Treatment of Paraquat Poisoning with the Membrane Oxygenator

A Case Report

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SUMMARY

A fatal case of progressive pulmonary fibrosis in a 13-year-old boy, due to poisoning by the weed-killer paraquat, is described. Attempted treatments included extracorporeal circulation. The management is discussed in the light of the histological observations, and the pathophysiology of the condition.


Paraquat (1,1'-dimethyl-4,4'-bipyriHium chloride) is a herbicide which is used throughout the world. It is marketed commercially as a 20% concentrate (Gramoxone), a reddish-brown liquid. Cases of paraquat poisoning have been widely reported and over 200 deaths have occurred after accidental or intentional ingestion of the chemical. The lethal dose is not known, but ingestion of very small amounts, estimated at 15 - 20 ml paraquat, has caused death. We recently treated a patient with paraquat poisoning. To our knowledge, this is the first case of paraquat poisoning to be reported in South Africa. This herbicide is readily available to the farming community. We believe the extremely severe toxicity of this substance has not been appreciated in South Africa.

CASE REPORT

Clinical History

The patient was a 13-year-old Coloured boy who lived on a fruit farm. Three weeks before admission to Groote Schuur Hospital he had been ill for a few days with a painful throat and vomiting. Although this subsided, he remained generally unwell and listless. A week before admission he became short of breath and 4 days later he was admitted to Hottentots-Holland Hospital with increasing dyspnoea, general malaise and mild fever. Bronchopneumonia was diagnosed and he was treated with ampicillin. Three days later he was transferred to Groote Schuur Hospital as he failed to respond to antibiotics. He denied any contact with toxins, pigeons or any other substances known to cause alveolitis.

On admission the patient was well nourished and had a temperature of 37.6°C. He was cyanosed and the most striking physical sign was his tachypnoea of 60 breaths per minute. There were a few crepitations in the chest and breath sounds were bronchovesicular throughout. There were no signs of cardiac failure.

Laboratory Investigations

The patient's urine contained a trace of protein. His haemoglobin concentration was 12 g/100 ml and the white cell count 12 640/μl with 65% polymorphs, 30% lymphocytes and 5% eosinophils. The patient's ESR was 112 mm/1st h, creatinine 0.6 mg/100 ml and blood urea 24 mg/100 ml.

Serum bilirubin, alkaline phosphatase and aspartate aminotransferase were all within normal limits. The pO2.

Fig. 1. Chest X-ray film on admission, showing diffuse pulmonary infiltrate.
on 28% oxygen by mask was 41 mmHg, the pCO₂ 36.2 mmHg, and the pH 7.36. A chest X-ray film showed diffuse bilateral infiltration (Fig. 1). An air bronchogram was visible in the left upper zone.

A clinical diagnosis of interstitial pneumonia of unknown cause was made. To establish the diagnosis an open lung biopsy was performed. At thoracotomy it was noted that the lungs were woody, poorly aerated and diffusely thickened. A frozen section indicated that the diagnosis was that of a diffuse interstitial fibrosis. There was no indication of granulomatous disease or of active infections such as tuberculosis.

Treatment and Subsequent Progress

In view of these preliminary findings, steroid treatment was started. As anticipated, the patient required intermittent positive pressure ventilation postoperatively. He was extremely difficult to ventilate, requiring high pressures to maintain an adequate tidal volume. It was, however, possible to achieve a pO₂ of 76 mmHg by using an inspired oxygen concentration of 50%. By the following morning his oxygen tension on the same concentration of inspired oxygen had fallen to 50 mmHg, despite the use of positive end-expiratory pressure. Moreover, his lung compliance had deteriorated.

It was this rapid deterioration in gas transfer and compliance which made us reconsider the possibility of toxin, particularly paraquat ingestion, as a cause for the deterioration. Only then did the patient’s young friend confirm that the patient had drunk one mouthful of Gramoxone, a brown liquid, from a Coca-Cola bottle in which the herbicide was stored in a garage. Immediately after the ingestion of the Gramoxone, the patient had developed a sore throat and had subsequently vomited for 24-36 hours. Neither the patient nor his friend was prepared to admit this originally.

Subsequent treatment was designed to reduce the active inflammatory process and lower the alveolar oxygen tension as far as possible. Steroid treatment was continued. Cyclophosphamide was started in a daily dosage of 50 mg intravenously. Arterial oxygenation was maintained by placing the patient on right atrial to left atrial extracorporeal bypass, using a Travisol silicone membrane oxygenator. A blood flow of 3 l/min was maintained through the oxygenator.

Arterial oxygenation was maintained at the level of 60 mmHg with this perfusion. The lungs were initially ventilated with air and subsequently with an air and nitrogen mixture yielding an inspired oxygen concentration of 15%.

During the initial postoperative phase the patient required sedation and curarization. Neurological examination could not be adequately carried out until 12 hours after the start of bypass. By this time it was appreciated that there had been severe brain damage. The patient died 36 hours later. At the time of his death arterial oxygen tension was still being maintained at a level of 60 mmHg and we are unable to pinpoint the episode or episodes which resulted in brain damage. It would appear that it occurred before the patient was established on bypass in the ward. This episode illustrates the high risk of producing irreversible brain damage while transferring severely hypoxic patients within the hospital. At postmortem the brain showed cerebral oedema.

Pathological Findings

Histological examination of the lungs showed a widespread active fibroblastic proliferation with obliteration of the normal pulmonary architecture (Fig. 2). This process was noted to a roughly equal degree both interstitially and within the alveoli. There were conspicuous islands of squamous metaplasia scattered focally throughout the affected fields. These islands were similar to the so-called ‘tumourlets’ which are sometimes seen in scarred lung tissue (Fig. 3). Other notable features included cuboidal metaplasia of alveolar lining cells, focal aggregates of polymorphonuclear leucocytes, a mild lymphocytic inflammatory infiltrate and occasional bundles of hypertrophic smooth muscle fibres. There was no evidence of necrosis, arteritis, granulomas or intra-alveolar hyaline membranes. Special staining techniques showed that the underlying alveolar framework had been retained and that mature collagen had not yet been laid down. These changes were interpreted as being compatible with the pulmonary changes seen in paraquat poisoning.

**DISCUSSION**

This patient showed the typical natural history of the effects of an intermediate dose of paraquat poisoning in which death occurred from progressive respiratory failure. Ingestion of larger quantities of paraquat lead to rapid pulmonary oedema with haemorrhage. Coincidental
with these changes may be rapid development of renal and hepatic failure. Death occurs within a few days. At the other end of the spectrum, ingestion of small amounts of paraquat results in general systemic illness, including sore throat, nausea, some liver damage and, perhaps, some renal damage and, after 4 days to 3 weeks, progressive pulmonary damage with a reduced gas transfer and compliance. Provided the pulmonary damage is not sufficient to require active supportive measures, spontaneous recovery is possible. As far as we know, patients with lung disease as extensive as that of our patient, have never been known to recover. Reports of recovery after ingestion of paraquat vary and the over-all mortality rate is between 33% and 50%. However, once the pulmonary complications have developed, the survival rate is very much lower.

The mechanism of paraquat toxicity seems to be related to the production of superoxide ions \( \text{O}_2^- \), a highly toxic and unstable species which is capable of producing direct tissue damage. Superoxide radicals are removed under normal circumstances by superoxide dismutase which catalyses the formation of hydrogen peroxide and oxygen. Hydrogen peroxide itself is capable of producing further cell damage by peroxidation of lipid components of cell membranes. The action of paraquat explains the natural history of the disease which it causes. At first there is a generalized effect on the tissues, whereby all tissues, including the gastro-intestinal tract, liver and kidneys, are affected. Subsequently, the burden falls on the lungs where the highest pressure and quantity of oxygen is present. It also supports the clinical observation that oxygen therapy aggravates the condition. This concept of the natural history has been confirmed in studies on laboratory animals. Paraquat binds avidly to soil and is inactivated. In agronomic use, therefore, any spillage is immediately rendered harmless.

Treatment is generally unsatisfactory. First-aid treatment includes the administration of fuller’s earth or bentonite by stomach tube and effective washout and purgation. Forced diuresis, haemodialysis and charcoal column perfusion have been used in an attempt to remove the absorbed paraquat from the plasma. There is no clear indication that any of these approaches has altered the natural history significantly.

Superoxide dismutase has been used to try to increase the elimination of superoxide ions by increasing their rate of metabolism. Some authorities claim a reduction in the rate of pulmonary fibrosis if corticosteroids and cyclophosphamide are used. The obvious treatment for relentless fibrous replacement of the lungs is lung transplantation which has been attempted.

It is important for the pathologist to consider the diagnosis of paraquat poisoning in the differential diagnosis of diffuse pulmonary fibrosis of short duration. A morphological feature shown to be of diagnostic significance is the presence of young, active intra-alveolar fibroblastic proliferation which tends to obliterate the alveolar septal outlines. The significance of the islands of squamous metaplasia resembling 'tumourlets' seen in this patient is uncertain, but these may represent regenerative terminal bronchiolar epithelium. Special staining techniques usually show well-preserved interalveolar septa and the absence of mature collagen. The presence of hyaline membranes and inflammatory cells varies from case to case. Accurate diagnosis of paraquat poisoning from frozen section obtained by open lung biopsy may be difficult without clinical suspicion.

Our patient was diagnosed too late to benefit from the first-aid or other measures designed to remove paraquat from the circulation. We were unable to detect any paraquat in his urine, which suggests that the toxin was already tissue-bound. By the time we made the diagnosis, respiratory supportive measures were essential. Our approach was to maintain life for a sufficiently long period for natural resolution to take place. This cannot occur in the presence of high alveolar oxygen tension. It was our intention to leave him on bypass for up to 2 weeks, while ventilating him with an air/nitrogen mixture. This technique of bypass has previously been used for this length of time in other pathological conditions. Had spontaneous remission not occurred on bypass, lung transplantation would have been the next most logical step.

REFERENCES

Fig. 3. Islands of squamous metaplasia which resemble 'tumourlets' (high-power photomicrograph \( \times 320 \) of lung biopsy specimen).