sounds, and there was generalised rebound tenderness but no muscular rigidity or hepatosplenomegaly. Rectal and pelvic examination were painful but normal. Neurological examination showed no abnormalities.

Laboratory values were: erythrocyte sedimentation rate 5 mm in first hour; haemoglobin 15·3 g/dl; packed cell volume 47%; leucocytes $7·8 \times 10^9$/l, with a shift to the left; thrombocytes 128×10^9/l; serum amylase 1110 U/l (normal <340 U/l); aspartate transaminase 43 U/l (normal <17 U/l); alanine transferase 42 U/l (normal <21 U/l); lactate dehydrogenase 321 U/l (normal <200 U/l); direct Coombs negative. Electrolytes, blood glucose, renal function, and urine analysis were normal. Chest *x*-ray examination showed cystic abnormalities of the left lung; abdominal *x*-ray examination was normal. Pancreatitis caused by choledochal obstruction was suspected and all oral drugs stopped. Within two days the fever, confusion, and hyperamylasaemia had disappeared. Retrograde cholangiopancreatography showed two stones in the gall bladder but normal choledochal and pancreatic ducts.

Drug-related pancreatitis was suspected and with informed consent she was rechallenged with 250 mg methyldopa. Within three hours the same symptoms had developed. Serum amylase activity rose from normal to 2105 U/l in 12 hours, serum lipase activity rose to 1200 U/l, and a transient leucocytosis with left shift developed. All symptoms subsided in 36 hours; serum amylase and lipase activities normalised within five days.

Comment

In these two patients increased serum and urinary amylase activities accompanied by fever occurred after administration of methyldopa and reappeared on rechallenge. Although the first patient did not show the classical symptoms of acute pancreatitis, the increased serum amylase and lipase activities were suggestive of clinically mild pancreatitis. The second patient suffered from serious symptoms of pancreatitis. Although she had concomitant cholelithiasis, this is unlikely to have caused the pancreatitis because the choledochal duct was normal.

Drug-induced pancreatitis has occurred with several drugs, such as chlorthalidone and frusemide,[2] but these were stopped in our patients and could not have caused the pancreatitis after rechallenge. We could find reports of only two other cases of possible methyldopa-associated pancreatitis[3 4] but believe that this may be more common than is generally thought.

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Withdrawal reaction from clobazam

Prolonged benzodiazepine treatment may lead to physical dependence and a characteristic withdrawal syndrome.[1-3] Clobazam (Frisium) is the first 1,5-benzodiazepine to be marketed, supported by the claim that therapeutic doses do not impair psychomotor performance,[4 5] and the drug has not been reported to cause dependence. We report two cases from our studies of withdrawal reactions from long-term, low-dose benzodiazepine treatment.

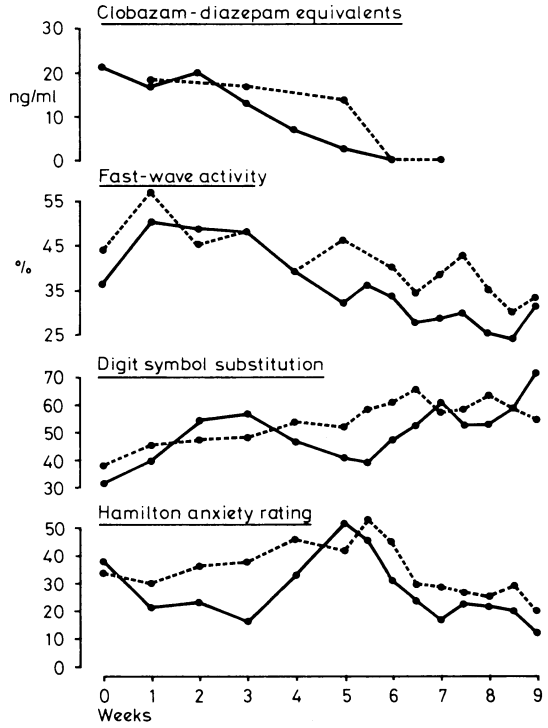
Case reports

Case 1—A 36-year-old man with chronic anxiety had been treated with benzodiazepines for two and a half years. He had been taking clobazam 20-30 mg daily for a year, but lately he had complained that the clobazam was having little effect. He therefore tried several times to discontinue the medication but could only stay off the capsules for a few days, becoming increasingly tense and anxious; his sleep was disturbed and he had bad shakes and perspired profusely. The symptoms disappeared on restarting the medication. He was gradually withdrawn from clobazam under supervision in our benzodiazepine withdrawal clinic using placebo-controlled double-blind conditions and assessment with several biochemical, physiological, and clinical measures. Plasma benzodiazepine concentrations were estimated using a radioreceptor binding assay.

Case 2—A 58-year-old man had a long history of anxiety and bouts of depression for which he had been prescribed benzodiazepines, mainly diazepam, up to 30 mg daily, for the past 16 years. He had been told that his affective disturbances might be due to diazepam addiction and hence he had tried several times to discontinue the medication but found that he could not tolerate the withdrawal symptoms, which subsided on restarting treatment. Clobazam 30 mg daily was substituted for the diazepam, and after six months he was referred to our withdrawal clinic. The clobazam was withdrawn in the same manner as in case 1.

In each case the withdrawal syndrome from clobazam was the same as that from other benzodiazepines—namely, a severe insomnia, tension, restlessness, anxiety, panic attacks, hand tremor, profuse sweating, difficulty in concentrating, nausea and dry retching, weight loss, palpitations, blurring of vision and photophobia, and muscle pains and stiffness. The symptoms started soon after the drug was stopped, lasted for 8-10 days, and improved rapidly. Both patients experienced several more episodes of anxiety and tension, which gradually subsided over the next few weeks.

The figure shows some changes in relevant variables. Clobazam (and its active metabolites) was still detectable in the plasma one week after stopping the drug, in accord with the long half life of *N*-desmethyl clobazam. The electroencephalographic fast-wave activity (13·5-26 Hz) diminished as withdrawal proceeded. Psychological performance (digit symbol substitution test) improved and the Hamilton anxiety scale ratings increased to a peak after withdrawal, returning to prewithdrawal level as the syndrome subsided.



Reaction to withdrawal from clobazam. Case 1 ●——●; case 2 ●- - -●. Plasma drug activity in diazepam equivalents plotted against a time scale: weeks 1-2, full dose; 3-4, half dose; medication stopped at the end of fourth week. Electroencephalographic fast-wave activity (13·5-26 Hz) is expressed as a percentage of total electroencephalographic activity. Digit symbol substitution is expressed as items completed in 90 seconds.

Comment

In the past 18 months we have withdrawn 26 patients from low-dose, long-term benzodiazepine treatment. All suffered from anxiety as either a neurotic state or a personality disorder; none were alcoholic or took other drugs. All had received benzodiazepines for at least a year, and all experienced some form of withdrawal reaction comprising anxiety and dysphoria and usually also perceptual changes. Anxiety

ratings rose as the drug was withdrawn but subsequently subsided, suggesting that the symptoms represented a true withdrawal syndrome and not the revival of the original anxiety. Furthermore, the perceptual changes, such as intolerance to light and sound, unsteadiness, and a feeling of motion, are untypical of anxiety. Some patients have complained of strange smells and a metallic taste.

Both our patients were originally taking other benzodiazepines before transferring to clobazam. They developed a typical syndrome on withdrawal of clobazam. We have not yet encountered a patient who has developed dependence on clobazam alone but would expect such cases to become apparent in due course.

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Self-poisoning with oral salbutamol

The oral bronchodilator drugs salbutamol (a selective $beta_2$-adrenoceptor agonist) and theophylline (a methylxanthine) are commonly used in the management of patients with airflow obstruction. Theophylline has a low therapeutic index and may be dangerous in overdosage.[1] Apart from one case report,[2] however, little information is available concerning poisoning with oral salbutamol. We describe 40 patients who ingested excessive quantities of salbutamol, and report their symptoms and outcome.

Patients and methods

We reviewed 40 patients who had been reported to the poisons unit during 1979 and 1980, allegedly having ingested excessive quantities of salbutamol (either tablets or elixir). The table shows details of the patients, the amounts of salbutamol ingested, and clinical findings.

All patients were admitted to hospital, where 20 received either gastric lavage or syrup of ipecacuanha to promote emesis. Cardiac rate and rhythm were monitored. In two patients serum potassium concentrations were 2·2 and 2·6 mmol(mEq)/l. No patient developed ventricular arrhythmias, and all remained haemodynamically stable. Beta-adrenoceptor-blocking drugs were administered to 10 patients. Propranolol was the drug most commonly used. The dose range was 5-10 mg by mouth in the four patients under 10 years of age, and 10-80 mg by mouth in the six patients over 10 years of age. Only one patient was given an intravenous beta-blocker (10 mg practolol). All patients made an uneventful recovery.

Clinical details of patients and amount of salbutamol ingested

	Patients under 10 years of age	Patients over 10 years of age
No and sex	20 (13M, 7F)	20 (4M, 16F)
Age range (years)	2–8	12–76
Amount of salbutamol ingested (mg):		
Range	5–100	14–240
Mean	37	74
Symptoms (No of patients):		
Muscle tremor	4	10
Flushing	5	3
Agitation	3	3
Palpitations	1	5
Sinus tachycardia:		
No of patients	12	14
Range of rates (beats/min)	140–220	110–160

Comment

Our findings support those of Morrison and Farebrother,[2] who described a 44-year-old woman who made an uneventful recovery after ingesting 200 mg salbutamol. Self-poisoning with oral theophylline may, however, be lethal. Helliwell and Berry[1] reviewed eight patients severely poisoned with oral theophylline; two patients died. Furthermore, as few as seven 225 mg tablets of sustained-release aminophylline have produced a highly toxic serum theophylline concentration of 146 mg/l (therapeutic range 8-20 mg/l).[3]

The difference in toxicity between salbutamol and theophylline may in part be explained by their differing actions on the heart and central nervous system. The tachycardia caused by salbutamol is probably reflex (secondary to peripheral vasodilatation,[4] a specific $beta_2$ effect), whereas that caused by theophylline is partly the result of direct cardiac stimulation.[5] This might explain why ventricular arrhythmias, common in theophylline toxicity,[1] were not observed in our patients (despite hypokalaemia in two). We also did not observe convulsions in our patients, although six were agitated. Fits are common in severe theophylline toxicity[1] and may be explained by a direct stimulatory action of theophylline on the cerebral cortex.

Charcoal haemoperfusion, the most effective treatment for severe theophylline intoxication,[3] is available in only a few specialist centres. Salbutamol overdosage requires no specific treatment. Although beta-adrenoceptor-blocking drugs were given to 10 of our patients, they were probably unnecessary. Such drugs should always be used with extreme caution in any patient with airflow obstruction who has ingested excessive quantities of salbutamol.

Our study emphasises the safety of salbutamol in overdosage. The difference in toxicity between oral salbutamol and theophylline has important implications in the prescribing of oral bronchodilator drugs.

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THE ELM TREE is so well known, growing generally in all counties of this land, that it is needless to describe it.

It is a cold and saturnine plant. The leaves thereof bruised and applied, heal green wounds, being bound thereon with its own bark. The leaves or the bark used with vinegar, cures scurf and leprosy very effectually; The decoction of the leaves, bark, or root, being bathed, heals broken bones. The water that is found in the bladders on the leaves, while it is fresh, is very effectual to cleanse the skin, and make it fair; and if cloaths be often wet therein, and applied to the ruptures of children, it heals them, if they be well bound up with a truss. The said water put into a glass, and set into the ground, or else in dung for twenty-five days, the mouth thereof being close stopped, and the bottom set upon a layer of ordinary salt, that the foeces may settle and water become clear, is a singular and sovereign balm for green wounds, being used with soft tents: The decoction of the bark of the root, fomented, mollifies hard tumours, and the shrinking of the sinews. The roots of the Elm, boiled for a long time in water, and the fat arising on the top thereof, being clean skimmed off, and the place anointed therewith that is grown bald, and the hair fallen away, will quickly restore them again. The said bark ground with brine or pickle, until it come to the form of a poultice, and laid on the place pained with the gout, gives great ease. The decoction of the bark in water, is excellent to bathe such places as have been burnt with fire. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)