ABC of Poisoning

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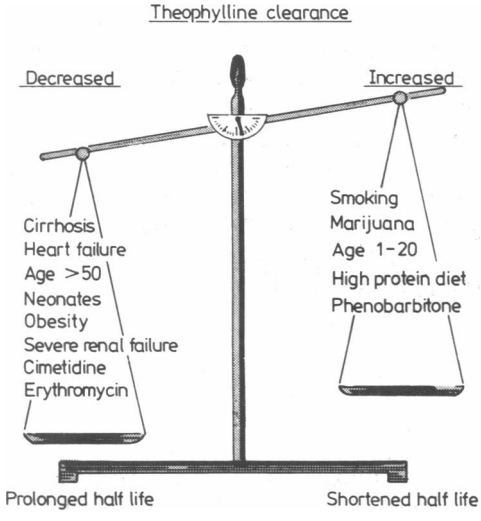
RESPIRATORY DRUGS

Theophylline

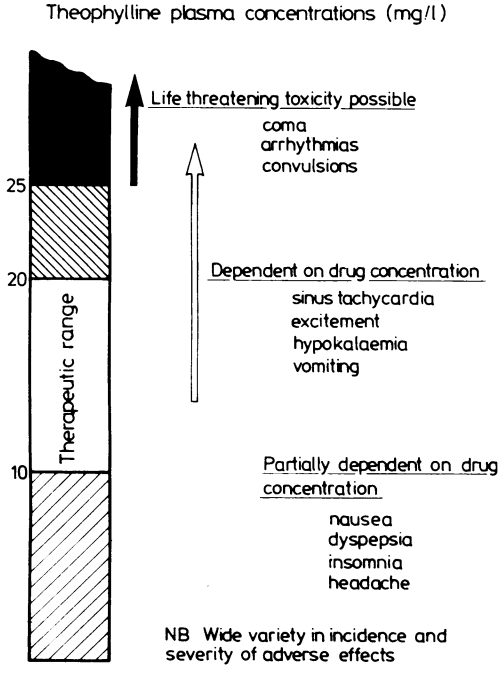


Of the drugs prescribed for respiratory disorders theophylline stands out as the one that most often causes severe toxicity, whether due to iatrogenic accidental, or deliberate poisoning. Theophylline (the active constituent of aminophylline) is a smooth muscle relaxant and inhibits inflammatory mediator release from mast cells. In addition to its use as a bronchodilator it is less commonly used in the treatment of primary apnoea of the newborn and in heart failure.

Adverse effects occur relatively often because it has a narrow therapeutic index and there is also a wide interindividual variability in theophylline clearance. Knowledge of the factors affecting clearance and use of the now widely available assays for measuring plasma theophylline concentrations should enable theophylline doses to be more precisely tailored to the individual patient. In the premature neonate relatively more theophylline is metabolised to caffeine, which has a similar effect to theophylline. If caffeine measurements are not available 10-15 mg theophylline per litre should be regarded as the top of the therapeutic range for neonates.

Iatrogenic poisoning has occurred because of miscalculation of dosage and occasionally because of the simultaneous prescription of two or more proprietary preparations containing theophylline. Most iatrogenic theophylline toxicity can be managed conservatively but some severe overdoses in neonates and children have, rarely, required active elimination procedures such as haemodialysis.

Acute poisoning



Deliberate self poisoning with oral theophylline is increasing. Patients may appear deceptively well on presentation because absorption is delayed owing to slow release preparations and, more rarely, bezoar formation. The toxic effects of an acute theophylline overdose are similar to those of chronic poisoning but are more dramatic. Abdominal pain, vomiting, and haematemesis my occur. Hyperventilation and tachyarrhythmias are common, and hypokalaemia is the major biochemical disturbance. Seizures occur and have been associated with a high mortality. During regular treatment plasma theophylline concentrations as low as 25 mg/l have been associated with severe toxicity, but very high concentrations can occur after a single acute overdose with relatively few toxic signs, and at least one patient has survived without serious sequelae with a plasma concentration of over 200 mg/l. Further factors apparently associated with more severe toxicity are: slow release preparations, pre-existing liver and cardiac disease, old age, severe hypokalaemia, metabolic acidosis, and ventricular arrhythmias.

Management

Management of acute theophylline overdose

1. Rapid clinical assessment with immediate resuscitation and hospital referral as necessary
2. Gastric lavage or emesis
3. Oral activated charcoal (repeat every two hours)
4. Take blood and urine for urgent estimation of electrolytes, urea, glucose, arterial gases, and theophylline, and other toxicology as required. Repeat measurements of blood electrolytes, arterial gases, and theophylline levels at least every six hours if possible
5. Correct dehydration and hypokalaemia
6. Treat convulsions with intravenous benzodiazepines
7. Continuous electrocardiographic monitoring. Most arrhythmias that do not cause any haemodynamic disturbance may be ignored. Many will respond to correction of coexisting hypokalaemia, acidosis, and hypoxia.
8. If there is inadequate response to general supportive measures consider haemodialysis or haemoperfusion

Every theophylline overdose should be regarded as potentially fatal and all patients closely monitored. Gastric lavage may be useful relatively late—that is, up to 12 hours after a slow release preparation has been ingested. Oral activated charcoal is effective in reducing absorption and increasing clearance of therapeutic doses of theophylline but its value in theophylline overdose is unproved. It has the advantage that it is safe. Serial plasma theophylline concentrations provide much more information than a single value. The concentrations may rise up to 24 hours after an overdose so an early low value may be misleading.

The vast majority of theophylline overdoses will respond to supportive measures. Prompt correction of any hypokalaemia will usually be the most aggressive treatment required. The commonly associated sinus tachycardia rarely requires treatment. Although non-selective β blockers may be helpful in non-asthmatic patients in counteracting the cardiovascular and metabolic toxicity in theophylline overdose, β blockers should not be given to patients with asthma because of the risk of precipitating severe bronchospasm. Verapamil has been used effectively for supraventricular tachycardias after theophylline overdose.

Active elimination procedures such as haemodialysis and in particular haemoperfusion have been shown to increase plasma clearance of theophylline. There has been no controlled study of their value in theophylline overdose, and no firm criteria for their use are apparent. Haemoperfusion or haemodialysis should be reserved for those patients whose hypotension, ventricular dysrhythmias, seizures, or intractable vomiting have not responded to supportive measures.

Adrenoreceptor stimulants

Some compound bronchodilator preparations

Proprietary name	Active ingredients
Expansyl (Smith, Kline and French)	diphenylpyraline ephedrine trifluoperazine
Franol Plus (Winthrop)	ephedrine phenobarbitone theophylline thenyldiamine
Phyldrox (Carlton)	ephedrine phenobarbitone theophylline
Amesec (Eli Lilly)	aminophylline ephedrine
Asmapax (Nicholas)	ephedrine theophylline

In contrast to theophylline the β_2 stimulants such as salbutamol have a wide margin of safety. Fifty times the quantity of salbutamol in a single "puff" from an inhaler is used in nebulisers in hospital. When patients are correctly instructed the number of puffs required acts as a useful index of airways obstruction. β Receptor selectivity is lost with high doses of β_2 stimulants. Large oral and systemic overdoses of salbutamol have occurred without severe toxicity, but sinus tachycardia, tremor, headache, and hypokalaemia have been reported. Recently the question of inhaler abuse has arisen. Whether it is the fluorocarbons in the propellant or the salbutamol which is the more active agent in producing the required "buzz" is uncertain. There is less experience of other β_2 stimulants in overdose. Toxicity appears to be similar, although electrocardiographic changes implying temporary ischaemia have been reported after iatrogenic parenteral terbutaline overdose. Perhaps the biggest danger after a β_2 stimulant overdose in an asthmatic patient is the overenthusiastic use of β blockers.

The non-selective adrenoreceptor agonists such as isoprenaline are associated with more toxic effects but even so there seems to be a reasonable safety margin with the inhaled preparations. Life threatening arrhythmias from isoprenaline overdose require the use of an intravenous β blocker, such as propranolol. If there is a history of asthma atenolol may be safer. Oral ephedrine is also sometimes used in the treatment of asthma, and patients who take overdoses of this drug may develop a variety of toxic features including headache, nausea, vomiting, irritability, pyrexia, dilated pupils, opisthotonus, convulsions, hallucinations, and hypertension. Sedation and very occasionally β or α blockers, or both, may be required.

Various compound bronchodilator preparations are also available. Some preparations are combined with sedatives. As well as being dangerous in the treatment of asthma they may cause diagnostic confusion in overdose. Some iatrogenic problems may occur because prescribers are not aware of the constituents of compound preparations.

Other respiratory drugs

Acute overdose of antituberculous drugs

	Clinical features
Isoniazid	Coma Convulsions Respiratory distress Metabolic acidosis Hyperpyrexia Hyperglycaeamia
Rifampicin	Bright red skin pigmentation Red discolouration of plasma and urine Liver damage
Ethambutol	Nausea Abdominal pain Fever Mental confusion Visual hallucinations Optic neuropathy

Compound cough mixtures and cold remedies may contain a variety of opioids, antihistamines, and sympathomimetic and mucolytic agents. The management of opioid and antihistamine overdose is covered elsewhere. The various sympathomimetic agents cause acute behavioural disturbances including visual and auditory hallucinations as well as features of α and β overactivity. These may require specific treatment in the form of sedation or sympathomimetic blocking agents, or both. Chronic use of these drugs may cause behavioural disorders and hallucinations which remit on withdrawal of the drug.

Anticholinergic drugs—Agents such as ipratropium bromide are being used increasingly in the treatment of asthma. When administered by inhalation these have a wide safety margin, but accidental or deliberate self-poisoning with nebuliser fluid may cause pronounced anticholinergic poisoning. There have been a few reports of paradoxical bronchoconstriction after both aerosol or high dose nebulised anticholinergic compounds. The reaction to the aerosol is thought to be an allergic response, but the reaction to the nebulised solution may be due to inhalation of a non-isotonic solution.

Corticosteroids are occasionally taken in acute overdose but toxic effects are unlikely.

Sodium cromoglycate is of low toxicity and overdose needs no specific treatment.

Antituberculous drugs—Isoniazid overdose in the UK is relatively unusual, but several serious cases have been reported in the USA, particularly among Eskimos and North American Indians. It is occasionally abused for its hallucinogenic effects. Acute ingestion of over 6 g is associated with severe toxicity and mortality. Maintenance of a patent airway and control of convulsions are of paramount importance. Pyridoxine (1 g intravenously for every gram of isoniazid ingested or 5 g in 50 ml intravenously at 15 minute intervals until convulsions are controlled) has been reported to produce a significant reduction in mortality. Suitable preparations of pyridoxine are available (see previous article on emergency drugs). The value of active elimination techniques such as dialysis and haemoperfusion is unknown. Pyrazinamide may cause liver damage when used in treatment, particularly in patients with a history of liver disease; similar toxicity may occur in acute overdose. The management of acute ethambutol and rifampicin overdose is supportive.

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Is it still considered necessary for doctors and nurses to wear face masks when attending women in the labour ward?

This precaution is no longer taken during normal labour, but face masks are still used for special procedures such as operative delivery or inserting an epidural catheter. Years ago puerperal infection was a common cause of morbidity and even death after hospital confinement, and there was indirect evidence that droplet spread from attendants caused streptococcal puerperal infection.[1] Nowadays sepsis is less of a problem: although infection may still be a hazard to neonates, puerperal sepsis after vaginal delivery caused only eight maternal deaths in England and Wales during the last three year period for which figures are available. Furthermore, there is controversy over whether face masks alter infection rates in clinical practice. Most investigations of the efficiency of surgical masks have used bacterial counts on blood agar plates rather than infection rates among patients, and have shown that different types of mask differ in their ability to filter small particles.[2] There is, however, little confirmation that masks prevent clinical infection. In a British operating theatre masks were abandoned for six months without any increase in the rate of wound infection,[3] and a study in an American children's hospital failed to show that masks prevented attendants picking up respiratory infection from patients[4]—though spread in the opposite direction has not been studied. The surgical mask is a potent symbol of medical mystique and power. There has been little research on the psychological effects of masks on either wearers or patients, but masked faces seem unlikely to reassure a woman in labour. Now that maternity hospitals are trying to establish a friendlier image the use of masks is being minimised, particularly as their clinical benefits remain unproved.—JAMES OWEN DRIFE, senior lecturer in obstetrics and gynaecology, Leicester.

1 Paine CG. The aetiology of puerperal infection with special reference to droplet infection. *Br Med J* 1935;i:243-6.
2 Rogers KB. An investigation into the efficiency of disposable face masks. *J Clin Pathol* 1980;**33**:1086-91.
3 Orr NWM. Is a mask necessary in the operating theatre? *Ann R Coll Surg Eng* 1981;**63**:390-2.
4 Murphy D, Todd JK, Chao RK, Orr I, McIntosh K. The use of gowns and masks to control respiratory illness in pediatric hospital personnel. *J Pediat* 1981;**99**:746-50.

Correction

Do emergency tests help in the management of acute medical admissions?

An error occurred in this paper by Gerald Sandler (13 October, p 973). In the right hand column on p 975, two lines from the bottom, the number should have been £10m, not £42½m as stated.