Original articles

Pulse therapy with cyclophosphamide and methylprednisolone in patients with moderate to severe paraquat poisoning: a preliminary report

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Abstract

***Background* – Severe paraquat poisoning causes considerable morbidity and mortality. High doses of cyclophosphamide and dexamethasone have been used to treat patients with paraquat poisoning, but with mixed results. The use of pulse methylprednisolone and cyclophosphamide was investigated in the treatment of moderately severe paraquat poisoning.**

***Methods* – During a six-year period 87 patients with paraquat poisoning were admitted to hospital, of whom 33 had moderate to severe intoxication. Seventeen patients received conventional treatment and served as historical controls, and 16 received intravenous infusions of cyclophosphamide 1 g daily for two days and methylprednisolone 1 g daily for three days.**

***Results* – There were no differences between the groups in age, sex, severity of paraquat poisoning (as assessed by urine dithionite tests), or in the time elapsed from ingestion to presentation at hospital or to the beginning of haemoperfusion. No differences were seen in biochemical measurements on the third day after paraquat poisoning. The mortality in the pulse therapy group was lower than that in the control group (4/16 (25%) versus 12/17 (70·6%), p = 0·01). All fatalities were from progressive respiratory failure.**

***Conclusions* – Pulse therapy with cyclophosphamide and methylprednisolone may be effective in preventing respiratory failure and reducing mortality in patients with moderate to severe paraquat poisoning. Further controlled studies are needed to confirm this and to establish the mechanisms.**

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Keywords: paraquat, sodium dithionite urine test, pulse therapy, cyclophosphamide, methylprednisolone.

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Paraquat is a widely used bipyridyl contact herbicide with a good safety record when used properly. Most cases of paraquat poisoning are due to suicidal ingestion of the compound. There are three stages of severity of paraquat poisoning[1]: (1) mild poisoning can cause oral irritation and gastric upset, but recovery is usually complete; (2) moderate to severe poisoning may result in acute renal failure, hepatitis and pulmonary fibrosis often leading to death after 2–3 weeks; and (3) acute fulminant poisoning causes death within a few days from multiple organ failure and cardiovascular collapse.

The treatment of paraquat poisoning – which includes adsorbents, drugs,[2] radiotherapy,[3] haemodialysis, and haemoperfusion[4] – is disappointing. In one study dexamethasone given intravenously in a dose of 8 mg three times a day for two weeks and then orally in a dose of 0·5 mg three times daily for two weeks and intravenous cyclophosphamide in a dose of 5 mg/kg body weight daily in three doses for two weeks or until a maximum cumulative dose of 4 g was reached was associated with a 75% survival rate.[5] However, another study[6] which used the same treatment protocol did not show any benefit. Most deaths following ingestion of paraquat occur from pulmonary fibrosis and respiratory failure. Because of encouraging reports of the use of pulse therapy with cyclophosphamide 1 g/day and methylprednisolone 1 g/day for three days in patients with severe lung damage due to systemic lupus erythematosus (SLE)[7 8] and Wegener's granulomatosis,[9] we have investigated its use in patients with moderate to severe paraquat poisoning.

Methods

The study was approved by the medical ethics committee of Chang Gung Memorial Hospital and all patients gave informed consent. In all patients with suspected paraquat poisoning, urine samples, taken on arrival at the emergency department, were tested by the dithionite reaction. The sodium dithionite test is based on the reduction of paraquat by sodium thionite under alkaline conditions to its stable blue radical ion, a "navy blue" or "dark blue" colour indicating significant paraquat ingestion and subsequent poor prognosis.[10] Patients were

Clinical data of the two study groups

	Conventional therapy group (n=17)	*Pulse therapy group (n=16)*
Age (years)	31·7 (10·2)	29·4 (14·4)
M:F	9:8	7:9
Acute renal failure*	10 (58·8%)	10 (62·5%)
Serum creatinine (μmol/l)*	209·2 (130·8)	189·8 (105·0)
Hepatitis*	5 (29·4%)	6 (37·5%)
Serum alanine aminotransferase (ALT) (U/l)*	36·5 (18·8)	35·6 (46·8)
Hypoxia*	3 (17·6%)	4 (25%)
Arterial blood Pao_2 at room air (kPa)*	10·9 (2·0)	11·7 (1·8)
Mortality	12 (70·6%)	4 (25%)†

* Biochemical data of renal, liver, and lung functions on the third day after paraquat ingestion (for definition see Methods section).
† $p<0·02$ (χ^2 with Fisher's exact test).

therefore classified as having moderate to severe poisoning if the urinary dithionite reaction yielded a navy blue or dark blue colour, or mild poisoning if the urine paraquat tests were colourless or light blue.[10] There were no facilities to measure plasma levels of paraquat.

From July 1992 to June 1994 41 patients with paraquat poisoning were admitted, 16 of whom had moderate to severe poisoning and were admitted within 24 hours of ingestion and survived for more than three days. These were enrolled in the study and were treated with pulse therapy of cyclophosphamide and methylprednisolone. Thirteen patients with fulminant poisoning and 12 with mild poisoning were excluded. The control group comprised 17 patients with moderate to severe poisoning, who were admitted within 24 hours of ingestion and who survived for three days, of the total of 46 admitted with paraquat poisoning between July 1989 and June 1991. Eleven patients with fulminant poisoning who died within three days of intoxication and 18 patients with mild poisoning were excluded.

TREATMENT PROTOCOL

After gastric lavage with normal saline, active charcoal in magnesium citrate solution was given to both groups of patients through a nasogastric tube to prevent further absorption of paraquat from the gastrointestinal tract. All patients were haemoperfused for eight hours within 24 hours of paraquat ingestion. In the treatment group all patients received 1 g cyclophosphamide daily for two days and 1 g methylprednisolone daily for three days following haemoperfusion. The infusions were administered over two hours. Arterial blood gas tensions, white cell count, serum creatinine levels, chest radiography, and liver function tests were regularly checked.

DEFINITIONS[6]

Patients were considered to have developed acute renal failure if the serum creatinine level rose above 130 pmol/l or hepatitis if serum alanine aminotransferase (ALT) levels were >70 U/l (normal value <35 U/l) or total bilirubin was >35 pmol/l. Patients were considered to be hypoxic if the arterial oxygen tension (Pao_2) when breathing room air was <9 kPa.

DATA ANALYSIS

The measurements in the two groups were compared using unpaired t tests, and the outcome of the 33 patients in the two groups was compared by the χ^2 and Fisher's exact tests. A p value of <0·05 was considered significant.

Results

Of the 33 patients enrolled in the study, most were young adults. All were suicidal and had ingested 24% liquid paraquat concentrate. There were no differences between the groups in age, sex, time elapsed from ingestion to arrival at the emergency room (6·41 (6·57) versus 6·00 (5·80) hours), the beginning of haemoperfusion (8·59 (7·38) versus 8·29 (5·69) hours) or the timing of urine paraquat tests following ingestion (7·00 (6·93) versus 6·21 (4.55) hours), and the severity of paraquat poisoning (seven "navy blue" and nine "dark blue" versus six "navy blue" and 11 "dark blue"). There was no difference in the incidence of acute renal failure, hepatitis, or hypoxia on the third day following paraquat ingestion in the two groups (table).

The fatality rate was significantly lower in the treatment group (25%) than in the control group 12/17 (70·6%) ($p<0·01$, χ^2 test; corrected by Fisher's exact test, $p<0.02$). All fatalities were from respiratory failure.

Leucopenia (white blood count <3000) was the only major complication of pulse therapy and occurred in six of the 16 cases (37·5%), but in all spontaneous recovery was complete within one week. Pulse therapy was well tolerated, although minor complications including hair loss and acne were noted in some patients.

Discussion

These data suggest that pulse therapy with cyclophosphamide and methylprednisolone improves the prognosis of patients with moderate to severe paraquat poisoning. All deaths were from progressive respiratory failure and a reduction in inflammatory change in the lungs is the likely mechanism. There were no severe complications, which suggests that it is safe and well tolerated. Retrospective studies[10–12] have shown that both plasma and urine concentrations of paraquat within the first 24 hours of intoxication are good predictors of outcome. The absence of plasma paraquat concentrations is a limitation of this study, but plasma paraquat levels fall very quickly after an overdose and an error of an hour in the estimate of the time of ingestion can mean a change in survival from 30% to 70%.[13] The urine dithionite test can be performed easily and quickly, giving a reasonable guide to the severity of poisoning and likely prognosis[14] at the time of admission.

In conclusion, our results suggest that pulse therapy with cyclophosphamide and methylprednisolone may be an effective and safe way to treat patients with moderate to severe paraquat poisoning as determined by the urine dithionite test. Prospective controlled studies are required to confirm this observation.

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