

## Paraquat Poisoning

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### Introduction

Poisoning by pesticides and other agricultural chemicals is a major public health problem worldwide, especially in developing countries. Globally, there are about 20,000 annual fatalities and more than 2 million hospitalizations due to poisoning by pesticides and agricultural chemicals.<sup>1</sup> There were approximately 340,000 cases of agricultural and horticultural poisoning reported in the United States during 1985 through 1990, with 97 deaths. Paraquat poisoning accounted for only 0.34% of those cases, but paraquat poisoning had the highest mortality rate, accounting for 13% of all fatal cases.<sup>2</sup> Severe paraquat poisoning is characterized by multiple-organ failure, involving mainly the lungs, kidneys, and liver. The lung is a major target organ in paraquat poisoning, and respiratory failure from lung injury is the most common cause of death. It is important to make an early diagnosis and to start appropriate treatment as soon as possible. This article presents a case of fulminant paraquat poisoning and discusses the pathophysiology and management of paraquat poisoning.

### Case Report

A 34-year-old woman was admitted to the emergency room of Chulalongkorn Hospital, Bangkok, Thailand, 4 hours after ingesting about 20 mL of 24% paraquat (Gramoxone), with suicidal intent. She experienced nausea and vomiting shortly after ingestion and was brought to the hospital by her relatives. In the emergency room she reported sore throat and epigastric pain, but denied any shortness of breath or any difficulties breathing. She reported no underlying medical problems, and had been working at a farm, where she had access to herbicides. Physical examination in the emergency room revealed an alert, fully conscious woman in no acute distress, with blood pressure

100/50 mm Hg, heart rate 110 beats/min, respiratory rate 16 breaths/min, and temperature 36.5°C. Her blood oxygen saturation (measured via pulse oximetry while breathing room air) was 95%. Her oral mucosa was erythematous and edematous. Both lungs were clear to auscultation. The remainder of physical examination was unremarkable.

Initial complete blood count, electrolyte, and liver function tests were within normal ranges. A chest radiograph was clear, without definite infiltrates, and the cardiac contour was normal (Fig. 1). Electrocardiogram revealed sinus tachycardia. Urine dithionite test was strongly positive, confirming the presence of paraquat. We obtained a blood level for paraquat, and the patient was given 100 g of activated charcoal plus 100 mL of 70% sorbitol via nasogastric tube. We started administering intravenous fluid, and the patient was admitted to the medical intensive care unit for close observation and further evaluation.

After admission the patient was given a repeated dose of activated charcoal and sorbitol. Other supportive treatments included intravenous fluids and analgesics to control her epigastric pain. In the following 24 hours, the patient experienced increasing epigastric pain, severe dysphagia, and

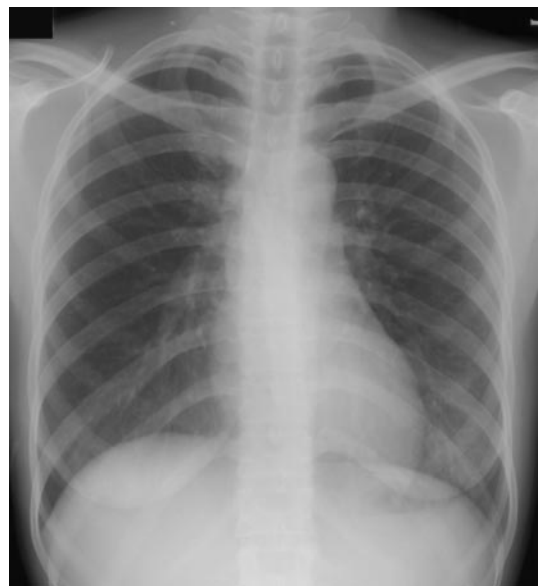


Fig. 1. Initial chest radiograph.

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Fig. 2. Day-3 chest radiograph, showing bilateral infiltrates, pneumomediastinum, and pneumopericardium.

progressive shortness of breath. A subsequent chest radiograph revealed bilateral lower-lobe and perihilar infiltration. Blood chemistries on day 2 revealed elevated blood urea nitrogen, creatinine, and liver enzymes. Her arterial blood gas values on day 2 were pH 7.48,  $P_{aCO_2}$  32 mm Hg, and  $P_{aO_2}$  56 mm Hg. She required increasing supplemental oxygen to keep her oxygen saturation above 88%.

On day 3 the chest radiograph revealed bilateral infiltrates, pneumomediastinum, and pneumopericardium (Fig. 2). She became increasingly hypoxemic and required intubation and mechanical ventilation. Her renal function deteriorated, with markedly increased blood urea nitrogen and creatinine levels, and her urine output decreased. Hemodialysis was started. Progressive multiple-organ failure ensued, and she died on day 4 after admission. Her initial blood paraquat level at 6 hours after ingestion was 1.98  $\mu\text{g/mL}$ .

### Discussion

This case represents a typical presentation of fulminant paraquat poisoning. The patient had a high blood paraquat level 6 hours after ingesting a large amount of concentrated paraquat, and developed multiple-organ failure within 24 hours. Patients with severe paraquat poisoning may be asymptomatic soon after ingestion, but deteriorate quickly within a few hours. This patient also developed pneumomediastinum and pneumopericardium, probably secondary to air leak from necrotizing lung parenchyma or ruptured esophagus. Pneumomediastinum in paraquat poisoning indicates a very poor prognosis, with a mortality rate of almost 100%.<sup>3</sup>

Paraquat (1,1' dimethyl-4-4'-bipyridylum dichloride) is a nonselective, contact herbicide widely used in agricultural industries around the world. It was first synthesized in 1882 as a redox indicator, and its herbicidal property was recognized in the 1950s. In humans, paraquat is highly toxic, with an estimated lethal dose in adults of about 3–6 g of paraquat ion. The most common route of poisoning is ingestion (either intentional or accidental) of the concentrated solution. In Thailand and other developing countries, paraquat is one of the most common suicidal ingestions. Dermal exposure also has been reported to result in severe paraquat poisoning, especially in the presence of pre-existing skin lesions.<sup>4</sup> Inhalation of sprayed paraquat solution usually causes local irritation but rarely results in important systemic absorption. To prevent accidental ingestion and decrease the amount of paraquat absorption, many manufacturers add dye, stenching agents, and emetics to concentrated solutions.

After it is ingested, the gastrointestinal tract absorbs < 20% of paraquat. The presence of ulcerated mucosa or an empty stomach increases the fraction of paraquat absorbed. Blood levels peak within a few hours after ingestion. Paraquat is not actively metabolized in the body, and more than 90% is excreted unchanged by the kidneys. After absorption, paraquat is distributed to highly perfused organs such as the lungs, kidneys, liver, and muscles, and remains partly in the intravascular space.

Paraquat concentration in the lung parenchyma is very high (10–20 times greater than in plasma) because of active, energy-dependent uptake of paraquat by type 1 and type 2 alveolar epithelium, via the polyamine uptake pathway.<sup>5</sup>

At the tissue level, paraquat is reduced to paraquat radicals in the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH). Paraquat radicals then react with oxygen molecules and generate superoxide anion ( $O_2^-$ ). An excessive amount of superoxide anion results in the formation of hydroxyl free radicals ( $OH^-$ ), which can damage cells via lipid peroxidation and inhibition of essential cellular enzymes. This explains why the lungs are the target organs in paraquat poisoning: high tissue concentrations from active uptake and abundant oxygen react with paraquat and form reactive oxygen radicals.<sup>5</sup>

The clinical manifestations of paraquat poisoning range from local irritation to multiple-organ failure and death. Paraquat (especially concentrated paraquat) is corrosive and can severely injure skin, eyes, and gastrointestinal mucosa. Esophageal ulceration can cause severe pain and dysphagia. Perforated esophagus is not uncommon a few days after paraquat ingestion, and it may lead to severe mediastinitis and death. Systemic manifestations depend on the amount of paraquat ingested, and patients can be classified into 3 categories:<sup>6</sup>

1. Mild poisoning: < 20 mg paraquat ion per kilogram of body weight. These patients may have gastrointestinal symptoms but usually fully recover.

2. Severe poisoning: 20–40 mg paraquat ion per kilogram of body weight. These patients usually develop severe caustic lesions in the gastrointestinal tract, acute renal failure, and progressive pulmonary fibrosis. Deaths occur in 2–3 weeks, from severe respiratory failure.

3. Fulminant poisoning: > 40 mg paraquat ion per kilogram of body weight. These patients suffer multiple-organ failure leading to death within hours to a few days after ingestion.

The patient described above ingested about 20 mL of 24% paraquat, which was about 67 mg paraquat ion/kg in 50-kg person. Lung injury in severe or fulminant paraquat poisoning is characterized by diffuse alveolar damage, with destruction of alveolar epithelium, pulmonary edema, and hemorrhage in the early phase. If the patient survives this destructive phase, there will be ongoing intense proliferation of fibroblasts and collagen deposition in the lung, leading to progressive pulmonary fibrosis and hypoxemic respiratory failure within a few weeks.

The diagnosis of paraquat poisoning is usually straightforward from the accurate history of exposure. However, diagnosis can be difficult in children when the history is unclear, or in other unusual circumstances, such as homicide.<sup>7</sup> The urine dithionite test can quickly confirm the presence of paraquat in urine. Plasma and urine paraquat levels measured within 24 hours of exposure can help predict the likelihood of patient survival, but usually are not helpful in guiding management, because the test has a long return time and lacks general availability. A paraquat blood level of > 1.6  $\mu\text{g/mL}$  12 hours after ingestion is universally lethal. According to the nomogram, our patient's paraquat level of 1.98  $\mu\text{g/mL}$  at 6 hours predicted a survival likelihood of < 20%.<sup>8</sup>

Initial management of paraquat poisoning focuses on prevention of further absorption and gastrointestinal decontamination. Adsorbent should be given as soon as possible. Commonly used adsorbents are activated charcoal (1–2 g/kg) and Fuller's earth (1–2 g/kg), given with a cathartic such as 70% sorbitol. Hemoperfusion has been shown to decrease paraquat levels in humans and to improve survival in animals, but there are insufficient data to support any survival benefit in humans. Hemodialysis should be reserved for patients with acute renal failure.

Other general supportive care includes fluid and electrolyte management and pain control. Oxygen supplementation should be avoided if possible, because it can potentiate paraquat-induced lung injury.

There is no specific effective antidote for paraquat. In sporadic case reports, clinicians have used various treatments, such as antioxidants (high-dose vitamin C or E), N-acetylcysteine, nitric oxide supplement, corticosteroids, cytotoxic agents, or paraquat antibodies in treating paraquat poisoning, with various outcomes. The combination of cyclophosphamide and corticosteroids may offer some benefits in moderate-to-severe cases, by preventing ongoing inflammation and pulmonary fibrosis.<sup>9</sup> There are also a few reported cases of lung transplantation after paraquat poisoning.<sup>10</sup>

In conclusion, the patient with severe paraquat poisoning has a poor prognosis. Because there is no specific antidote, the important approaches are to prevent accidental exposure and to pursue aggressive decontamination and prevention of further absorption after ingestion.

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