominant hypnotic effect in adults but may cause hallucinations in children while orphenadrine causes not only loss of consciousness but convulsions, hypotension, marked anticholinergic effects, and, not infrequently, death.

Since it is difficult to predict the effects in an individual, observation should take account of the time of ingestion, speed of absorption, and expected duration of action of the drug concerned. Management is supportive throughout. Syrup of ipecacuanha is usually effective in spite of the antiemetic properties of the antihistamines. Anticonvulsants may be used when central nervous system excitation or convulsions are problems.

Clinical features of H₁ antagonist overdoseCentral nervous system:

Sedative –

drowsiness, headache,
nystagmus, coma

Anticholinergic –

blurred vision, hallucinations
fixed dilated pupils,
hyperreflexia, tremors,
excitement, convulsionsCardiovascular system:

Hypotension, tachycardia, arrhythmias

Respiratory system:

Depression

Gastrointestinal system:

Dry mouth, nausea, constipation

Metabolic:

Hyperpyrexia, especially in children

H₂ blocking drugs

Given the rapid increase in the use of H₂ blocking drugs, it would have been surprising if there had not been reports of overdose. In practice, both cimetidine and ranitidine can be taken in massive overdose without ill effect. Serious toxic effects from cimetidine have been seen in patients with renal failure, in whom long term treatment has led to neurological complications.

Non-barbiturate anticonvulsantsCommonly used non-barbiturate anticonvulsants

Carbamazepine

Ethosuximide, methsuximide

Phenytoin

Primidone

Sodium valproate

Sulthiame

Troxidone

Overdose with non-barbiturate anticonvulsants occurs less often than with other sedative or hypnotic drugs. It seems to be most common in patients with epilepsy, and a particular problem after overdose is knowing when to start treatment again. After an overdose with a single anticonvulsant the overall toxicity is low and deaths are rare. Complications are most common when combinations of drugs have been taken.

Specific problems

Carbamazepine is structurally related to the tricyclic antidepressants and has some anticholinergic activity. Patients tend to react violently when aroused. Opisthotonus and convulsions may occur. Various cardiac problems including bradycardia and complete heart block have been reported.

Phenytoin overdose rarely causes deep coma, although nystagmus and ataxia are common. Loss of oculocephalic and oculovestibular reflexes may occur at times when the patient is able to carry out commands.

Primidone is metabolised to phenobarbitone and phenylethylmalonamide. Both the parent drug and metabolites are active. A distinctive feature of primidone poisoning is the occurrence of crystalluria, although this does not seem to lead to renal failure.

Sodium valproate is rapidly absorbed, so gastric emptying may not help. Behavioural disturbances and aggression may occur. Thrombocytopenia and platelet dysfunction have been reported in patients on high therapeutic doses. Such problems are likely to be more pronounced after an overdose, particularly if another "antiplatelet" drug such as aspirin has been taken, but overt haemorrhagic features are rare.

Sulthiame is a sulphonamide derivative with weak carbonic anhydrase inhibitor activity. It has a weak antiepileptic effect and much of its efficacy may be due to its inhibitory effect on the metabolism of phenytoin and phenobarbitone given concurrently. It may cause crystalluria leading to renal tubular obstruction.

If a significant amount of drug has been taken within the previous four hours gastric emptying should be carried out provided there are no contraindications. Thereafter, general supportive and symptomatic management is the mainstay of treatment. Recovery may be slow because of the slow elimination of most of these drugs. Haemoperfusion has been reported to improve the clinical condition of patients who have taken carbamazepine and have extreme complications, but not much drug is removed. Other methods of active elimination such as forced diuresis or haemodialysis are ineffective. Phenobarbitone may be actively removed, but this does not seem to hasten recovery from primidone overdose. With sodium valproate the risk of haemorrhage should be remembered, particularly if invasive procedures such as gastric lavage or catheterisation are carried out. After sulthiame overdose it might be beneficial to make the urine alkaline to prevent crystalluria and renal impairment. Measurement of plasma concentrations rarely affects the acute management of the patient. With all these drugs the main value of measuring plasma concentrations is to indicate when to restart maintenance treatment.

Common toxic manifestations

Nausea

Vomiting

Drowsiness

Ataxia

Nystagmus

Coma

Specific problems

Carbamazepine

React violently

Convulsions

Cardiac arrhythmias

Primidone

Crystalluria

Sodium valproate

Thrombocytopenia

Platelet dysfunction

Sulthiame

Crystalluria

Hypoglycaemic agents

Drugs and household products taken in overdose by 386 diabetic patients

Oral hypoglycaemic agents	46
Insulin	18
Benzodiazepines	102
Paracetamol	72
Household products	35
Phenothiazines	30
Tricyclic antidepressants	26
Barbiturates	18
Aspirin	17
Alcohol	14
Paracetamol/dextropropoxyphene	14
Monoamine oxidase inhibitors	9
Antibiotics	3
β -Blockers	2
Diuretics	2
24 patients had taken multiple overdoses	

Overdose with hypoglycaemic agents

Signs and symptoms:

Sympathetic overactivity	— Anxiety, tremor, hunger, sweating, palpitations
Neuroglycopenia	— Blurred vision, drowsiness, confusion, abnormal behaviour, coma, focal CNS signs
Biochemical	— Hypoglycaemia, hypokalaemia, acidosis

Treatment:

Oral glucose	
Intravenous dextrose 50%	
Glucagon (?)	
Potassium	
Bicarbonate	
Oxygen	
Dexamethasone	} For cerebral oedema
Mannitol	

The clinical signs of overdose with insulin or any oral hypoglycaemic agent are similar in diabetic and non-diabetic patients. The severity of symptoms depends on the depth and the duration of hypoglycaemia and is influenced by the drug's duration of action. The most serious problems tend to occur when the hypoglycaemic agent is taken together with alcohol.

Treatment

If the patient is conscious and cooperative oral glucose or sucrose should be given followed by adequate oral carbohydrates until the blood sugar concentration is stable. If the patient cannot take glucose by mouth, give 50 ml 50% dextrose (25 g glucose) intravenously. Repeat this after 10 to 15 minutes if the patient has not regained consciousness and start a dextrose infusion. Glucagon 1 mg intramuscularly or intravenously is an alternative but is unreliable because its action depends on the presence of liver glycogen stores and the ability to mobilise glucose. If the first injection of glucagon fails further doses are unlikely to succeed.

If, after one hour, the patient remains unconscious with a normal blood sugar value cerebral oedema is likely. This should be treated conventionally with dexamethasone, oxygen, and 20% mannitol, if there is no contraindication. Large amounts of parenteral dextrose (over 25 g glucose per hour) may be needed for long periods. If necessary this is best given as 10% or 20% solution via a central line. Blood sugar concentrations should be measured often until the clinical condition is stable. Hypokalaemia is treated with potassium replacement, and acidosis may be corrected with bicarbonate. Reversible neurological deficits may take several days to recover. There is no evidence that an artificial pancreas or excision of the injection site confers any advantage over conventional therapy.

Self-poisoning in diabetic patients

Although most overdoses of hypoglycaemic agents are taken by diabetics, these patients are just as likely to take overdoses of other drugs. In these circumstances the patient may present in hyperglycaemic, ketoacidotic coma (especially if admission to hospital is delayed), and the diagnosis of overdose may be missed. In such cases, if control of the blood glucose and correction of the metabolic disturbances do not produce the expected recovery, toxicological analyses should be considered as part of the investigations.

Other drugs

For information and advice in cases of poisoning contact the following centres and ask for "poisons" information

National Poisons Information Service

Guy's Hospital	Ordinary inquiries	01-407 7600
London	Emergency inquiries	01-635 9191

Belfast	Royal Victoria Hospital	0232 40503
Cardiff	Cardiff Royal Infirmary	0222 569200
Dublin	Jervis Street Hospital	Dublin 745588
Edinburgh	Edinburgh Royal Infirmary	031-229 2477

Poisons information also available from other centres:

Birmingham	Dudley Road Hospital	021-554 3801
Leeds	Leeds General Infirmary	0532 432799
Newcastle	Royal Victoria Infirmary	0632 325131

The National Poisons Information Service is pleased to provide information on the symptoms, toxicity, and management of poisoning with all drugs. It monitors cases of unusual drug overdose to maintain the database needed to answer inquiries, and welcomes reports of such cases, especially for those agents where the Committee on Safety of Medicines invites special care in the reporting of adverse reactions. Recently, with the collaboration of the drug manufacturers, efforts have been made to include in the database not only marketed drugs but also products undergoing largescale clinical trials, since overdose cases have been reported at this stage.

National Poisons Information Service—Guy's Hospital

Guidelines for users

(1) The caller should be ready to give the name of the suspected agent(s) involved as accurately as possible. Since the manufacturer's name or other details may also be needed, container(s) should, if possible, be at hand. In addition the following information is usually required.

- (a) the patient's name and age
- (b) time of exposure
- (c) any apparent signs or symptoms
- (d) treatment already given

(2) Patients or relatives should not be asked to telephone the information service since inquiries from the general public cannot be answered. The emergency information service answers inquiries only from hospitals, general practitioners, and other emergency services.

(3) The caller may subsequently receive a follow up questionnaire requesting information regarding the outcome of the poisoning. These should be filled in and returned to the information service as they are essential to permit the compilation of acute poisoning in man, especially where new or uncommon compounds are involved.

(4) Direct telephone lines are available to the poisons information service (01-635 9191). Only callers requiring information on the emergency treatment of poisoning should use this number. All other inquiries, including requests for less urgent information and laboratory requests, should be made through the Guy's Hospital switchboard (01-407 7600), extensions 4001-4003).

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This is the concluding article of part 1 of the ABC of Poisoning. Part 1 will be published as a book early next year, and part 2 will appear in the *BMJ* next year.

Medical Education

Audit of admission to medical school: III—Applicants' perceptions and proposals for change

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Abstract

Applicants to St Mary's Hospital Medical School were asked to comment freely on the process of selection. They were particularly concerned about the role of interviews, excessive emphasis on academic achievement, the problem of rank-ordering choices on the UCCA form, and possible biases in selection. These concerns and the results of our survey suggest that candidates should not be asked to rank their choices in order of preference, that UCCA applications for medicine should be subject to an early closing date, that as many applicants as possible should be interviewed, that applicants should be encouraged to apply after taking A levels, that educational opportunity should be taken into account in assessing A level grades, and that mature students should be encouraged, not least by providing mandatory awards for a second degree in medicine.

"The medical profession seems to be biased towards the very academic, probably male student, who has a long family history in medicine and a public school education. They seem in my experience less interested in your character and whether you have the right temperament to make a good doctor and have the ability to get on with and communicate with a wide range of people, especially in a difficult situation."—
APPLICANT TO ST MARY'S HOSPITAL MEDICAL SCHOOL, 1980.

Applicants to St Mary's Hospital Medical School in 1980-1 were invited to enter "any comments or criticisms of the medical school selection process" on a blank sheet of the questionnaire (Q1), which was sent on receipt of the UCCA application.^{1 2}

We consider here applicants' criticisms of the admission system, and make suggestions for change in the light of those criticisms and of the findings of our survey.

Applicants' comments

Comments were made about the application process by 54% of applicants who completed Q1.

Excessive emphasis on academic achievement—Two hundred and

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