

Acute Paraquat Poisoning

Report of a Survival Case Following Intake of a Potential Lethal Dose

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Abstract: When properly used, paraquat (PQ) is a widely used bipyridil herbicide with a good safety record. Most cases of PQ poisoning result from intentional ingestion, with death resulting from hypoxemia secondary to lung fibrosis in moderate to severe poisonings. With high ingestion volumes (>50 mL of a 20% wt/vol formulation), death results from multiple organ failure and cardiovascular collapse within 1 week after intoxication. The present report describes a successful clinical case regarding the intoxication of a 15-year-old girl by a presumed lethal dose of PQ. The adolescent ingested approximately 50 mL of a commercialized concentrate (20% wt/vol of dichloride salt) formulation of PQ. High serum and urinary levels of PQ confirmed the bad prognosis. However, the therapeutic protocol followed in the present clinical case led to a positive outcome. Besides the measures for decreasing PQ absorption and increasing its elimination, other protective procedures were applied in aiming to reduce the production of reactive oxygen species (ROS), to scavenge ROS, to repair ROS-induced lesions, and to reduce inflammation. The status-of-the-art concerning the biochemical and toxicological aspects of PQ poisoning and the pharmacologic basis of the respective treatment is also presented.

Key Words: paraquat poisoning, oral ingestion, lung toxicity

Since its introduction in agriculture in 1962,¹ the widespread nonselective contact herbicide paraquat (PQ), used as desiccant and defoliant in a variety of crops, has caused thousands of deaths from both accidental and voluntary ingestion, as well as from dermal exposure. It may be considered as one of the most toxic poisons frequently used for suicide attempts. A large oral dose of PQ (>30 mg kg⁻¹ in humans) rapidly leads to death from multiorgan failure, with lung damage consisting of disruption of alveolar epithelial cells, hemorrhage, edema, and infiltration of inflam-

matory cells into the interstitial and alveolar spaces.¹ Smaller doses of PQ (from 16 mg kg⁻¹) may also lead to death, but this occurs after several days as a result of a progressive lung fibrosis, by proliferation of fibroblasts, and excessive collagen deposition, showing that the main target organ for PQ toxicity is the lung.¹ The direct cellular toxicity of PQ is essentially due to its redox cycle (Fig. 1): PQ is reduced enzymatically, mainly by the reduced form of nicotinamide adenine dinucleotide phosphate–cytochrome *P*-450 reductase, the reduced form of nicotinamide adenine dinucleotide phosphate–cytochrome *c* reductase, and the reduced form of nicotinamide adenine dinucleotide:ubiquinone oxidoreductase (complex I), to form a PQ monocation free radical. The PQ monocation free radical is then rapidly reoxidized in the presence of oxygen, thus resulting in the generation of the superoxide radical.¹ This then sets in the well-known cascade, leading to generation of the hydroxyl radical and consequent deleterious effects. Nowadays, no antidote or efficient treatment of PQ poisoning has been identified, the survival depending on the amount ingested and the time elapsed until the patient is submitted to intensive medical measures to inactivate and eliminate PQ.

The aim of this article is to report a successful clinical case regarding the intoxication of a young girl who ingested a potentially lethal dose of PQ.

CASE

A 15-year-old girl voluntarily ingested approximately 50 mL of a commercialized PQ formulation (20% wt/vol of PQ dichloride salt), corresponding to nearly 10g of PQ ingested. The weight of the girl was 47 kg. Twenty minutes after ingestion the adolescent vomited, the gastric contents having a greenish appearance. She was taken to a local hospital about 2 hours 30 minutes after ingestion. After admission she was immediately submitted to a gastric lavage with physiologic 0.9% NaCl solution. Mineral adsorbent (100 g of Fuller earth) was subsequently given to reduce further absorption of PQ into the bloodstream. The patient was then transferred to the intensive care unit. She was conscious, anxious, with a coherent speech, presenting a slightly sinus tachycardia (around 110 heartbeats min⁻¹) and a respiratory rate approximately 22 cycles min⁻¹, with no fever and hemodynamically stable. There was no history of respiratory or other illness. Chest radiograph, hemogram, and blood chemistry were all normal. No erosion lesions were noted in the oral cavity. The remainder of physical examination was unremarkable. The ingestion was

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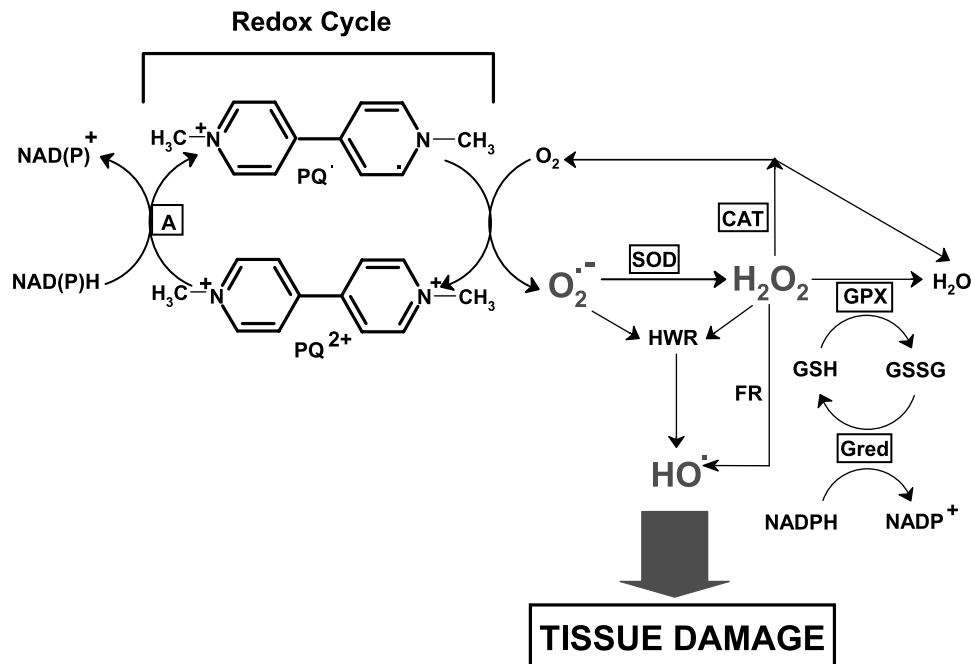


FIGURE 1. Schematic representation of the mechanism of PQ toxicity. A indicates cellular diaphorases. CAT, catalase; FR, Fenton reaction; Gred, glutathione reductase; GPX, glutathione peroxidase; HWR, Haber-Weiss reaction; PQ^{•+}, PQ cation radical; PQ²⁺, paraquat; SOD, superoxide dismutase or spontaneously.

confirmed by a qualitative sodium dithionite test on a urine sample. The initial urine colorimetric test showed a dark blue color.

Analysis of urine samples collected at 4, 6, 10, 16, 20, 26, 30, 42, and 50 hours after ingestion revealed values of 102.83 (prehemoperfusion), 87.07 (during hemoperfusion), 11.97 (after hemoperfusion), 22.99 (prehemoperfusion), 9.45 (after hemoperfusion), 5.75 (prehemoperfusion), 0.25 (after hemoperfusion), 0.35 (prehemoperfusion), and 0.20 mg L⁻¹ (after hemoperfusion), respectively. Fifty-eight hours after ingestion, PQ in the urine was lower than the quantification limit. The PQ levels in the serum samples at the same times were lower than the quantification limit of the method, with the exception of the first, second, and third sampled times where it was found (3.5, 1.75, and 0.95 mg L⁻¹ of PQ, respectively). Serum and urinary levels of PQ were undetectable 20 and 72 hours after ingestion, respectively.

In the face of the severity of the intoxication, with high serum and urine PQ levels, it was followed an aggressive therapeutic protocol. The patient was submitted to hemoperfusion during 4 days, in 7 sessions of 3 hours each. The first session was initiated 4 hours after ingestion. The observed complications were electrolyte disturbances, with hypokalemia, hypomagnesemia, and hypophosphatemia. Severe alterations in the coagulation tests due to the heparin used during the hemoperfusion did not require immediate correction. Only after the last session was protamine sulfate needed. Thrombocytopenia evolved, but it was resolved after suspension of hemoperfusion.

Pharmacotherapy was initiated with (1) 15 mg kg⁻¹ cyclophosphamide (CP) in 100 mL of a 5% dextrose solution perfused over 60 minutes once daily after hemoperfusion during the first 2 days of hospitalization; (2) 15 mg kg⁻¹ methylprednisolone (MP) in 200 mL of a 5% dextrose solution perfused over 60 minutes and repeated once daily for 3 consecutive days always after hemoperfusion; (3) 100 mg kg⁻¹ desferrioxamine (DFO) in 500 mL

of a 5% dextrose solution in continuous intravenous perfusion at 21 mL hour⁻¹ during 24 hours in 1 administration started after the first hemoperfusion session; (4) 300 vitamin E mg/p.o. twice daily after hemoperfusion; (5) *N*-acetylcysteine (NAC) was administered after the first hemoperfusion session in a dose of 150 mg kg⁻¹ in 500 mL of a 5% dextrose solution perfused during 3 hours; subsequently, it was given 300 mg kg⁻¹ in 500 mL of a 5% dextrose solution in continuous perfusion at 21 mL hour⁻¹ during 3 weeks.

After 3 days, MP was suspended, and the patient received 5 mg of intravenous dexamethasone (DX) every 8 hours during the next 5 days, with posterior withdraw therapy regime for approximately 20 days. In addition, the patient received prophylaxis for stress ulcer (40 mg omeprazol, i.v., twice daily) and for opportunistic infections (one tablet daily containing 800 mg cotrimoxazol and 160 mg of trimethoprim). The patient did not develop renal or hepatic failure. No signs of infection were noted from long-term steroid therapy. Initial pulmonary function tests and chest radiograph at the time of admission were normal. However, on day 7, computerized axial tomography (CAT) of the thorax revealed areas of pulmonary densification, with ground-glass attenuation at the lung base possibly indicating initial edema as a sign of fibrosis. Pulmonary function tests also showed alterations in the CO diffusion. The hospitalization lasted 22 days. At discharge time CO diffusion test and CAT were all normal. Six months later, all the parameters were standard.

DISCUSSION

In the present report a successful clinical case is presented regarding the intoxication of a young girl by a presumed lethal dose of PQ.

Previous works^{2,3} reporting human PQ poisoning show that the plasma and urine concentration within the first 24 and 48 hours postintoxication are good predictors of outcome. The initial urine colorimetric test showed dark blue color. The appearance of strongly positive dithionite tests in urine and the PQ serum concentration 4, 6, and 10 hours after ingestion^{2,3} were indicators of a poor prognosis.³ Despite undetectable levels of PQ in the serum 10 hours after ingestion, the very high concentration of PQ in urine was certainly predictive of a fatal outcome.³ According to survival probability using the criteria of the study by Scherrmann et al,³ Proudfoot et al,² and Hart et al,⁴ the likelihood of mortality falls into death from pulmonary fibrosis.

Because there are no known antidotes for PQ and there are no chelating agents capable of binding the PQ in the blood or other tissues, over the past 40 years, strategies in the management of PQ poisoning have been directed toward the modification of the toxicokinetics of the poison by either decreasing its absorption⁵ or enhancing its elimination. Such approaches are intended to prevent the accumulation of PQ in tissues and include procedures such as induced emesis or diarrhea, gastric lavage, administration of oral absorbents, hemodialysis, and hemoperfusion.⁶ No vomit induction was performed because the formulation already contained an emetic, and the young girl vomited, which certainly contributed to the positive outcome despite the high quantities of PQ that were absorbed and quantified in the serum and urine. After admission, she was immediately submitted to a gastric lavage with physiologic 0.9% NaCl solution, a successful measure in some cases of heavy PQ poisoning.⁶ Mineral adsorbent (100 g of Fuller earth) was subsequently given to reduce further absorption of PQ into the bloodstream. The supporting references for this therapeutic measure not only include *in vitro*⁷ and *in vivo*⁸ studies demonstrating the strong and tight binding of PQ to this adsorbent but also some successful cases of PQ poisoning treatment.⁹ The patient was then submitted to hemoperfusion, which seems to be an indispensable treatment for patients with acute PQ poisoning,¹⁰ increasing the chance of survival if started early within 4 hours after ingestion and showing higher extraction ratios¹¹ for PQ when compared to hemodialysis.

Beside these treatments, additional protective measures were also adopted: (1) those aimed to prevent the generation of reactive oxygen species, namely, the effective control of iron distribution by DFO; (2) those aimed to scavenge reactive oxygen species (ROS), including the maintenance of effective levels of antioxidants such as vitamin E; (3) those aimed to repair the ROS-induced lesions, particularly the maintenance of effective levels of glutathione by administering NAC; and (4) those aimed to reduce inflammation by DX, MP, CP, and NAC.

Pharmacotherapy was initiated with CP and MP. Although high doses of CP and DX treatments, including intravenous CP (5 mg kg⁻¹ d⁻¹) and DX (24 mg d⁻¹) for 14 days have been correlated with 75% survival rate after PQ poisoning,¹² a subsequent study¹³ did not demonstrate the usefulness of this approach. Therefore, the efficacy of high-dose CP and DX in PQ poisoning remains controversial.

Recently, a report¹⁴ demonstrated that pulse therapy with CP and MP might be effective in preventing respiratory failure and reducing mortality in patients with moderate to severe PQ poisoning. Pulse therapy with MP is known as a strong anti-inflammatory treatment in clinical practice,¹⁴ suppressing ROS production by neutrophils and macrophages, and in the arachidonic acid cascade.¹⁵

Furthermore, CP exerts a wide range of immunomodulatory effects that influence virtually all components of the cellular and humoral immune response, and reduce the severity of inflammation,¹⁶ therefore contributing to the overall effect. In addition, CP-induced leukopenia 1 to 2 weeks later may contribute to reduce pulmonary inflammatory process of PQ-poisoned patients.¹²

Taking into account the involvement of ROS in the toxicity of PQ, compounds that can interfere with their generation and propagation of oxidative stress may be useful therapeutic tools in the treatment of PQ poisoning. It has been shown that DFO can exert its protective effects not only by iron chelating (and thus inhibiting the PQ-induced generation of hydroxyl radicals) but also by blocking the uptake of PQ by the alveolar type II cells.¹⁷ Concerning the use of vitamin E (α -tocopherol), this lipid-soluble vitamin exerts its antioxidant effects by scavenging free radicals and stabilizing membranes containing polyunsaturated fatty acids,¹⁸ which may prevent the cytotoxic effects of PQ. The use of vitamin E is described in several survival cases after PQ poisoning.¹⁹

NAC has also been used with success in massive PQ poisoning.²⁰ NAC, the acetylated derivative of the amino acid L-cysteine, was administered because it is an excellent source of sulfhydryl groups. NAC is indeed converted in the body into cysteine, the rate limiting amino acid for glutathione synthesis, promoting detoxification and acting directly as a free radical scavenger.²¹ Exposure of human alveolar cells *in vitro* to PQ has been shown to induce apoptotic cell death, perhaps via oxidative stress mechanisms, this toxic effect being inhibited by NAC, an effect attributed to the direct scavenging action of its sulfhydryl group.²² In addition, it was previously shown that the administration of NAC to PQ-challenged rats delayed the PQ-induced release of chemoattractants for neutrophils in the bronchoalveolar lavage fluid and significantly reduced the infiltration of inflammatory cells, suggesting that NAC can also confer its protective effect by delaying inflammation.²³

At the fourth day after intoxication, 5 mg of intravenous dexamethasone were administered every 8 hours during the next 5 days to prevent the inflammation.²⁴ Prolonged therapy with steroids may increase survival in a refractory late-stage, but not in an early-stage state of adult respiratory distress syndrome.²⁵ This effect is attributable to the downregulation of circulating macrophages, as well as of collagenase activity, and promotion of the proliferation of type II pneumocytes.²⁵ Therefore, repeated pulse and continuous steroid therapy may prevent further inflammation and damage of pulmonary tissues by superoxide anion in patients affected by severe PQ poisoning.

In conclusion, the therapeutic protocol followed in the present clinical case was coincidental with a positive outcome. We conducted an intensive and aggressive treatment based on the high ingestion volume, confirmed by the high urine and serum PQ levels. The prognosis of this intoxicated girl resembles those patients with moderate to severe poisonings, which, after a morphologically characterized early destructive phase of alveolar type I and type II epithelial cells, develop a second proliferative phase defined by alveolitis, pulmonary edema, and infiltration of inflammatory cells.¹ For this reason our protocol may not be applied to fulminant intoxications where multiorgan failure is the main cause of death. It is hoped that the present therapeutic approach may be valuable for other intensive care units in the management of this very common intoxication. Nevertheless, further controlled studies are required to confirm the usefulness of our protocol.

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