Cyclophosphamide treatment of paraquat poisoning

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Poisoning with the herbicide paraquat will result in one of three clinical syndromes. Mild poisoning is associated with oral mucosal irritation and ulceration and gastrointestinal discomfort, but recovery usually occurs with simple supportive measures. In contrast, severe poisoning, which can occur as a result of the ingestion of as little as one mouthful of the agricultural preparation, leads to death within a few days of admission from a combination of respiratory, hepatic and renal failure and cardiovascular collapse despite full intensive care support. Less severe poisoning is commonly associated with acute renal failure, hepatitis, and progressively more severe respiratory failure which frequently results in death from inadequate gas exchange secondary to a proliferative bronchiolitis/alveolitis which may occur as late as six weeks after ingestion.\(^1\) After poisoning, but before the development of respiratory failure severe enough to require ventilatory support and sedation, there is often an interval which the patient, close relatives, and health care staff find extremely distressing. It is probably in this group of patients that active treatment is most likely to achieve benefit.

The lung is a major target for paraquat toxicity because of the active, energy-dependent uptake of the herbicide by alveolar cells, subsequent cellular reduction of the paraquat to a monocation radical and, in the presence of oxygen, the formation of a dication and the reactive superoxide species \(\text{O}_2^–\). It is thought that amplified generation of further reactive oxygen species results in profound cellular injury and pulmonary fibrosis.\(^3\) In animals and cell suspensions pretreatment with nitric oxide synthetase inhibitors or paraquat-specific monoclonal antibodies or Fab fragments can reduce injury.\(^4\) Physicians caring for patients with paraquat poisoning would welcome a treatment that influenced the outcome, particularly as a review in 1990 commented that vitamin E, superoxide dismutase, ascorbic acid, desferrioxamine, selenium, radiotherapy, niacin, N-acetylcysteine, various polyamines, \(\beta\)-propranolol, fibrinolytic agents, colchicine, corticosteroids, other immunosuppressive drugs, and cyclophosphamide were not of proven value.\(^6\) The rapid fall in blood levels of paraquat, and the relative inefficiency of haemodialysis or charcoal haemoperfusion in removing the poison, probably explains the lack of influence on survival of treatments whose main effect is to eliminate paraquat.\(^7\)

Treatments which are only effective if given before the paraquat are clearly of little use clinically. Encouraging results of a treatment regimen which included cyclophosphamide and dexamethasone was first published 10 years ago,\(^8\) and a similar study on 47 patients was reported in 1992.\(^9\) In this paper no beneficial effect was seen even if the analysis excluded those in the trivial and mortally poisoned groups. It is difficult to reconcile the results of these two papers but case selection could explain the results. Cyclophosphamide is inert until activated by microsomal enzymes. In the presence of liver disease dosing is not straightforward and it is possible that this may have influenced the results.\(^10\)

In this edition of Thorax Lin et al report on their experience in patients with paraquat poisoning, some of whom received cyclophosphamide and methylprednisolone as part of their management.\(^11\) Their series includes 87 patients which, since there are only approximately 14 deaths per year recorded from this cause in England and Wales, is a volume of experience that no British hospital can match.\(^12,13\) They report the outcome of a subgroup of patients with moderate to severe poisoning as judged by a urine test on admission and who subsequently survived a further three days. An historical control group is compared with a group who received two 1 g doses of cyclophosphamide on consecutive days and three 1 g doses of methylprednisolone daily for three days. Although the paper can be criticised for its reliance on urine estimations, the interpretation of plasma measurements are even more critically dependent on an accurate estimation of the time of ingestion.\(^14\) The urine test is easy to perform and gives a reasonable guide to the likely prognosis.\(^15\) A urine test may well be all that is available in the areas where poisoning with paraquat is most common. The doses of cyclophosphamide and methylprednisolone are well below those used in many other serious disorders which have a better prognosis than moderate to severe paraquat poisoning. In the subgroup 12 out of 16 patients who had received cyclophosphamide and methylprednisolone survived compared with only five survivors of 17 in the standard therapy group. Predictably, no serious side effects were reported. Randomised, controlled trials of treatment of a condition as rare as paraquat poisoning are clearly difficult to carry out and, in the meantime, it is important to base clinical judgements on therapy on the best available evidence. Despite the fact that this study is inadequately controlled, open, and liable to more than one interpretation, the size of the experience, the safety profile of the therapy, and the favourable outcome in the treated group make a persuasive case for recommending the treatment, at least until a more effective alternative is described.

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