Survival after massive intentional overdose of paraquat

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To the Editor: Survival following oral ingestion of a large volume of paraquat is rare. Our patient ingested approximately 200 ml of paraquat and survived, following aggressive intervention. He developed oral pharyngeal ulceration, acute lung injury, haematemesis, haemoptysis and renal failure. He was treated with a combination of pulse methylprednisolone, vitamins C and E, and N-acetylcysteine. We propose a rationale for high-dose antioxidant treatment in addition to corticosteroids and intensive care.

Case report

A 20-year-old man was referred to our critical care unit 16 hours after the intentional ingestion of several mouthfuls of paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride (Gramoxone; Syngenta, Namibia)), taken directly from a 5-litre container. He vomited approximately a cupful of blood several hours after the ingestion, and vomited greenish fluid several times thereafter. He was given milk by his family, taken to a local hospital and transferred to our care.

On admission the patient was lucid and had normal levels of arterial blood gases. His blood pressure was 130/70 mmHg, his pulse rate 80 beats/min and his respiratory rate 20/min; urea, creatinine and electrolyte levels were normal; the white cell count was 1.6×109/l; examination of the urine showed 2+ blood and protein; and the chest radiograph was normal. Serum creatinine kinase peaked at 532 U/l on day 3 (MB fraction 10%). Liver function was normal. His posterior pharynx was erythematous. Immediate management comprised 50 g activated charcoal 4-hourly per nasogastric tube until his stools were black (day 5), and intravenous 0.9% saline 80 ml/hour.

Aggressive treatment was introduced in view of the grim prognosis. He was given intravenous methylprednisone 1 g stat and daily for 3 days, vitamin C 100 mg 4-hourly for 14 days, and an infusion of N-acetylcysteine at 150 mg/kg for 1 hour, 50 mg/kg over the next 4 hours, then 100 mg/kg daily for 4 days. Vitamin E, 50 mg daily, was commenced on day 5 for 12 days, when oral medication was possible after cessation of activated charcoal treatment.

Renal failure developed on day 2; haemodialysis was commenced on day 5 and continued up to day 15. The patient became tachypnoeic and hypoxic on day 3 and had bilateral chest crackles on auscultation. A chest radiograph showed bilateral mild infiltrates and he was given supplemental 40% oxygen via a facemask. Renal function returned to normal. His hospital stay was complicated by episodes of haemoptysis, nosocomial pneumonia on day 14, and right axillary and subclavian vein thrombosis on day 20 attributed to a central venous catheter. He was discharged on day 15 and continued on oral anticoagulant treatment.

Discussion

Survival following a massive overdose of paraquat is extremely rare. We used a combination of corticosteroid and antioxidant treatment on the hypothesis that mortality is due to respiratory failure and that the toxicity is primarily oxidant mediated. We were unable to measure paraquat levels as the recommended urine dithionite test for paraquat was not available at our institution. The volume of paraquat solution ingested by our patient was estimated to be about 200 ml (several mouthfuls). The lethal dose according to the manufacturer is 3 - 5 mg/kg (10 - 15 ml of the 20% solution). The history and clinical course of the patient conformed to massive ingestion of paraquat attenuated by the combination of intensive care and high-dose antioxidant and corticosteroid treatment.

Accidental paraquat poisoning is common globally because of its widespread use as a herbicide in agriculture. Systemic absorption usually occurs via exposed skin during spraying of paraquat. High-dose exposure occurs with oral ingestion, usually as a suicide attempt. Based on the low lethal dose, oral ingestion is almost invariably fatal because of progressive diffuse alveolar damage and rapidly progressive acute respiratory distress syndrome (ARDS).

Approximately 20% of ingested paraquat is absorbed.[1] An empty stomach and pre-existing gastrointestinal ulceration increase absorption. Toxicity is manifested by oedema and ulceration of the mouth, pharynx, oesophagus, stomach and intestines. Paraquat has multiple sites of toxicity. It is rapidly metabolised to peroxynitrite, the effects of which depend on the site of action as well as the levels of antioxidant achieved *in vivo* and duration of exposure.[2] It is a strong oxidant and nitrating intermediate that reacts with proteins, lipids and DNA via direct or radical mediated mechanisms. This results in altered enzyme activities and signalling pathways[2] and a major disruption of nicotinamide adenosine dinucleotide phosphate (NADPH)-dependent cellular processes.[3]

The lungs are the primary target organ of paraquat toxicity and account for the mortality in most instances.[4] Pulmonary damage is a result of oxidative stress to the alveolar epithelium which actively takes up paraquat (and

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its metabolites). Acute pulmonary oedema and early lung damage may occur within a few hours of acute severe exposure. Haemorrhage, proteinaceous oedema fluid, and leucocyte infiltration into alveolar spaces may occur, followed by rapid proliferation of fibroblasts.[5] Delayed pulmonary damage resulting in pulmonary fibrosis occurs between 7 and 14 days after ingestion. Our patient appears to have had an attenuated delayed pulmonary reaction, probably as a result of the therapeutic intervention. He had several episodes of haemoptysis and mild pulmonary infiltrates that did not progress to florid respiratory failure and ARDS. Reversal of pulmonary fibrosis several months after ingestion of paraquat has been reported.[5] Circulatory failure has also been reported in patients who ingested a large volume of concentrated (20%) solution. Shock and death within 48 hours of ingestion has been reported.[4]

As toxicity progresses, centrizonal hepatocellular injury may develop, manifesting as hepatocellular enzyme elevation and hyperbilirubinaemia. Renal toxicity may play an important role in determining survival because normal tubular cells actively secrete paraquat into the urine, thereby decreasing its toxicity. Haemodialysis was only introduced in our patient when renal failure manifested; he recovered renal function within 14 days.

Other sites of injury include skeletal and cardiac muscle, which manifests with elevated muscle enzymes. Our patient had a transient elevation in his muscle enzymes which peaked on day 3. We submit that muscle injury might have been attenuated by treatment.

The results of management of paraquat poisoning have been disappointing. These have included adsorbents, pharmacological approaches[6] and radiotherapy,[7] haemodialysis and haemoperfusion.[8] Our patient's therapeutic regimen maximised antioxidant effects with available agents, including N-acetylcysteine based on the regimen for paracetamol overdose, vitamin C, and vitamin E. N-acetylcysteine significantly improves mortality in paraquat-intoxicated rats,[9] and its use in lung disease was extrapolated from its application in idiopathic pulmonary fibrosis.[10] High-dose corticosteroid treatment was determined from the study by Chen *et al*.[11] Methylprednisolone improved histology but not oxygenation in a rat model of paraquat-induced lung injury.[12] Other studies, however, have not shown improvement in histology and surfactant in rats that were pre-treated with methylprednisolone.[13] Repeated pulses of methylprednisolone and cyclophosphamide with continuous dexamethasone therapy showed a 54% improvement in survival (p=0.027) in patients with a 50 - 90% predictive mortality.[14,15]

Intravenous cyclophosphamide has been recommended,[16] but we elected not to use it in our patient as it may be toxic and its therapeutic rationale is not clear. Decreased vitamin C and E levels have been demonstrated in rats after paraquat administration,[17] and vitamin E has neuroprotective effects on rat striatal neurons after oxidative stress caused by paraquat, providing further rationale for the use of these vitamins.[18] These antioxidants might have contributed to the treatment of oxidant stress associated with paraquat toxicity.

There have been no reports on the use of N-acetylcysteine together with methylprednisolone and other antioxidants such as vitamins C and E. We propose that our patient survived a potentially lethal dose of paraquat because of the massive doses of antioxidants administered. Fig. 1 outlines the rationale for our therapeutic intervention and the proposed mechanism of toxicity. Human studies are impossible, and prevention of paraquat toxicity is important. We recommend that large doses of antioxidants and corticosteroids are given empirically in the event of poisoning, which may also be a potential therapeutic strategy for acute lung injury of other causes.

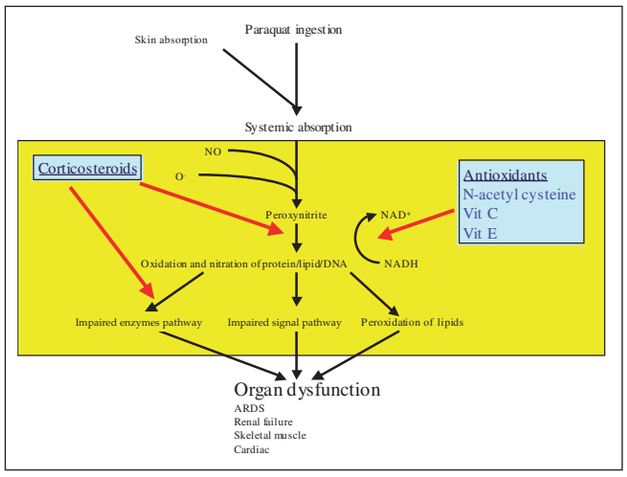

Fig. 1. Schematic representation of the metabolism, toxicity and proposed sites of action of drugs (red arrows) used in the management of paraquat toxicity.

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Coronary spasm and thrombosis in a bodybuilder using a nutritional supplement containing synephrine, octopamine, tyramine and caffeine

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To the Editor: A young, previously healthy bodybuilder suffered an acute myocardial infarction in the absence of known cardiovascular risk factors or demonstrable atherosclerotic plaque. The infarction probably resulted from coronary spasm, platelet activation and *in situ* thrombosis triggered by the chronic consumption of a 'nutritional supplement' which contains synephrine, octopamine, tyramine and caffeine.

The 39-year-old bodybuilder presented after developing new-onset angina pectoris with vegetative symptoms during a bodybuilding competition. He had no previous medical history or cardiovascular risk factors, and denied ever using androgenic anabolic steroids. He had been involved in competitive bodybuilding for 7 years. He had been taking for several years a 'nutritional supplement' that contains synephrine (oxedrine), octopamine, tyramine (sympathomimetic amines) and caffeine. The preparation also contains several 'nutrients', of which the herb St John's wort has significant pharmacological actions on the nervous system.[1] In the 3 months preceding the competition concerned, he had taken a daily dose equivalent to 40 mg synephrine, 400 mg caffeine, and an unspecified amount of tyramine and octopamine. Synephrine is more potent than the other sympathomimetic amines. Its action is similar to that of phenylephrine, an alpha-adrenergic agonist,[2] and it has been used for treating hypotension in doses of about 100 mg 3 times a day. Octopamine has about one-hundredth the potency of noradrenaline.

The patient had restricted his fluid intake and increased his carbohydrate intake during the 36 hours before the competition. Physical examination was normal. The electrocardiogram showed a wide right bundle-branch block that resolved after several hours, and 1 mm ST-segment elevation in leads II, III, aVF, and V4-6. There was evidence of renal impairment, with creatinine at 171 µmol/l and urea at 11 mmol/l, and creatine kinase (CK) levels of 8 500 IU/l. The troponin T level was normal on admission, but rose to 0.53 ng/ml after 6 hours, and 1.9 ng/ml after 24 hours. Echocardiography demonstrated a dyskinetic basal interventricular septum, with mild biventricular hypertrophy. Oral aspirin, clopidogrel and bisoprolol and intravenous nitroglycerine, enoxiparine and eptifibatide were initiated, and he was hydrated with intravenous 0.9% saline. Coronary angiography showed a thrombus in the proximal left anterior descending artery, with diffuse spasm in the mid- and distal segments (Fig. 1), which resolved after the administration of intracoronary nitroglycerine. A 4.5 mm bare metal stent covering the lesion was successfully positioned. His low-density lipoprotein, high-density lipoprotein and triglyceride levels were respectively 2.1, 0.31 and 1 mmol/l, the fasting homocysteine level was normal, and anti-phospholipid antibodies were absent. He was discharged fully recovered and remains symptom-free 6 months later.

Discussion

The acute myocardial infarction in this young, previously healthy bodybuilder in the absence of known cardiovascular risk factors or demonstrable atherosclerotic plaque was probably caused by coronary spasm, platelet activation and *in situ* thrombosis.

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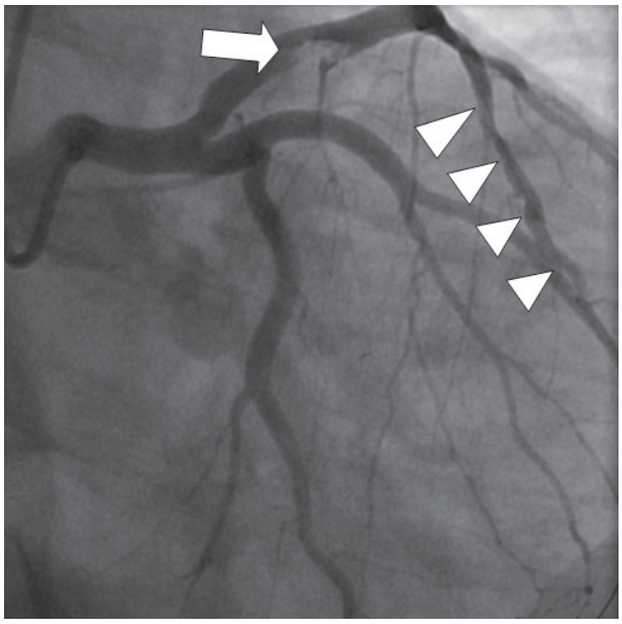

Fig. 1. Diagnostic coronary angiogram (postero-anterior view), demonstrating thrombus in the proximal left anterior descending coronary artery (arrow), and diffuse spasm of the mid and distal segments of the vessel (arrowheads).

The USA's Food and Drug Administration (FDA) banned the sale of products containing ephedrine alkaloids in 2004 because of associated cardiovascular toxicity.[3] Synephrine and octopamine are structurally similar to norepinephrine, and have been associated with acute myocardial infarction and ischaemic colitis. [4-7] Both are trace endogenous bioamines, agonists of the α1, α2, β1 and β3 adrenoreceptors, are found in human plasma, platelets, sympathic nerves and adrenal tissue, and are present in *Citrus aurantium* (Seville orange, bitter orange), an ingredient in dietary supplements marketed for weight loss.[8-10] In animal studies, synephrine increased cardiac output and caused vasoconstriction and ventricular arrhythmias.[11,12] Bitter orange has been identified as a cause of resistant hypertension, syncope, myocardial infarction, tachycardia and ventricular fibrillation, and exacerbated coronary spasm in tobacco smokers.[5] Prolonged administration, or the combined consumption, of synephrine with octopamine and caffeine may result in haemodynamic effects.[13-16] A single dose of bitter orange extract containing the equivalent of 50 mg synephrine significantly increased the systolic and diastolic blood pressures, as well as the heart rate, of healthy young adults for up to 5 hours.[17]

The risk of adverse cardiovascular events may be higher in persons with pre-existing underlying cardiovascular disease. Caffeine enhances the cardiovascular and central nervous system effects of adrenergic amines though augmentation of catecholamine release.[18-20] The enhanced sympathetic activity increases platelet reactivity. Although an underlying atheromatous plaque has not been excluded with absolute certainty in our patient, it seems very likely that use of a nutritional supplement containing synephrine, octopamine, tyramine and caffeine, combined with intravascular dehydration and impaired renal function, triggered coronary spasm and thrombosis of a major proximal coronary artery. Constituents of St John's wort are inhibitors of serotonin, noradrenaline and dopamine uptake in the synaptic cleft,[1] which may potentiate the effects of alpha-adrenergic stimulants and thereby enhance their vasoconstrictor activities.

The safety of over-the-counter supplements containing synephrine has been called into question.[4-8] Consumers consider dietary supplements to be safe, but these are currently not subjected to scientific scrutiny, and some contain potentially harmful ingredients. The use of supplements containing the combination of synephrine, octopamine, tyramine and caffeine may constitute a risk of cardiovascular toxicity. There is a need for centralised monitoring of clinical adverse events in consumers using nutritional supplements.

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