Experience with paraquat poisoning in a respiratory intensive care unit in North India

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ABSTRACT

Introduction: Paraquat poisoning is an uncommon entity in India. We report our experience of managing five patients with paraquat poisoning using immunosuppressive therapy.

Methods: Retrospective analysis of 84 patients admitted with a diagnosis of poisoning over the last eight years was performed. The data were presented in a descriptive fashion.

Results: Five (5.9 percent) out of the 84 patients were admitted with a diagnosis of paraquat poisoning. All patients were mechanically ventilated. All patients had hepatic failure with median peak bilirubin being 22.1 +/- 15.1 mg/dL (range 8.4-45.5). Four of the five patients had renal failure (median peak creatinine 3.8 +/- 1.5 mg/dL; range 3.4-11.1) requiring renal replacement therapy. All patients were treated with intravenous methylprednisolone 15 mg/kg/day for three consecutive days and intravenous cyclophosphamide 10 mg/kg/day for two consecutive days, followed by intravenous dexamethasone 4 mg thrice a day until recovery or death. Two out of the five patients survived. Three died because of severe acute respiratory distress syndrome and multiorgan dysfunction syndrome.

Conclusion: Paraquat poisoning is an uncommon entity in India, and is associated with a high mortality rate. There is a potential role for immunosuppressive therapy in patients with moderate to severe poisoning.

Keywords: cyclophosphamide, immunosuppression, methylprednisolone, paraquat, poisoning

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INTRODUCTION

Poisoning by pesticides and other agricultural chemicals is a major public health problem worldwide, especially in the developing countries. There are about 20,000 annual fatalities and more than two million hospitalisations due to poisoning by pesticides and other agricultural chemicals[1]. Paraquat, a widely-used herbicide, remains a major cause of death in developing countries such as Pakistan and Sri Lanka. In fact, more than 200 deaths were reported in the first two decades after its widespread use began in 1958. Although freely available as a liquid concentrate (29.1%) in the Indian market for agricultural use, it is an uncommon poisoning in India with only a single case report described from India[2].

Paraquat is highly toxic and causes damage to the lungs, liver and kidneys. Paraquat poisoning can be classified into three categories, namely[3]: mild poisoning (20 mg paraquat ion per kilogramme of body weight) in which the patients generally have minor gastrointestinal symptoms but usually fully recover; severe poisoning (20-40 mg paraquat ion per kilogramme of body weight) in which the patients develop acute renal failure, acute lung injury and progressive pulmonary fibrosis with death occurring in two to three weeks from respiratory failure; and fulminant poisoning (40 mg paraquat ion per kilogramme of body weight) in which the patients develop multiple organ failure leading to death within hours to a few days after ingestion. In patients with "fulminant poisoning", death occurs due to circulatory failure in one to four days. Ingestion of smaller amounts primarily results in progressive pulmonary damage secondary to diffuse alveolar damage with resultant acute respiratory distress syndrome[3,4].

The cytotoxic effects of paraquat have been attributed to the generation of superoxide radicals after reduction of paraquat by intracellular oxidases and amplified generation of further reactive oxygen species results in profound pulmonary injury[5]. In this context, the use of immunosuppressive therapy (combination of glucocorticoids and cyclophosphamide) has been shown to be beneficial in improving survival in those patients with

moderate to severe poisoning and progressive pulmonary fibrosis[5]. We report our experience of treating five patients of paraquat poisoning with immunosuppressive therapy.

METHODS

The computer records of patients admitted during the period April 1998 to March 2006 to the Respiratory Intensive Care Unit (RICU) with a diagnosis of poisoning were reviewed. Patients with the admitting diagnosis of paraquat poisoning were selected. The original case records of the patients were then retrieved from the central registration department. Demographical information such as age and gender, clinical status at admission to ICU, including the details of organ failure, were recorded. Details of the clinical manifestations and serial investigations like liver and renal function tests, and arterial blood gases were recorded. Details of the patient's stay in RICU, APACHE II scores, treatment and outcomes were noted. At admission to the RICU, diagnosis of paraquat poisoning was established on the basis of the clinical history and documentation of the poisoning bottle.

Patients were classified to have renal dysfunction if the serum creatinine was between 1.2-3.4 mg/dL and renal failure if the creatinine was ≥3.5 mg/dL or if the urine output was less than 500 ml/day. Renal replacement therapy was initiated if the patient had complications such as oliguria, metabolic acidosis (pH <7.1) and fluid overload. Either hepatic dysfunction or hepatic failure was classified if the bilirubin was <6 mg/dL or ≥6 mg/dL, respectively. Patients with PaO_2/FiO_2 ratio of 200-300 or <200 as classified as having acute lung injury or acute respiratory distress syndrome, respecitvely. Cardiovascular dysfunction was said to be present if the patient had dopamine requirements <5 μg/kg/minute and cardiovascular failure if the dopamine requirements was ≥5 μg/kg/minute.

All patients with severe and fulminant paraquat poisoning were started on the same day of hospital admission on intravenous methylprednisolone 15 mg/kg/day for three consecutive days, intravenous cyclophosphamide 10 mg/kg/day for two consecutive days followed by intravenous dexamethasone four milligrams thrice a day until recovery or death[6,7]. The patients were clinically screened for any evidence of infection and routine blood cultures were performed in all patients. Informed consent was taken from all patients or their relatives as per protocol. The statistical package StatsDirect (StatsDirect version 2.5.6 for MS-Windows, StatsDirect Ltd, England, 2005. http://www.statsdirect.com) was used to perform the statistical analysis. Activity and outcome parameters of the respiratory ICU patients are presented in a descriptive fashion (mean ± standard deviation [SD] or median with range).

RESULTS

There were 1,290 admissions in the RICU during this period and 84 (6.5%) patients were admitted with a diagnosis of poisoning and acute respiratory failure (Table I). Organophosphorus compounds constituted the majority of cases of poisoning (61.9%). Five out of the 84 (5.9%) patients (two males, three females) were admitted with paraquat poisoning. All the patients were managed initially at a primary health centre where gastric lavage was performed in all cases. The mean (SD) dose of paraquat ingested was 28.8 (20.1) mg/kg body weight (median 30; range 6-60). The patients presented after a median of 18 (range 18-46) hours. All patients had ingested paraquat orally; the intent was suicidal in three cases, homicidal and accidental in one case each. The mean age of these patients was 21.4 years (SD 3.8; range 18-26). All patients had local corrosive symptoms, dyspnoea

Table I. Aetiology of poisoning in 84 patients admitted with respiratory failure to the respiratory intensive care unit.

Diagnosis	Number of patients (%) (n=84)	Mortality number (%) (n=17)
Organophosphates	52 (61.9)	8 (15.4)
Barbiturates	8 (9.5)	0
Paraquat	5 (5.9)	3 (60)
Benzodiazepines	4 (4.8)	0
Carbon monoxide	3 (3.6)	0
Others		
Unknown	3 (3.6)	1 (33.3)
Methanol	1 (1.2)	1 (100)
Ethanol	1 (1.2)	0
Lithium	1 (1.2)	0
Corrosive	1 (1.2)	1 (100)
Printer dye	1 (1.2)	1 (100)
Carbamate	1 (1.2)	0
Organochlorates	1 (1.2)	1 (100)
Mercury fumes	1 (1.2)	1 (100)
Opiates	1 (1.2)	0

and jaundice. None of the patients were febrile at admission or showed any clinical evidence of focus of infection. Routine blood cultures done in all patients were sterile.

The clinical presentations, investigations, hospital course and outcome of the patients are shown in Tables II and III. Chest radiographs revealed diffuse alveolar opacities in all the patients. The mean PaO_2/FiO_2 ratio at admission was 135.3 (SD 47.9, range 66.7-193.3) while the lowest PaO_2/FiO_2 ratio was 118.2 (SD 38.9, range 66-160). Four patients were mechanically ventilated while one patient was managed with controlled oxygen therapy (Table III). Two patients were managed with low tidal volume ventilation strategy with tidal volumes of 6 ml/kg, while two patients were managed with pressure-controlled ventilation. Four patients had oliguria and renal failure requiring renal replacement therapy (three – haemodialysis, one – continuous venovenous haemodiafiltration). All the patients developed hepatic failure during the hospital stay. All the patients received immunosuppressive therapy as per protocol.

Table II. Clinical presentation, investigations, hospital course and outcome of five patients with paraquat poisoning admitted to the respiratory intensive care unit.

Parameters	Results
Age, mean ± SD (years)	44.9 ± 12.6
Male/female	2/3
Clinical findings	
Fever	0
Local symptoms of corrosive burns	5
Oliguria	4
Jaundice	5
Dyspnoea	5
Intent of poisoning	
Suicidal	3
Accidental	1
Homicidal	1
Investigations, hospital course and outcome	
Consolidation on chest radiograph	5
Raised transaminases and alkaline phosphatase	5
Admission bilirubin, mean ± SD (mg/dL)	11.2 ± 7.9
Admission creatinine, mean ± SD (mg/dL)	6.5 ± 4.5
Peak bilirubin, mean ± SD (mg/dL)	22.1 ± 15.1
Time to peak bilirubin, mean ± SD (days)	5.6 ± 4.5
Peak creatinine, mean ± SD (mg/dL)	6.9 ± 4.2
Acute renal failure requiring renal replacement therapy	4
Modality of dialysis	3 HD, 1 CVVHD
PaO_2/FiO_2 score, mean ± SD	135.3 ± 47.9
Time to dialysis after presentation, mean ± SD (hours)	8.3 ± 3.3
APACHE II scores, median (range)	19 (13-22)
Duration of RICU stay, mean ± SD (days)	6.2 ± 5.8
Duration of hospital stay, mean ± SD (days)	6.8 ± 6.7
Survival	2

HD: haemodialysis; CVVHD: continuous venovenous haemodiafiltration; APACHE: acute physiology and chronic health evaluation; PaO_2: partial pressures of oxygen; FiO_2: fraction of inspired oxygen.

The median ICU and hospital stay was two (range 2-14) days and three (range 2-15) days, respectively. The hospital course was complicated by the occurrence of ventilator-associated pneumonia (Day 6) secondary to *Pseudomonas aeruginosa* and *Clostridium difficile* colitis (Day 12) in one patient; no other patient developed any other episode of infection. There was no incidence of pneumothorax. Two out of the five patients survived, while three patients died of multiorgan system failure (renal, hepatic and cardiovascular) and acute respiratory distress syndrome.

DISCUSSION

Our report suggests that paraquat poisoning is an uncommon entity in India. Over the last eight years, we have encountered only five cases, and a MEDLINE search revealed only one previously reported case[2]. Although we did not confirm the presence of paraquat by the urinary dithionite test and plasma paraquat levels, the clinical history and presentation, and documentation of paraquat make the diagnosis certain. The median dose of paraquat ingested (28.8 mg/kg) falls in the severe poisoning category and all patients had raised bilirubin levels suggesting significant exposure. Also, a recent analysis found that none of the 18 described prognostic systems, which included the use of plasma paraquat and urinary dithionite levels, have been validated in a large cohort[8]. Haemodialysis was reserved for patients with acute renal failure. All patients in our study received immunosuppressive therapy. In this cohort, using Suzuki's model for survival[9], all had a respiratory index >1.5 (mean 7.2, range 4.62-10.6). Despite the presence of severe poisoning in all five patients, two survived. This is similar to survival seen in other studies with a similar regimen (about 32%)[10].

Management of paraquat poisoning has remained mostly supportive and the results of treatment for paraquat poisoning, including absorbents, pharmacological approaches[11], radiotherapy[12], haemodialysis and haemoperfusion[13,14] were disappointing. Currently, there are no true

Table III. Time-frame showing clinical details of the individual patients admitted to the RICU with paraquat poisoning.

Case	Case 1	Case 2	Case 3	Case 4	Case 5
Baseline characteristics					
Age/sex	20/F	18/M	25/F	18/M	26/F
Quantity of paraquat ingested (mg/kg)	18	60	6	30	30
Intent	Accidental	Suicidal	Suicidal	Suicidal	Homicidal
Time to presentation (hours)	46	38	21	19	18
Serum creatinine at admission (mg/dL)	3.4	11.1	7.1	10.2	0.6
Serum bilirubin at admission (mg/dL)	12.6	6.3	5.6	7.0	24.5
Peak serum bilirubin (mg/dL)	15.6	8.4	45.5	12.6	28.7
Time to peak bilirubin (days)	2	2	11	3	10
Admission PaO_2/FiO_2 value	260	350	316	340	303
Lowest PaO_2/FiO_2 value	94	66	121	150	160
APACHE II scores	19	22	19	19	13
ICU course and outcome					
Modality of dialysis	HD	CVVH	PD	HD	nil
Time of dialysis after onset of renal failure (hours)	12	10	6	5	nil
Mechanical ventilation	Yes	Yes	Yes	Yes	No
Mode	VCV	PCV	VCV	PCV	-
Occurrence of infections	-	-	VAP (*Pseudomonas aeruginosa*), *Clostridium difficile* colitis	-	-
ICU stay (days)	2	2	14	2	11
Hospital stay (days)	2	2	16	2	12
Survival	dead	dead	alive	dead	alive

APACHE: acute physiology and chronic health evaluation, PaO_2: partial pressures of oxygen, FiO_2: fraction of inspired oxygen, VCV: volume controlled ventilation, PCV: pressure controlled ventilation, VAP: ventilator associated pneumonia, HD: haemodialysis, CVVHD: continuous venovenous haemodiafiltration

pharmacological antagonists for paraquat and there are no chelating agents capable of binding the poison in the blood or other tissues[15]. Paraquat poisoning is characterised by severe pulmonary inflammation, and is also the primary cause of death seen with this poisoning[4]. Importantly, survivors of paraquat poisoning have near-normal lung function at three-month follow-up[16]. Thus, if the paraquat-induced lung inflammation can be attenuated, the survival of patients can be greatly improved[5]. One major step towards attenuation of lung inflammation has been the use of immunosuppressive drugs including glucocorticoids and cyclophosphamide[6,10,17-19]. Two randomised controlled trials have suggested a definite trend in benefit with immunosuppressive therapy in patients with moderate to severe poisoning with a mortality of 43/72 in the immunosuppression arm and 59/72 in the control arm (odds-ratio 0.76, 95% confidence interval [CI] 0.62-0.94). Thus, five (95% CI, 3-14) patients need to be treated with immunosuppression to prevent one death[10,19].

In our study, we used immunosuppression in all severe intoxications, and two out of the five patients did survive. The other three patients had fulminant poisoning and probably had insufficient time for immunosuppression to have any pharmacodynamic action. In conclusion, paraquat poisoning is an uncommon entity in India, and is associated with a high mortality rate. There is a potential role for immunosuppressive therapy in patients with moderate to severe poisoning.

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