ABC of Poisoning

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SEDATIVE AND HYPNOTIC DRUGS

Most patients admitted to hospital with acute poisoning have taken sedative or hypnotic drugs, so every doctor needs to be aware of the principles of management. The term "sedative and hypnotic drugs" encompasses several pharmacological groups, and clinical practice has established certain agents (or groups of agents) in such roles as anxiolytics, hypnotics, muscle relaxants, and anticonvulsants. Nevertheless, their actions overlap and, particularly in overdose, there are probably more similarities than differences. Historically ethanol, the chloral derivatives, barbiturates, glutethimide, methaqualone, and benzodiazepines have all enjoyed their vogue. Currently the benzodiazepines have replaced barbiturates as the "broad spectrum" agents of choice, and chloral derivatives are commonly used for the very young and old. Chlormethiazole and some of the phenothiazines are also advocated for sedation in the elderly; the antihistamine phenothiazines are widely used for sedation in children.

Clinical patterns

Coma	
Grade	
1	Drowsy, responds to commands
2	Responsive to mild painful stimulation
3	Minimal response to maximal painful stimulation
4	No response to maximum painful stimulation

Cerebral function monitor tracing from a woman unconscious after barbiturate overdose. The improvement in the trace occurred many hours before any clinical recovery was apparent.

The usual effect of a sedative or hypnotic overdose is global depression of cerebral function which then remits gradually. The time course depends on the amount of drug taken, its pharmacokinetic behaviour, and the patient's tolerance, rather than the drug's hypothetical therapeutic role.

Unexpectedly prolonged coma (or rising drug concentrations in the plasma) may result from the continuing absorption of large amounts of drug remaining in the gut or the appearance of long lasting active metabolites. Focal neurological signs are uncommon except cerebellar ones and should alert the clinician to an alternative or coexisting disease. Pupillary changes occur non-specifically and vary with time, although more predictable effects may be seen with glutethimide (dilatation) and chloral hydrate (constriction), but pinpoint pupils are a sign of opioid toxicity until proved otherwise.

General measures

So far as possible the amount and type of drug(s) taken and the time of ingestion must be established. Most hypnotic overdoses are uncomplicated, but large doses and the presence of alcohol may make it worth while to empty the stomach early to prevent problems. Emesis and gastric lavage without airway protection using an endotracheal tube are contraindicated if the patient does not have a brisk gag reflex.

(1) Take 10ml blood 50ml urine 50ml vomit or first return from gastric aspiration					
(2) Label specimens carefully:	<table border="1"> <tr> <td>Name</td> <td>Sample</td> </tr> <tr> <td>Date</td> <td>Time</td> </tr> </table>	Name	Sample	Date	Time
Name	Sample				
Date	Time				
(3) Store specimens carefully					
(4) Arrange for toxicological analysis if a management decision will be taken on the result					
(5) If in doubt contact a poisons information unit					

A knowledge of plasma drug concentrations rarely affects management in sedative or hypnotic overdosage. The main exceptions are when the diagnosis is in doubt and invasive neurological investigations are being considered and when the clinician wants to detect accumulation of a drug after prolonged "therapeutic" dosage. If active elimination is being considered plasma drug concentrations are useful to assess the efficacy of the procedure. Most hypnotics can be detected in a toxicological screen, but much time and effort can be saved by contacting a clinical toxicologist or the analytical laboratory staff before sending samples, to ascertain the relevance of screening the plasma, urine, or gastric aspirate.

Complications

The airway will become obstructed unless the patient is nursed in the coma position until he becomes alert enough to maintain his own airway. Central respiratory depression occurs less often with benzodiazepines than with barbiturates, but the combination of hypnotics and other central nervous system depressants (usually alcohol) has an additive, if not synergistic, effect. Major respiratory depression is suggested by a decreased respiratory rate or reduced minute volume, but arterial blood gas tensions and pH must be measured to define precisely the severity of the problem. If there is respiratory depression the patient should be mechanically ventilated. A primary respiratory acidosis may well be compounded by a secondary metabolic acidosis resulting in overt acidaemia. Any correction of acidaemia will tend to cause hypokalaemia. Aspiration pneumonitis is the other main respiratory complication, which occurs when the patient vomits while his gag reflex is impaired. Treatment is conventional, but prevention is preferable. Occasionally, non-cardiac pulmonary oedema may appear as a sign of direct toxicity to the pulmonary capillaries; if encountered it should be managed in the usual way.

HOSPITAL Pathology Department Specimen Arterial blood Date 4 June 1984 Ward		Name J. Brown Hosp. No. 463724 Age 42 Sex O Consultant RDK
Report Arterial blood gases Pao ₂ 7.0 kPa Paco ₂ 7.5 kPa pH 7.21 HCO ₃ 21 mmol/l Base excess -7

Hypotension is caused by a combination of central action and a direct action on the heart, producing a mixture of peripheral vasodilatation and myocardial depression. The initial management is to administer fluids to restore the central venous pressure; if the hypotension still persists a positive inotrope (such as dobutamine) may be used. Cardiac arrhythmias may occur secondarily to metabolic derangements. Skin blisters, pressure neuropathy, and rhabdomyolysis (with myoglobinuria, which may precipitate acute renal failure) may all be caused by pressure from prolonged immobility, or occasionally as a direct toxic effect of the drug.

Barbiturates

British name	American name	Approximate half life (h)
Cyclobarbitone	Cyclobarbitol	12
Heptabarbitone	Heptabarbitol	12
Quinalbarbitone	Secobarbitol	24
Pentobarbitone	Pentobarbitol	24-48
Amylobarbitone	Amobarbitol	24-48
Butobarbitone	Butobarbitol	48

In overdosage duration of coma bears no constant relationship to the therapeutic half life

Prediction of the depth and duration of symptoms is notoriously difficult. Depending on the patient's tolerance to the drug, he may be comatose with a "therapeutic" plasma concentration of the drug or conscious with a "toxic" concentration. In acute overdose the period of deepest coma often occurs before the drug's peak plasma concentration. The elimination half life may be substantially different after an overdose from that after therapeutic use, and enzyme induction may occur during the course of the overdose. For these reasons plasma concentrations can act only as an approximate guide, and the overriding factor in management must be the clinical condition of the patient. Active elimination may be considered in the few severely poisoned patients who do not respond adequately to general supportive measures or who develop life threatening complications—for example, pneumonia, or acute renal failure. The most effective is haemoperfusion; haemodialysis and forced alkaline diuresis are ineffective for short acting barbiturates and should be considered only for phenobarbitone or barbitone. Forced alkaline diuresis carries the risk of prejudicing an already compromised haemodynamic equilibrium.

Benzodiazepines

Name	Approximate half life (h)
Triazolam	2 - 4
Temazepam	3 - 13
Oxazepam	4 - 24
Lorazepam	9 - 16
Nitrazepam*	17 - 48
Flurazepam*	47 - 100
Medazepam*	21 - 36
→ Diazepam*	
Ketazolam*	24 - 72
Chlordiazepoxide*	
Chlorazepate*	
→ Nordiazepam	
Przepam*	

(* Active metabolites important)

The general principles of barbiturate overdose apply equally well to the benzodiazepines. Tolerance occurs with long term use, and the half life after a therapeutic dose is a rough indicator of the duration of toxicity after an overdose. Though respiratory depression is less of a problem with pure benzodiazepine toxicity, synergy with other central nervous system depressants may be unexpectedly great, so the patient must be carefully observed until his condition is definitely stable. Active elimination is of no benefit, and the clinical usefulness of benzodiazepine receptor antagonists has yet to be established.

Chloral preparations

Chloral	Dichloralphenazone
Chloral hydrate	Butyl chloral hydrate
Chloral betaine	Triclofos

Up to 30% of patients in coma grades 3 and 4 from chloral poisoning may develop cardiac arrhythmias

- correct any metabolic disturbance
- use antiarrhythmic drugs as necessary

Chloral preparations are all metabolised within minutes of absorption to the pharmacologically active substance trichloroethanol. Apart from gastro-oesophageal mucosal irritation, the clinical manifestations of toxicity resemble those caused by ethanol. Profound respiratory and cardiac depression may occur, and cardiac arrhythmias are not uncommon, although usually they are not sustained and cause no haemodynamic embarrassment. If clinically important, however, such arrhythmias respond well to propranolol. Proteinuria and jaundice are rare complications. If supportive measures fail to prevent the patient's condition from deteriorating haemodialysis and haemoperfusion can both increase clearance of the drug.

Miscellaneous

Name	Approximate half-life* (h)
Ethinamate	2
Methypyrion	4 - 5
Carbromal	7 - 15
Meprobamate	6 - 16
Glutethimide	6 - 24
Ethchlorvynol	19 - 32
Methaqualone	20 - 60

(* All may be considerably increased in overdosage)

Glutethimide—a piperidinedione drug—is more powerful than barbiturates both as a hypnotic and as a cardiac and respiratory depressant. Complex biotransformation processes produce a range of active metabolites during the course of an overdose, and these probably cause the characteristic fluctuating level of consciousness observed as the patient recovers. Dilated pupils are among the expected clinical signs of its anticholinergic activity, whereas cerebral oedema, convulsions, and sudden apnoea may complicate the clinical course of severe poisoning. Forced diuresis and haemodialysis do not remove useful amounts of glutethimide and the former may well exacerbate any haemodynamic problems. Haemoperfusion is, however, the treatment of choice in the rare case where full supportive care fails to prevent deterioration.

Chlormethiazole undergoes extensive hepatic metabolism and thus has a short half life after a single dose, but after infusion or overdose the half life may be prolonged. Clinically, increased salivation and rhinorrhoea occur, but atropine should be used only if frequent oropharyngeal suction fails to control the problem. Since this drug is often prescribed to alcoholics it is prudent to assume that alcohol may also be present in cases of chlormethiazole overdose and that the alcohol withdrawal syndrome may complicate the later stages of recovery. Conventional treatment for withdrawal is indicated.

Antihistamine phenothiazines exert an anticholinergic effect. After overdose cardiovascular and neurological signs of sympathetic overactivity occur, often with paradoxical excitability and metabolic derangements. Any metabolic acidosis should be corrected and other complications treated on their own merit.

Curiosities—Although methaqualone was withdrawn from the British market in 1981, cases of overdose still occasionally occur. There is a characteristic clinical pattern of upper motor neurone pyramidal signs and more cardiovascular than respiratory depression. Carbromal and some of the less well known barbiturates (barbitone, aprobarbitone) may be brought into Britain from abroad; the general principles of management outlined above should be followed in treatment of overdosage.

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The illustration of a cerebral function monitor tracing is reproduced by permission from Maynard D, Prior FP, Scott DF, *Br Med J* 1969;ii:545-6, and that on blood gases is adapted, by permission from Cohen RD and Woods HF. Disturbances of acid base homeostasis. *Oxford Textbook of Medicine*. OUP, 1983.

Methaqualone

1960 1981

RIP

NPIS received 12 enquiries in 1983