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ORIGINAL ARTICLE

Clinical Characteristics of Paraquat Poisoning in 22 Chinese Children

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Abstract
Objective To retrospectively analyze the clinical characteristics and experience of Chinese children with paraquat poisoning.
Methods Twenty-two children with paraquat poisoning who presented to the hospital from October 2007 through September 2012 were enrolled into this study. The clinical indices of these cases were collected and analyzed.
Results All the children were poisoned due to oral ingestion of paraquat. Different degrees of damage were found in multiple systems in their bodies. All of them were administered pulse therapy using methylprednisolone (20 mg/kg/d×3d) and Gamma globulin (total 2 g/kg divided into 3 d to 5 d) in the early stage. Prednisone was then given orally for 4wk to 8 wk. The total mortality rate of the patients was 63.6 % (14 of 22 patients died). Statistical differences ($P<0.05$) were found between the surviving and dead patients, with regard to age, plasma paraquat levels, the highest levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, total bilirubin, direct bilirubin, indirect bilirubin, blood urea nitrogen, creatinine and pH value, the lowest levels of PaO_2, $PaCO_2$ and SaO_2. Plasma paraquat level was positively related to pH value, but was negatively related to PaO_2, $PaCO_2$ and SaO_2 levels. None of the patients died from hepatic and renal complications. Pulmonary fibrosis was the most severe complication and the primary cause of death.
Conclusions Paraquat poisoning is difficult to cure. In this study, pulmonary fibrosis was the primary cause of death. Treatment by administering large doses of glucocorticoids and Gamma globulin proved to be effective in the early stage. However, the treatment may not reverse the development of pulmonary fibrosis. The long-term prognosis of paraquat poisoning was not optimistic. The plasma paraquat level could be a significant factor in predicting the prognosis.

Keywords Paraquat · Poisoning · Glucocorticoid · Pulmonary fibrosis

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Introduction

Paraquat (1, 1′-dimethyl-4, 4′-bipyridylium dichloride) is a highly efficient contact herbicide that has intense toxicity for humans. People could be poisoned through skin contact, respiratory tract, oral ingestion and other causes. Treating paraquat poisoning is very difficult because no specified antidotes exist. The widespread use of paraquat has obviously increased the number of children with paraquat poisoning either through accidental or intentional ingestion. This study aimed to investigate the clinical characteristics and experience of children with paraquat poisoning in authors' hospital through retrospective analysis.

Material and Methods

Twenty-two children with paraquat poisoning who were hospitalized in the Qilu Hospital of Shandong University from October 2007 through September 2012 were the objects of this study. The clinical indices of these children were collected and retrospectively analyzed. Data with normal distribution were expressed as mean ± standard deviation and were statistically analyzed through nonparametric Mann–

Whitney *U* test. Spearman's correlations were used to determine the relationship between the indicators. *P* value<0.05 was considered to be statistically significant. The data were analyzed using the IBM SPSS Statistics 20 software.

Results

The 22 patients comprised 18 boys and 4 girls whose ages ranged from 10 mo to 14 y (6.84±3.81y). All children were poisoned by taking paraquat orally. A 10-mo-old infant was poisoned by his mother, who chewed food to feed him after orally taking paraquat. Two children were poisoned by licking empty bottles of paraquat. The other children ingested paraquat to commit suicide with a maximum dosage of 20 mL. The length of hospital stay was 7 d to 24 d. The time that elapsed from paraquat ingestion to hospitalization in authors' department was within 24 h, except for an 11-y-old girl who was admitted into the authors' department 6 d after poisoning because of the concealment of paraquat ingestion. The patients showed various types of symptoms (Table 1).

Sixteen children had leucocytosis with white blood cell (WBC) count of 10.21×10^9/L to 20.99×10^9/L (14.89±3.31×10^9/L). Five children had normal WBC count of 4.56×10^9/L to 6.39×10^9/L (7.82±1.63×10^9/L). One child had leucopenia with a WBC count of 3.47×10^9/L. Fifteen children had microscopic hematuria (BLD1+~3+). Seven children had proteinuria (PRO1+~2+) simultaneously. The plasma paraquat levels ranged from 0.01 μg/mL to 14.02 μg/mL (5.39±4.68 μg/mL).

Fifteen patients had hepatic and renal function injuries. The serum alanine aminotransferase(ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), blood urea nitrogen (BUN) and creatinine (Cr) levels of these patients increased within 3 d after poisoning. These indices reached the peak within 7 d to 10 d as follows: ALT (56U/L to 469U/L, mean 203.27±113.23U/L), AST (46U/L to 587U/L, mean 155.05±134.89U/L), GGT (41U/L to 286U/L, mean 134.40 ± 78.01U/L), TBIL (23 μmol/L to 151.7 μmol/L, mean 72.28±42.93 μmol/L), DBIL (9.1 μmol/L to 105.9 μmol/L, mean 50.38±31.71 μmol/L), IBIL (5 μmol/L to 45.8 μmol/L, mean 21.90±12.73 μmol/L), BUN (11.71mmol/L to 40.09 mmol/L, mean 26.10±7.89 mmol/L), Cr (108 μmol/L to 773 μmol/L, mean 307.80±220.31 μmol/L). These indices of patients with hepatic and renal function injuries improved after reaching the peak, except for five patients who abandoned therapy. None of the patients died from hepatic or renal complications.

Table 1 Clinical manifestations of patients with paraquat poisoning

Clinical manifestations	Number of patients (%)
Vomiting	22/22(100)
Alimentary tract hemorrhage	14/22(63.6)
Abdominal pain	14/22(63.6)
Oppression in chest	18/22(81.8)
Dyspnea	14/22(63.6)
Fever	2/22(9.09)
Oliguria	15/22(68.2)
Microscopic hematuria	15/22(68.2)
Proteinuria	7/22(31.8)
Dizziness	7/22(31.8)
Seizure	1/22(4.55)

Ten children exhibited electrolyte disturbance, including hypokalemia (2.20 mmol/L to 3.49 mmol/L, mean 3.08±0.41 mmol/L), hyponatremia (119 mmol/L to 133 mmol/L, mean 128.20±4.49 mmol/L) and hypochloraemia (66 mmol/L to 108 mmol/L, mean 87.90±10.12 mmol/L). The causes of the electrolyte disturbances could have been the renal injuries and the low intake of food. The recovery of hypokalemia was very slow with 18 d as the longest period.

None of the children exhibited respiratory symptoms and abnormal arterial blood gas (ABG) analysis results within 24 h. The respiratory symptoms began about 5 d after poisoning (*e.g.*, chest tightness) with pH (7.44±0.03), PaO_2 (67.38±4.41 mmHg), $PaCO_2$ (37.73±2.51 mmHg), HCO_3^-(25.22±2.10 mmol/L) and SaO_2 (90.61±2.02 %). The abnormal ABG analysis results of 14 children with progressive dyspnea were due to respiratory alkalosis within 7 d to 10 d after poisoning with pH (7.54±0.06), PaO_2 (48.42±3.67 mmHg), $PaCO_2$ (29.16±2.90 mmHg), HCO_3^- (25.34±1.50 mmol/L) and SaO_2 (81.14±3.39 %). The hyperventilation due to hypoxemia had resulted in decline $PaCO_2$ levels and elevated pH values. Treatment through oxygen inhalation could not effectively ameliorate hypoxemia. The continued type I respiratory failure state did not improve in 14 d of exposure, with pH (7.49±0.04), PaO_2 (37.56±5.08 mmHg), $PaCO_2$ (32.76±2.81 mmHg), HCO_3^-(24.74±1.61 mmol/L) and SaO_2 (71.78±6.08 %), which ultimately resulted in the death of the children. No apparent abnormal ABG analysis results of survivors were detected during their hospital stay.

Lung injuries were found in 20 children through CT examination. The lung markings increased within 3 d to 5 d after poisoning. Pulmonary alveoli exudation and consolidation appeared within 7 d to 10 d after poisoning. Pulmonary fibrosis ultimately appeared on approximately the 14^{th} day after poisoning. However, a 4-y-old child had lobus medius pulmonis fibrosis, 6 d after poisoning. The brain MRI examination of a 13-y-old boy with seizures after poisoning showed multiple pallium abnormal signals. These abnormal phenomena signified toxic encephalopathy. The brain MRI was reviewed 7 d after the seizures and showed that the extent of the lesion had decreased.

All children were given gastric lavage, gastrointestinal mucoprotective agent, liver and myocardium protection, cell anti-oxidants and other treatments. All patients were initially administered glucocorticoid treatment. Methylprednisolone (20 mg/kg/d×3d) was given as an impulse treatment. Gamma globulin (2 g/kg divided into 3 d to 5 d) was simultaneously given. Prednisone was given orally for 4 wk to 8 wk. The oxygen inhalation and mechanical ventilation treatments were carefully chosen because these treatments could aggravate pulmonary fibrosis through the excessive production of oxygen-free radicals. Children were given hemodialysis or peritoneal dialysis if the creatinine (Cr) level was higher than 500 μmol/L.

Nine children died during hospitalization, five children abandoned therapy and eight children exhibited improved conditions, which allowed them to be discharged from the hospital. Eight children remained alive until December 2012. The total mortality rate was 63.6 %. The other seven patients had different degrees of pulmonary fibrosis, except for the one 10-mo-old infant. The surviving patients were younger than the dead patients. The plasma paraquat levels of the surviving patients were obviously lower than the dead ones. The peak levels of ALT, AST, GGT, TBIL, DBIL, IBIL, BUN and Cr in the surviving patients were noticeably different from those of the dead ones. The highest levels of pH and the lowest levels of PaO_2, $PaCO_2$ and SaO_2 were also different between the surviving and dead patients (Table 2). The correlation analysis of the plasma paraquat level with the highest level of the pH and the lowest level of PaO_2, $PaCO_2$ and SaO_2, revealed that the plasma paraquat level was positively related to the pH value (rho=0.550, P=0.008), and was negatively related to the level of PaO_2 (rho=−0.627, P=0.002), $PaCO_2$ (rho=−0.552, P=0.008) and SaO_2 (rho=−0.554, P=0.007).

Discussion

Oral intake of paraquat was the most frequent route of poisoning. The plasma paraquat level reached the peak within 1 h to 4 h after poisoning, then decreased through renal excretion and tissue deposition, including lung, liver, kidney, body fluids and muscle. Paraquat can deposit in great amounts in the lung. The lung tissue concentration could maintain a high level even with the decrease of the plasma concentration, which leads to long-lasting and persistent lung injury [1]. This phenomenon was obvious in the index study. Pulmonary fibrosis was the most common long-term complication of paraquat poisoning. The mechanism of paraquat toxicity was not completely clear. Paraquat toxicity is consistently viewed as having two aspects: oxygen-derived free radicals [2, 3] and mitochondrial injuries [4].

In the present study, the authors found that the alimentary tract symptoms were extensive, which indicated the powerful mucous membrane contact injury effect of paraquat. A 12-y-old boy had serious seizures. Huang et al. reported five cases with paraquat-induced convulsions and death [5]. Epilepsy-like convulsions induced by paraquat were believed to result in death despite being seldom observed. Wu et al. found apparent microglia activation in substantia nigra and striatum within 1 wk after intoxication using the rat paraquat-poisoning model. Astrocyte edema and neuron apoptosis were also observed in the rat [6]. MRI was used to

Table 2 Comparison between profiles of alive and dead patients with paraquat poisoning

Characteristic	Alive (n=8)	Dead (n=14)	P
Age (year)	4.42±2.99	8.22±3.60	0.024*
Plasma paraquat level (μg/mL)	0.30±0.24	8.31±3.19	<0.001*
Highest ALT level (U/L)	29.75±18.48	210.79±114.69	<0.001*
Highest AST level (U/L)	32.25±11.49	163.07±136.19	0.003*
Highest GGT level (U/L)	27.13±12.99	143.01±73.35	<0.001*
Highest TBIL level (μmol/L)	9.41±4.53	67.56±44.87	<0.001*
Highest DBIL level (μmol/L)	3.73±3.62	46.96±33.04	<0.001*
Highest IBIL level (μmol/L)	5.68±3.08	20.60±13.16	0.001*
Highest BUN level (mmol/L)	8.86±6.87	26.30±8.15	<0.001*
Highest Cr level (μmol/L)	62.38±29.40	322.07±221.31	0.001*
Highest pH value	7.42±0.02	7.55±0.05	<0.001*
Lowest PaO_2 level (mmHg)	87.50±2.44	40.21±5.62	<0.001*
Lowest $PaCO_2$ level (mmHg)	37.74±2.03	28.73±2.65	<0.001*
Lowest SaO_2 level (%)	95.38±1.69	74.14±5.86	<0.001*

* P<0.05; *ALT* Alanine aminotransferase; *AST* Aspartate aminotransferase; *GGT* γ-glutamyl transferase; *TBIL* Total bilirubin; *DBIL* Direct bilirubin; *IBIL* Indirect bilirubin; *BUN* Blood urea nitrogen; *Cr* Creatinine; *PaO_2* Arterial partial pressure of oxygen; *$PaCO_2$* Arterial partial pressure of carbon dioxide; *SaO_2* Arterial oxygen saturation

study the neuroimaging of patients with paraquat poisoning which revealed that paraquat could damage the CNS in acute phase and in recovery phase [7]. The CNS toxicity of paraquat frequently focuses on the substantia nigra. Paraquat could induce caspase-3 expression in substantia nigra neurons and hasten neuron apoptosis. However, Bartlett et al. reported that paraquat cannot pass through the blood brain barrier in rhesus macaque [8], thus the mechanism of CNS injury remains un-clear to date.

No specific antidotes for paraquat poisoning are available. The key point of the treatment is to control pulmonary fibrosis. Glucocorticoids and immunosuppressive agents are usually used to treat pulmonary fibrosis. Lin et al. reported the use of methylprednisolone (1 g/d×3d) and cyclophosphamide (15 mg/kg/d×2d) as pulse therapy in the beginning, followed by dexamethasone (20 mg/d) until PaO_2>80 mmHg. The researchers again used methylprednisolone (1 g/d×3d) and cyclophosphamide (15 mg/kg/d×1d) if PaO_2<60 mmHg. This protocol could obviously improve survival rate [9]. They also reported that repeated pulses of methylprednisolone and cyclophosphamide were better in reducing mortality rate than high doses of dexamethasone and cyclophosphamide [10]. However, the authors found that glucocorticoids did not have a good long-term effect. Tasi et al. showed that methylprednisolone pulse therapy did not effectively treat paraquat poisoning [11]. Zhi et al. also reported that Edaravone could effectively treat pulmonary injury induced by paraquat as a free radical scavenger [12]. Mohammadi-Karakani and Ghazi-Khansari et al. reported that captopril and lisinopril could ameliorate paraquat toxicity in the mitochondria [13, 14]. Glutathione reductase and pirfenidone reportedly ameliorate paraquat toxicity in the CNS and lungs [15, 16].

In the present study, authors found that pulmonary fibrosis could not be reversed and that the prognosis of paraquat poisoning is still pessimistic even with the use of large dose of methylprednisolone and long-term oral prednisone. Tsai et al. reported that young age, low plasma paraquat level, low Cr level, female gender and low elapsed time since poisoning could predict high survival rate [11]. In the present study, authors found that the surviving patients were younger, and that their plasma paraquat levels were lower compared with the dead patients. The authors believed that younger children possibly came in contact with paraquat accidentally, whereas the older children possibly took oral paraquat deliberately, which accounted for the higher dose taken. The peak ALT, AST, GGT, TBIL, DBIL, IBIL, BUN and Cr levels of the surviving patients were noticeably different from those of the dead patients, but the authors found that these indices had improved before death. Yang et al. found that the spectrum of liver injury in patients with paraquat poisoning is mild and transient, which does not cause death [17]. Acute kidney injury is frequently reported with paraquat poisoning in humans [18]. In the index study, the authors found that the spectrum of liver and renal injury was the common manifestation of paraquat poisoning in children, but the injury was transient and non-fatal. The spectrum of lung injury, which was developing and fatal, was different from that of the liver and renal injuries. Huang et al. reported the correlation between paraquat amount, plasma paraquat concentration, base excess value and survival time [19]. A positive relationship was found between the plasma paraquat level and pH value, and negative relationship was found between the plasma paraquat level and the level of PaO_2, $PaCO_2$ and SaO_2. The authors believe that plasma paraquat level may be a significant factor in the prognosis of paraquat poisoning in children. Arterial lactate and pentraxin-3 were also reported as prognosis predictors for paraquat poisoning [20, 21]. However, no recognized index was found that could accurately predict prognosis.

Conclusions

The children suffering from paraquat poisoning had multisystemic injuries. Progressive respiratory failure caused by pulmonary fibrosis was the primary cause of death. The treatment was difficult. Glucocorticoids and Gamma globulin therapy took effect in the early stage, but the long-term prognosis remained pessimistic. No recognized indicator that could accurately predict prognosis was found. However, the plasma paraquat level may be a potential predictor.

Conflict of Interest None.

Role of Funding Source None.

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