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CASE REPORT

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A fatal case of suicidal pentoxifylline intoxication

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Abstract Pentoxifylline is a xanthine derivative used in the treatment of peripheral vascular disease. It is considered to be a safe drug and to the best of our knowledge there are no reports in the medical literature of cases of fatal poisoning. There is only one previous report of a young woman who tried to commit suicide by taking a large amount of the drug but recovered. We report the case of a 54-year-old man who took a massive dose of pentoxifylline and died after 24 h from refractory shock. The blood levels of pentoxifylline were as high as 32.5 μg/ml where the average therapeutic level is 1.3 μg/ml.

Key words Pentoxifylline · Overdose · Suicide · Gastrointestinal bleeding

Introduction

Pentoxifylline (3,7-Dimethyl-1-(5-oxohexyl) xanthine) is a methylxanthine derivative used in the treatment of peripheral vascular disease (Johnson et al. 1994; USPDI 1995). The pharmacological action may reflect the summation of different effects on multiple sites. An improvement in erythrocyte flexibility appears to be due to inhibition of phosphodiesterase and a resultant increase in AMPc in red blood cells. Reduction of blood viscosity may be the result of decreased plasma fibrinogen concentrations and inhibition of platelet aggregation (USPDI 1995). It is considered to be a safe drug although some adverse effects have been reported including nausea, gastrointestinal disturbances, dizziness and headache. Bleeding events have usually been reported in association with bleeding risk factors (Dettori et al. 1989; Oren et al. 1991; Reynolds 1993). An overdose of pentoxifylline may be associated with fever, faintness, flushing, hypotension, drowsiness, agitation, seizures and atrioventricular block (Dettori et al. 1989; Snazjder and Bentur 1984; USPDI 1995). Some reports deal with accidental intoxications in children (Garnier et al. 1986).

The use of this drug in a suicide event is extremely infrequent and, to the best of our knowledge, only one previous failed attempt has been published (Snazjder and Bentur 1984). In this paper we report a case of suicide by taking pentoxifylline.

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Case report

A 54-year-old man was admitted to the University Hospital after an episode of vomiting where the womitus had a "coffee-grounds" appearance. He was known to suffer from type-I diabetes mellitus which had progressed from retinopathy to blindness, and right lower limb (through the middle femoral third) and left foot amputation. The current treatment included insulin, salbutamol, furosemide and pentoxifylline. Family members reported a voluntary intake of pentoxifylline (Hemovás) 2 h prior to admission. The number of tablets taken was estimated to be between 50 and 60 (20–24 g). On admission physical examination revealed symptoms consistent with shock. Arterial blood gasometry values were: pH 7.20, pO_2 35 mm Hg, pCO_2 51.5 mm Hg and CO_3H^- 19.7 mEq/l. The most relevant analytical alteration was severe hypokalemia.

ECG revealed many ectopic supraventricular beats associated with a high variation rate in the PR interval were considered as consistent with AV dissociation. By oral endoscopy there was an ulcerative esophagitis. A large amount of blood was seen in the oesophagus and stomach, intermingled with tablets. The patient was taken to the critical care unit with the following diagnosis:

– Respiratory insufficiency with hypoxemia and hypocapnia and metabolic acidosis due to cardiac failure
– Hypokalemia in relation to chronic intake of furosemide and salbutamol.

Although treatment with dopamine and dobutamine was initiated, the central venous pressure began to increase and oliguria was refractory to furosemide bolus. An episode of atrial fibrillation was controlled with amiodarone. The hemodynamic status progressively worsened and the patient needed mechanical ventilation but died 24 h after admission.

A medico-legal autopsy was performed with the following findings: in the upper gastrointestinal tract there was some blood-stained semi-liquid content, but no overt bleeding was present. The heart weighed 590 g and the left ventricle was 2 cm thick. A cir-

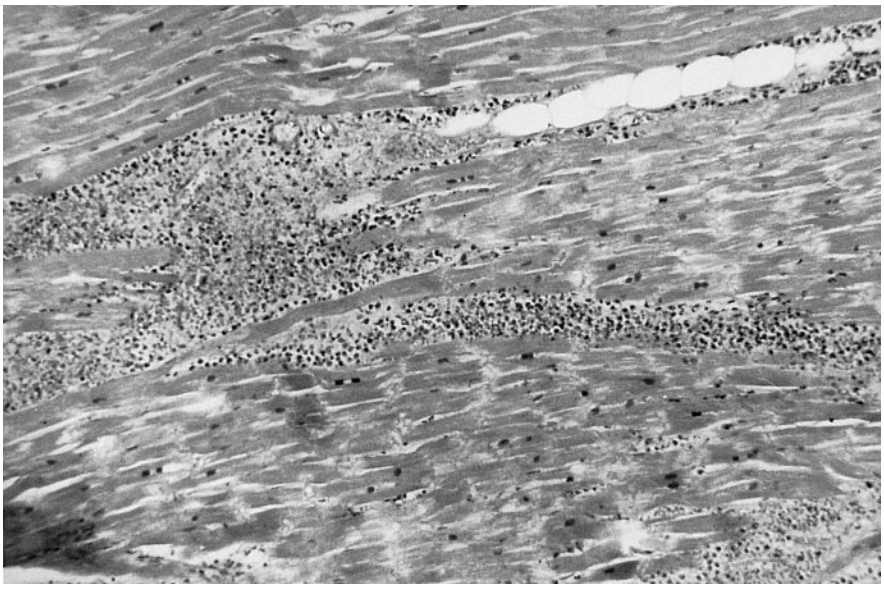

Fig. 1 Histological section from the myocardium, showing well-established ischaemic lesions with heavy leucocytic infiltration and interstitial haemorrhage (HE × 75)

cumferencial subendocardial haemorrhagic lesion affecting most of the left ventricle was seen on gross examination. The histopathology showed marked eosinophilia of myocardial fibres with loss of nuclei. Interstitial polymorphonuclear infiltration, intermingled with abundant nuclei debris, was conspicuous, as was interfibrillar haemorrhage (Fig. 1). Coronary atherosclerosis was severe (luminal obstruction was more than 75% in all the three main epicardial arteries), but no acute complications were identified. Both lungs were congestive and showed alveolar oedema.

Gastric contents and peripheral venous blood were submitted for toxicological analyses. No urine was available in the bladder at the time of autopsy.

Materials and methods

Gastric content screening and blood levels of pentoxifylline were determined as follows:

About 10–30 ml of gastric contents were made basic with alkaline buffer (pH 9.8), extracted with ethyl acetate (10 ml) and centrifuged. The organic extract was evaporated to dryness, redissolved in 10 ml ethyl acetate and 1 ml was injected for GC-MS at analysis.

GC-MS was performed with a Hewlett-Packard 5890 series II (Palo Alto, Calif.) coupled to a Hewlett-Packard 5971A mass selective detector (MSD) equipped with a HP-ultra 2 capillary column (cross-linked methylphenylsilicone 12.5 m × 0.2 mm i.d. × 0.33 μm film thickness). The oven temperature was programmed from 130 °C (1 min hold) to 250 °C at 15 °C/min (5 min hold), injector (splitless 0.75 min) and interface temperatures were 280 °C and 290 °C, respectively. The helium carrier flow was 0.8 ml/min and the MSD was used in the electron impact mode at 70 eV. The electron multiplier voltage was set at 300 V above autofine voltage. Under these working conditions the retention time for pentoxiphylline was 14.8 min and the main peaks in the scan mode were 221, 180, 193, 278 m/z.

To determine blood levels a stock solution of pentoxiphylline was prepared in methanol (1 mg/ml). Pentoxiphylline-free plasma was spiked with 1.0, 2.0, 3.0, 4.0 and 5.0 μg/ml of pentoxiphylline. As an internal standard SKF-525A was used at a concentration of 1000 μg/ml.

For the extraction procedure Bond Elut Certified columns (varian) were inserted into a vacuum manifold and conditioned by washing once with 2 ml methanol and 2 ml desionized water. Phosphate buffer (pH: 8.0) 2 ml was added to the column to prevent drying before applying the sample and 1 ml of blood was poured into the column reservoir and drawn slowly through the column. Elution of pentoxiphylline was performed with 2 ml of ethyl acetate, evaporated to dryness at 60 °C under N_2 and redissolved in 10 μl. From this eluate 1 ml was injected into a Hewlett-Packard 6890 GC (Palo Alto, Calif.) coupled with a flame ionization detector (FID) and equipped with a HP-ultra 2 capillary column (cross-linked methylphenylsilicone 12.5m × 0.2 mm × 0.33 μm film thickness). The oven temperature was programmed from 130 °C (hold 1 min) to 250 °C at 15 °C/min (5 min hold). Injector and detector temperatures were 280 °C and 290 °C, respectively. The helium carrier flow was 0.8 ml/min. Under these conditions the retention times of pentoxiphylline and SKF-525A were 14.8 and 9.5 min, respectively.

Regression of four concentrations was good ($r = 0.998$) and the recovery from whole blood ranged between 80–91%.

Plasma levels of pentoxiphylline in the sample were 32.5 μg/ml (mean of five determinations).

There was no evidence of alcohol or other drugs, including drugs of abuse.

Results and discussion

We feel that the fatal outcome of the patient was directly related to the massive intake of pentoxifylline. This resulted in cardiac failure and respiratory insufficiency, leading to severe acidosis. The clinical picture was well established on admission, 2 h after the intake. A peak blood concentration is expected to be reached between 2 and 4 h after ingestion (USPDI 1995). Bleeding complications have usually been reported in cases with known bleeding risk factors (Dettori et al. 1989; Oren et al. 1995; Reynolds 1993). Although our patient did not have any bleeding risk factor, it is our opinion that the presence of blood in the upper gastrointestinal tract was related to the drug intake. In this respect the massive ingestion and the extremely high blood levels reached should be emphasized.

In the present case, the role of bleeding did not seem to be as relevant as the peripheral vascular dilatation and dis-

turbance of the normal heart rhythm leading to shock. This was a non-reversible condition in a patient with diabetic vasculopathy and severe coronary atherosclerosis. The role of other drugs in the pathogenesis of shock was ruled out by toxicological investigation of the gastric contents, where only pentoxifylline was found. The serum levels of glucose were only slightly increased and inconsistent with hypoglycemia and ketoacidosis.

Arrhythmia is a well-recognised adverse effect of pentoxifylline, but its occurrence has rarely been documented (Reynolds 1993: Snazjder and Bentur 1984; USPDI 1995). To the best of our knowledge in the only case where ECG was recorded bradycardia and first and second degree atrioventricular block were registered (Snazjder and Bentur 1984). In this case the amount ingested was much lower (4–6 g) than in our case, and the patient, a 22-year-old healthy woman, recovered completely.

Finally, it is worth noting that the plasma concentration reached was as high as 32.5 μg/l for a therapeutic range between 0.8 and 1.8 (Moffat et al. 1986).

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