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Hadassah University Hospital and Osteoporosis Institute, Jerusalem, Israel
R CHISIN, MD, resident in nuclear medicine
C MILGROM, MD, attending orthopaedic surgeon
J MARGULIES, MD, resident in orthopaedic surgery
M GILADI, MD, resident in internal medicine
M STEIN, MD, resident in surgery
H KASHTAN, MD, resident in surgery
H ATLAN, MD, PHD, chairman, department of nuclear medicine

Correspondence to: Dr J Y Margulies.

Fatal overdosage of phenylpropanolamine

Considerable interest has recently been expressed in the medical, pharmaceutical, and lay press, about the toxicity of proprietary cold cure preparations containing phenylpropanolamine available "over the counter." Side effects and morbidity from drugs containing phenylpropanolamine are fairly common,[1] but only five deaths have been reported,[2 3] although the manufacturer of one preparation containing phenylpropanolamine knows of two others (Menley and James, USA, data on file). In two of the reported cases death occurred three and five days after ingestion of the drug and the patients showed clinical and necropsy features of the adult respiratory distress syndrome.

Case report

A 15 year old previously healthy girl admitted to having taken eight or nine capsules of Contac 400 (phenylpropanolamine 50 mg and belladonna alkaloids 0·2 mg in a sustained release preparation) at one time as a deliberate overdosage. On admission to hospital some six hours later she was drowsy but rousable and cooperative. Blood pressure was 160/120 mm Hg (phase V) and pulse 140/min regular. She had a harsh grade III/VI systolic ejection murmur at the left sternal edge, which was not radiating. She did not have cardiac failure, and her general condition was satisfactory. Gastric lavage did not yield recognisable drug fragments. Serum potassium concentration was 3·3 mmol(mEq)/l; urea and other electrolyte concentrations were normal. Her urine was normal on admission but subsequently showed a transient 2% glycosuria with a plasma glucose concentration of 12·3 mmol/l (220 mg/100 ml).

Her sinus tachycardia persisted (100-140 beats/minute), but her blood pressure settled to 130-140/80-90 mm Hg. Her condition did not give rise to undue concern until about 30 hours after ingestion of the drug, when she developed increasing breathlessness, frothy haemoptysis, persistent tachycardia, and bilateral crepitations at both lung bases. There was no right heart failure. Chest *x* ray examination showed diffuse bilateral pulmonary infiltrates. She was given frusemide 40 mg intravenously and orally, and because her tachycardia was thought to be due in part to excess sympathomimetic drive she received a single oral dose of metoprolol 50 mg.

One hour later she collapsed with an unrecordable blood pressure and persistent sinus tachycardia. Endotracheal intubation was followed by intermittent positive pressure ventilation, and despite continuing hypotension 2-3 cm positive end expiratory pressure was later introduced because of persistent pulmonary oedema. She became anuric and did not respond to further intravenous frusemide, dobutamine, or large doses of methylprednisolone. There was no evidence of gastrointestinal haemorrhage, and a coagulation screen excluded disseminated intravascular coagulation. Intensive resuscitative activity was continued for four hours, carotid and femoral pulsation being easily maintained. Brain death was confirmed in the usual way before resuscitation was finally abandoned.

At necropsy there was no macroscopic abnormality of the heart. The lungs were very congested with increased capillary wall permeability and features compatible with early adult respiratory distress syndrome. A toxicological screen on blood removed shortly before death did not show evidence of any other ingested drugs, and indeed did not detect any circulating phenylpropanolamine.

Comment

Phenylpropanolamine is chemically similar to amphetamine and ephedrine. Adverse effects include hypertensive crises, cerebrovascular accidents, seizures, psychotic and other reactions similar to those induced by amphetamine, acute renal failure, myocardial damage, and cardiac arrhythmias. The potential for interaction with other drugs such as antihypertensives and monoamine oxidase inhibitors needs emphasis.[3] Side effects have arisen both from therapeutic doses of drugs containing phenylpropanolamine and from quite small overdoses.

The fact that this patient's collapse was delayed until some 32 hours after ingestion of the drug and that two of the five other reported deaths occurred after an even longer delay,[4 5] together with the pathological features of these three cases, suggests that the adult respiratory distress syndrome was responsible. Physicians should be aware that the syndrome may develop after quite small overdoses of drugs containing phenylpropanolamine. If appropriate treatment had been introduced in this previously healthy young woman at an earlier stage death might have been avoided.

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Medical Department, Peel Hospital, Galashiels, Selkirkshire TD1 3LQ
A W LOGIE, MB, FRCPED, consultant physician
CATHERINE M SCOTT, BSC, MPS, staff pharmacist

Correspondence to: Dr A W Logie.

Treatment of septic arthritis due to Mycobacterium kansasii

Septic arthritis due to atypical mycobacteria is rare and frequently eludes diagnosis; moreover, there are no clear guidelines for treatment.

Case report

A 39 year old Cambridgeshire man presented with pain in the right knee for six months. He remembered no specific injury but had sustained several minor injuries in the past when playing football. Examination showed tenderness on the medial aspect of the knee but no effusion. He failed to respond to conservative treatment and an arthroscopic biopsy specimen showed non-specific synovitis. His symptoms persisted and six months later he developed an effusion and was reinvestigated. Blood count, sedimentation rate, liver function tests, and a knee radiograph were normal. Clear fluid was aspirated from the joint; normal cultures of this were sterile, but tubercle cultures grew a heavy growth of *Mycobacterium kansasii*. The strain was sensitive to rifampicin, ethambutol, ethionamide, capreomycin, thiacetazone, and cycloserine; moderately sensitive to streptomycin; and resistant to isoniazid and para-aminosalicylic acid. The diagnosis was confirmed by repeat culture. A careful review of the original synovial biopsy specimen showed giant cell granulomata, confirming that infection was present before arthroscopy.

One year previously a routine chest radiograph had shown localised emphysematous changes in the right upper zone. No evidence of pulmonary infection was found and subsequent radiographs remained unchanged. Treatment was started with ethambutol 900 mg daily and Rifinah (rifampicin/isoniazid) 600 mg daily. His progress was monitored both clinically and thermographically. After one month the results of these two procedures had not altered so pyrazinamide 2 g daily was added. A month later there was definite improvement. Four months after starting treatment he suddenly became jaundiced, so treatment was discontinued. A liver biopsy specimen showed non-specific inflammatory changes. His liver function tests returned to normal during the next four months. One year after the treatment was stopped there was no clinical or thermographic evidence of joint inflammation and he had returned to playing football.

Comment

This report underlines the importance of considering atypical mycobacterial infection in a patient with monoarticular arthritis. As in this case the diagnosis was made by culturing joint aspirate,

it is important to send synovial tissue for culture as well as histological examination.[1]

M kansasii is frequently resistant to standard antituberculous agents in vitro but may respond to these agents in vivo.[2 3] In most reported cases combination antituberculous therapy has been used and continued for 1·5-2 years,[1 2 4] sometimes with synovectomy and joint irrigation.[3 5] Our experience suggests that such long term and aggressive treatment may not be needed in an undamaged joint.

A good response to only three months' triple therapy has been reported in a patient with tenosynovitis due to *M kansasii*, the duration of therapy again being limited by toxic reactions.[4] Triple therapy is sometimes inadequate, as in our case, and agents such as pyrazinamide or erythromycin may have to be added.[3] Patients should be monitored clinically, but thermography offers a useful objective measure of response. Once this has been achieved it may be necessary to continue treatment for only six months at most.

We thank Mr M H Matthewson, Dr T Higenbottam, Dr G Neale, and Dr S Stone for their help with this patient; Mr G Parr in the Addenbrooke's Hospital rheumatology research unit for the thermography; and the Tuberculosis Reference Laboratory, Cardiff for the susceptibility test results.

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Addenbrooke's Hospital, Cambridge CB2 2QQ
S R CARROLL, MB, BS, senior house officer in rheumatology and rehabilitation
S W B NEWSOM, MD, FRCPATH, consultant microbiologist
J R JENNER, MD, MRCP, consultant in rheumatology and rehabilitation

Correspondence to: Dr J R Jenner.

Stress reduction by oxprenolol and placebo: controlled investigation of the pharmacological and non-specific effects

At least two factors contribute towards the efficiency of drug treatment: the pharmacological action of the drug and the patient's belief in its efficacy.[1] This belief is known as the placebo or non-specific factor. To measure its effect a no treatment control group is required. The experimental design gains strength if another group of subjects is included who receive the drug without being aware of its administration. There are ethical problems when drugs are administered without the recipients' awareness. Nevertheless, when subjects are told that they may or may not receive medication and give informed consent the deception becomes acceptable.

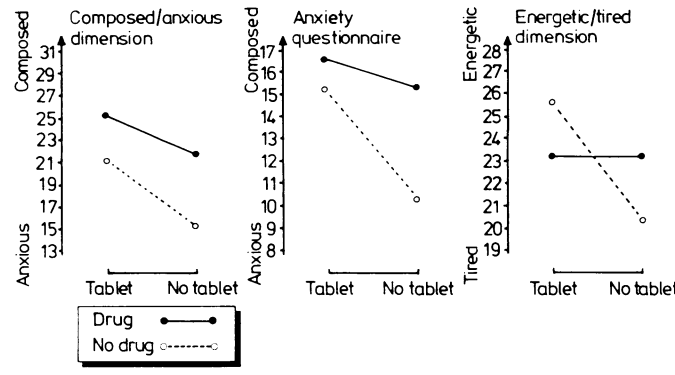
We have been able to test the effect of antistress medication in a training class. All police cadets in Western Australia are required to attend a necropsy demonstration, which they believe will be an unpleasant experience.

Among the β adrenergic blocking agents, oxprenolol (Trasicor) has been shown to reduce the effects of transient anxiety.[2-4] We therefore decided to examine the stress reducing effect of oxprenolol in a design which controlled for the effects of both medication and expectancy.

Subjects, methods, and results

The subjects were 63 men and five women (median age 20·2 years). They were seen as a group and the experiment was explained to them. The volunteers then completed two questionnaires, the "right now" form of the bipolar profile of mood states (POMS) and an anxiety questionnaire.[5] They also signed a consent form which had been approved by the Human Rights Committee.

The class was split into three divisions, each of which attended a different necropsy demonstration. When the subjects arrived at the morgue they received 100 ml orange juice, and half of them were given a placebo tablet. Half the number of subjects received 40 mg oxprenolol in their orange juice. Hence there were four different treatment groups—(*a*) those who received oxprenolol and a tablet (medication plus belief); (*b*) those who received oxprenolol but no tablet (medication without awareness); (*c*) those who received no drug but a tablet (unmedicated but believed that they were); (*d*) those not given a drug or a tablet (unmedicated and aware that they were a no treatment control group). Allocation to the groups was at random and data were evaluated blind.



Mean scores on composed/anxious dimension, anxiety questionnaire, and energetic/tired dimension. Each point on each graph based on 17 different subjects.

After the administration of orange juice with or without a tablet the cadets attended a brief lecture and 45 minutes later filed into the necropsy theatre where the body was lying. The subjects' pulse rate was recorded; they completed another POMS inventory and questionnaire and then watched the necropsy.

The mean heart rate of the subjects who received oxprenolol was 60·1/min, while that of the no drug groups was 72·6. This difference was highly significant ($F=52·11$; $p<0·001$). There was no significant change in heart rate due to administration of the tablet.

The figure shows the mean composed/anxious and energetic/tired POMS scores and results of the anxiety questionnaire. Three analyses of covariance were performed. Subjects who received oxprenolol were significantly more composed ($F=6·71$; $p=0·012$), as were those receiving a tablet ($F=6·77$; $p=0·012$), with no significant interaction. This implies that the drug effect was independent of the non-specific effect. Similar results were obtained when the anxiety questionnaire data were analysed.

On the energetic/tired dimension oxprenolol did not affect the subjects' response ($F<1$), but giving volunteers a tablet made them feel more vigorous ($F=5·43$; $p=0·024$).

Comment

These results show that 40 mg oxprenolol taken some 45 minutes before a stressful event reduces subjective anxiety. The pharmaceutical action of oxprenolol was independent of the additional, non-specific effect. Oxprenolol therefore seems to reduce transient stress without causing fatigue.

We are grateful to the Police Commissioner (Mr J H Porter, QPM) for permitting police cadets to volunteer. Trasicor was made available by Ciba-Geigy Australia Limited.

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Department of Psychology, University of Western Australia, Nedlands 6009, Australia
ALI A LANDAUER, BA, PHD, senior lecturer

Department of Forensic Pathology, Queen Elizabeth II Medical Centre, Nedlands 6009, Australia
DEREK A POCOCK, MB, DMJ, forensic pathologist

Correspondence to: Dr Ali A Landauer.