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Paraquat poisoning, what we should know: A review article

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Abstract---Paraquat (PQ) a brown syrupy liquid also known as methyl viologen is a commonly used herbicide in India. A highly toxic compound to humans, although, a large majority of fatalities from PQ poisoning are suicides. Accidental exposure is causing immense harm to farmers and agriculture workers, which is not documented. Accidental or deliberate ingestion has an extremely high case-fatality rate, and clinical features are due to generating reactive oxygen species which cause cellular damage ultimately leading to multiorgan failure. At present there is no antidote to PQ poisoning, various treatment modalities from immunosuppressants to antioxidants are used with no clear clinical efficacy. Elimination methods such as haemodialysis and haemoperfusion when done early have shown to be useful in few studies. Recently drug-like Edaravone and Perfenidone are being used but with no survival benefit. Neither proper information nor training on the use of PQ and personal protective equipment are provided by agriculture offices to farmers leading to accidental exposure. Hence paraquat use has been restricted in many parts of the world and an appeal for a ban in India is underway as a need for preventive measures. Though PQ poisoning is common in rural India, the data on PQ poisoning is limited to case reports and small case series. Most of the casualty medical officers and residents are unfamiliar with the clinical manifestations and management of PQ poisoning. Hence this review was conducted to understand the clinical features and management of PQ poisoning along with understanding the practice and health hazards faced by the farmers after accidental exposure.

Keywords---paraquat, paraquat poisoning, edavarone, perfenidone.

Introduction

Paraquat dichloride is a widely used and highly toxic herbicide 1. It is used to destroy weeds and prepare land for agriculture. It destroys plant tissue by disrupting photosynthesis and rupturing cell membranes, which allows water to escape leading to rapid desiccation of foliage 1. Poisoning with paraquat may be accidental or intentional and its often fatal.2 Paraquat acts by generation of free radicals, which destroy the lipid cell membrane and organelles. It specifically gets concentrated in lung tissue which has both acute and chronic consequences. The other organs commonly affected are the kidney, liver, and heart, leading to death anywhere between 5 and 31 days after lung injury.3Diquat is a related herbicide that is often formulated with paraquat. Mechanisms and clinical features of diquat are similar to those of paraquat.

History

Paraquat was first made commercially available as a herbicide in 1962, though its herbicidal properties were discovered in the 1950s and was synthesized much earlier.4 Paraquat dichloride 24% SL is the only formulation registered in India and is approved for weed control in nine crops.1

Toxic dose and fatality

Toxicity and survival after paraquat ingestion is dose dependent, consumption of as little as 10–20 mL of 20% paraquat is lethal.4 Clinical features of poisoning also depends on the amount consumed. Amount of PQ ingested is classified as mild (<10 mL), moderate (10–20 mL), and severe (>20 mL) 5. The case fatality for paraquat suicide attempts is very high compared to other pesticide poisoning, which ranges anywhere between 40 to 90%.1,6 But will approach 100% despite of various treatment when concentrated preparations are consumed.7 As there is no specific antidote for the paraquat poisoning.8

Mechanism of action

Paraquat once ingested gets absorbed rapidly from stomach, but absorption is incomplete. Only 20% of the ingested poison is absorbed. After absorption, it gets distributed to highly perfused organs like lungs, kidney, liver, and muscle. But it mainly effects lung and kidney. It remains unmetabolized and then largely gets eliminated unchanged in urine within 12-24 h (4,6). Paraquat concentration in the lung is 10–20 times greater than in the plasma.4 Because Paraquat has a structural similarity to naturally occurring polyamines, that are taken up by the alveolar cells by the energy-dependent uptake of the paraquat by a recently described diamine transport process located in the alveolar epithelial cells and the Clara cells of the airways and hence paraquat concentrates in alveolar type I and II cells. When accumulated, paraquat undergoes a NADPH-dependent one-electron reduction to form its free radical which almost instantly reacts with molecular oxygen to reform the cation and concomitantly produce superoxide anion.4,9. This oxidative stress leads to pulmonary damage (alveolitis and

fibrosis). Involvement of the lung in the form of diffuse alveolitis (over 1–3 days) and subsequent pulmonary fibrosis is the hallmark of paraquat poisoning 4. The acute respiratory distress syndrome sets in after 24–48 hours of exposure. At moderate doses, the initial lung injury develops into pulmonary fibrosis. This occurs due to rapid and excessive proliferation and differentiation of fibroblasts, resulting in loss of pulmonary architecture. Paraquat is also actively secreted by the kidney leading to its accumulation in the proximal tubular epithelial cells at higher concentrations.4 Paraquat causes vacuolation in the cells of the proximal convoluted tubules, thereby causing renal tubular necrosis.4 Renal failure is an early but reversible feature of paraquat poisoning. Maintenance of renal function reduces plasma paraquat levels, thereby minimizing accumulation in the alveoli.4 Hepatocellular injury occurs secondary to mitochondrial damage and endoplasmic reticulum degranulation 4.

Clinical features

Paraquat causes both local symptoms due to its caustic property and systemic manifestations.

Local manifestations

At the site of ingestion: Mucosal lesions of the mouth and the tongue are called “paraquat tongue”.4 (Figure 1) They appear within the first few days and may become ulcerated with bleeding. They can occur even with minimal amount of consumption and does not have any prognostic significans. Esophageal ulceration causes pain and dysphagia. This may progress to perforation, mediastinitis, and pneumomediastinum 4. When exposure occurs through skin and eyes local manifestations include irritation, skin blistering, and full-thickness burns. Though intact skin is an effective barrier to parquet absorption it can be life-threatening mainly in the presence of preexisting skin lesions or on prolonged exposure. Inhalational exposure usually causes local irritation but rarely results in significant systemic absorption. 4



Figure 1. Paraquat tongue: Coated with necrotic slough in a young male presenting to casualty

Systemic manifestations

The main symptoms and signs in patients studied include nausea, vomiting, epigastric pain.6 Many manufacturers add a potent emetic to formulations of

paraquat because experiments in primates had demonstrated a fivefold reduction in toxicity. When formulations containing an emetic is consumed vomiting can occur within 30 min than non-emetic preparations 10. Generally patient will be conscious. Any impairment in consciousness usually indicates either co-ingestion of other agents like ethanol or severe toxicity resulting in altered consciousness from hypoxia, hypotension and severe acidosis.⁷

Lung involvement is diagnosed based on hypoxemia and infiltrates on chest X-ray. The acute respiratory distress syndrome sets in after 24–48 hours of exposure 4. The patient typically develops increasing signs of respiratory involvement over 3–7 days and ultimately dies of severe anoxia due to rapidly progressive fibrosis up to 5 weeks later.⁷ Lung injury was documented in 61.8% in a study by Ravichandran R et al 11. Kidney injury is diagnosed by raising creatinine, oliguria and need for dialysis 11. A high urine output is desirable. However, as renal failure commonly develops over the first 24 h, close monitoring of fluid balance is required to do this safely.¹⁰ 7 In a retrospective study conducted by Ravichandran R et al in southindia with 55 cases acute kidney injury was documented in 81.8% and 56.3% had undergone dialysis.¹¹ In another study at Iran by with 44 cases by Delirrad M et al A Significant increases in serum creatinine was seen in 61% of patients.⁶

Hepatic dysfunction occurs in the form of raised bilirubin, aspartate (AST) and alanine aminotransferase (ALT). In a study by Ravichandran R et al 33.3% had bilirubin > 2 mg/dL. Elevation of (more than two times the upper normal limit) AST, ALT and alkaline phosphatase (ALP) was reported in 46.4%, 46.4%, and 24.4%, respectively. Acute hepatic failure was not noted in anyone.¹¹ Delirrad M et al Acute hepatitis was seen in 31.7% (n=13) of patients. Increased serum bilirubin was seen in 22% of patients, they observed that all patients with elevated bilirubin died. On the contrary, no survived patients had increased serum bilirubin 6. The clinical manifestation of PQ poisoning can be classified into three categories:

- mild poisoning, consumption of less than 20 mg PQ ion per kg of body weight
- severe poisoning, 20–40 mg PQ ion per kg of body weight
- Fulminant poisoning, more than 40 mg PQ ion per kg of body weight. (Table 1) 4,12, 13

Table 1
Clinical manifestation of PQ poisoning based on severity of dose

| Mild poisoning | Severe poisoning | Fulminant poisoning |
|---------------------------------|---|--|
| Minor gastrointestinal symptoms | Acute renal failure, acute lung injury and progressive pulmonary fibrosis | Rapid development of multiorgan failure (lung, kidney, liver) pancreatitis, myocarditis, refractory hypotension/coma |
| Usually recover fully | Death occurring in 2–3 weeks as a result of respiratory failure | Death within hours to a few days |

Diagnosis

Mainstay of Diagnosis is based on history of consumption of or exposure to PQ and identification of the container with PQ the patient has ingested. Clinical features like Early gastrointestinal symptoms like vomiting are non specific and will not help differentiate from other pesticide poisoning. Whereas the diagnostic signs like paraquat tongue, renal failure and jaundice and later development of hypoxia with involvement of lung may point towards paraquat poisoning. As About 90% of the absorbed paraquat is excreted unchanged in the urine within 12–24 h of ingestion.⁷ A simple and inexpensive Spot Urine Sodium Dithionite Test can be performed that readily detects paraquat in the urine of suspected cases at bedside. The test is based on the reduction of the paraquat cation to a blue radical ion by sodium dithionite in alkaline medium. To 10 mL of urine sample, 2 ml of freshly prepared 1% sodium dithionite in 1 *N* sodium hydroxide is added and mixed well. The development of blue or green colour indicates the presence of paraquat in the urine sample.¹⁴ If the urine sample turns black, it indicates the presence of very high concentration of paraquat and the test should be repeated after diluting the urine sample. The sodium dithionite test can detect paraquat up to a concentration of 1 µg/mL in a clear urine sample. ⁴ The test can also be performed as a quantitative test by using known concentrations of paraquat solutions and comparing the colour change in the urine sample.

Treatment

At present, there is no specific antidote for paraquat poisoning. So mainstay of treatment is symptomatic and supportive. Management of PQ poisoning can be mainly considered under three headings. (1) Prevention of further absorption by gastric decontamination, (2) Elimination of paraquat from circulation (hemodialysis), (3) Prevention and management of early and late complications of lung.

Prevention of further absorption

Gastric lavage can be given if the patient is conscious and no spontaneous vomiting at presentation, it should be followed by activated charcoal (1–2 g/kg) or Fuller's earth (1–2 g/kg).⁴ The use of gastric lavage without administration of an adsorbent has not shown any clinical benefit and should be avoided.⁴ Ideally it should be given within one hour of ingestion of paraquat ⁷. As paraquat is caustic few clinician do not recommend gastric lavage, it is also contraindicated in patient with compromised air way protection. Although animal experiments suggest that paraquat is absorbed poorly over 1-6 hour period, peak plasma concentrations are attained rapidly and evidence for the efficacy of gastric lavage in man is poor. It is likely to add very little to the amount removed by spontaneous vomiting and adsorbents. ^{7,10,15}

Insertion of a nasogastric (NG) tube for gastric lavage will also help to maintain nutrition later, NG tube should be inserted carefully as severe mucosal lesions may rupture leading to perforations. Patients are best kept nil per mouth. Mucosal lesions might be very painful and may need anticholinergic agents such as diphenhydramine (benadryl); an anesthetic, such as viscous lidocaine; and an

antacid or mucosal coating agent, such as magnesium or aluminum hydroxide, kaolin, or sucralfate. Antiemetics (5-HT₃ antagonists/phenothiazines) are also used to prevent vomiting. Antibiotics may be used for supervening infections.⁴

Elimination enhancement

Initial management includes rehydration, as the kidney is a major route of excretion of paraquat maintaining high urine output is important. Monitor fluid balance to avoid fluid overload and electrolyte imbalance. Forced diuresis is not recommended.⁴ Hemoperfusion, a modality to remove paraquat should ideally be started within 4 hours of exposure or ingestion.⁴ “Haemoperfusion (HP) is a method of filtering the blood outside the body to remove a toxin. Where the blood perfuses a filter composed of artificial cells filled with activated carbon or another microporous material and toxin get trapped in the microporous material.”¹⁶ There are various types of haemoperfusion, like traditional charcoal haemoperfusion. Recently, there are a newer generation of hemoperfusion cartridges (specific for toxin like paraquat) that are under trial to evaluate efficacy and cost-effectiveness.⁴

“Continuous” HP is not lifesaving but prolongs survival.¹⁷ Dinis-Oliveira et al. proposed a treatment strategy to use up to seven hemoperfusion sessions (6–8 hours duration) to be started within 4 hours of ingestion and maintained until plasma paraquat levels would be <0.2 mg/L.¹⁸ HP doubled the systemic clearance of paraquat but the efficacy of hemoperfusion in paraquat poisoning is controversial. The peak time of plasma paraquat is 1-3 hour, that of lung cells is 4-5 hour and nearly 90% of the paraquat disappears in the plasma 5-6 hour after ingestion.¹⁹ Thus HP is ineffective in reducing paraquat lung exposure unless it was started within 2 h post ingestion. Also paraquat is slowly redistributed back into the blood from the tissues, even after paraquat is eliminated from the blood by hemoperfusion. It is of no use in lethal dose poisoning.^{4,7,16} The overall case fatality in centres routinely performing HP/HD is still over 50%^{7,19}.

Recently a study conducted by Raghavendra Rao et al. in south india have shown a promising results for HP, they retrospectively analysed the patients and observed that, early haemoperfusion (≤ 6 hours) improved the survival rates compared to those who received late haemoperfusion (>6 hours). Also they observed that D were more in those patients who received only gastric lavage with symptomatic treatment as therapy compared to those who received haemoperfusion i.e., 92.1% vs 42.9% respectively.¹⁶ If the patient develops acute kidney injury, then standard indications for hemodialysis (HD) are applicable but it is always useful to start hemofiltration at the earliest to avoid subsequent development of acute kidney injury due to paraquat.⁴ However, such patients have a very poor prognosis in terms of their lung injury, so this is unlikely to change outcome.⁷

Prevention/management of pulmonary complications

Oxygen should not be administered unless SpO₂ levels are below 92%, as high concentrations of oxygen intensify the toxic effects. Once patient has developed ARDS, subsequent management of oxygenation and ventilation is identical to

ARDS due to any other etiology, ventilatory support in the cases of respiratory failure following paraquat poisoning does not help their survival. It seems that only noninvasive ventilation must be applied. 4,20

- *Immunosuppressants:* Cyclophosphamide, methylprednisolone and dexamethasone are used in various combination and doses for treatment. The theory is that as paraquat leads to an acute inflammatory response, interference with this may inhibit the processes that lead to lung fibrosis and death. But no one mode of treatment is shown to be effective in preventing lung injury or fibrosis once it is established.4,7
- *Antioxidants:* Paraquat poisoning initiates release of free radicals that cause depletion of antioxidants. Hence antioxidants has also been tried to reduce reactive oxygen species.
- *N-Acetyl cysteine* is rate-limiting in the synthesis of glutathione was found to increase the level of glutathione (antioxidant) in animal studies. Therefore, *N-acetyl cysteine* (150 mg/kg over 3 hours; 300 mg/kg over 24 hours for up to 3 weeks) has been tried to increase intracellular glutathione. However, there is insufficient information and studies in humans.

Desferrioxamine (100 mg/kg over 24 hours) has been used to chelate iron that acts as a catalyst in the production of hydroxyl radicals. No human studies have looked at the efficacy of Desferrioxamine in paraquat poisoning. High doses of vitamin C (300 mg twice daily orally). In animal studies, pre-treatment with intravenous vitamin C reduced oxidative stress from paraquat toxicity in rats, where as vitamin C given soon after paraquat ingestion worsened oxidative stress. The latter effect was reduced by the iron chelator, desferoxamine and therefore attributed to the promotion of the Fenton reaction and increased redox-cycling of metals 21. Vitamin E in deficient rats and salicylate which significantly reduced oxidative stress are used but no human studies are available.

In a case series from south india where 8 patients were treated with Pulse therapy- with Iv Cyclophosphamide 15mg/kg/day for 3 days Iv Methylprednisolone 1gm/day for 2 days Iv Dexamethasone 24mg/day for 5-7 days along with IV N-Acetyl cysteine 2g/day for 3days. Vitamin C (500mg/tab) 2 tablets thrice daily. Vitamin E (400 IU/ tab) 2tablets thrice daily. Only two survived. However, both the patients who survived had consumed only less than 50 ml of paraquat. 22 It is also unknown if adding glucocorticoid with cyclophosphamide to the standard care has unwanted side effects such as increasing the risk of infection. A systematic review by Li et al. 23 where glucocorticoid with cyclophosphamide were used in addition to standard care had a lower risk of deat, a randomized controlled trial by Gawarammana et al.24 with high-dose immunosuppression did not show improved survival in paraquat-poisoned patients.

Edaravone is a free radical-scavenging antioxidant, It was found that edaravone is beneficial for protecting the kidneys and liver from paraquat poisoning, however, Edaravone did not reduce pulmonary fibrosis and had no significant effect on the survival rate in a study conducted by Yi R et al.25. Perfenidone, (PFD) an antifibrotic drug used in treatment of idiopathic pulmonary fibrosis, can effectively improve the treatment efficacy in patients with pulmonary fibrosis

caused by acute PQ poisoning. Perfenidone was shown to improve the pulmonary function and arterial blood gas status of patients, without causing obvious liver and kidney damage. Moreover, the survival rate of the patients in PFD group was significantly higher than that in the NO-PFD group ($P < 0.05$) in a study conducted by Ren W et al.²⁶ Extracorporeal membrane oxygenation has been tried in acute paraquat poisoning as a bridge to bilateral lung transplantation patients from the last decade. However, lack of evidence and cost-effectiveness at this point hinders its recommendation in treatment of paraquat poisoning.⁴

Misuse of paraquat and its prevention

Paraquat dichloride is being used for 25 crops in India, whereas it is approved for use in only nine crops by the Central Insecticide Board and Registration Committee. This is in violation of the Indian Insecticides Act.¹ Paraquat apart from its use for suicides with high mortality rate is causing immense harm to farmers and agriculture workers, which are not documented. Pesticide Action Network (PAN), a civil society group, came up with a report on paraquat usage in India in 2015. Report says that, Farmers buy and use paraquat in an unsafe manner. It was found that paraquat is sold in plastic carry bags to farmers who demand 100ml or 200ml of the product, Awareness and training about how to use paraquat as well as other pesticides and taking personal protective measures is lacking among most of the respondents, which included farmers and agricultural workers. Paraquat is also reported to have links to reproductive problems and Parkinson's disease.¹

Paraquat has been banned in 32 countries, So far in India, only Kerala has banned the herbicide since 2011.¹ Doctors in Odisha's Burla district, who saw herbicide paraquat kill around 170 people in the past two years, demand that the government ban it in 2019. "After the PAN's report the issue was raised in Parliament too. The government said it would take measures to arrest counterfeit sale but nothing happened.²⁷

Paraquat beyond suicide Accidental exposure

Paraquat is toxic to humans when accidental exposure occurs through the skin and is highly toxic when inhaled, For agricultural uses, the Environmental protection agency (EPA) determined that particles used in agricultural practices are in the range of 400–800 μm . These spray droplets as per recommendation are too large to be inhaled. The farmers and workers reported numerous adverse health effects caused by paraquat such as irritation, itching, headache, vomiting, burning sensation, breathing difficulty, muscle pain, abdominal discomfort, lethargy, skin allergy and colour change, tiredness, nausea, giddiness, fever, eye burn, dizziness, diarrhoea, throat drying, shivering, sneezing and change in heart beat rate. ¹

Paraquat and parkinson's disease

Several studies have suggested that pesticide exposure and life in rural areas are significant risks factors for PD. Among other pesticides, paraquat (PQ) has been

linked to PD by epidemiological studies and experimental work in rodents, in which it causes lesions in the substantia nigra, pars compacta. 28 Paraquat is structurally similar to MPP+, a known fast-acting inducer of Parkinson's disease. Further prospective and high-quality case-control studies are required to substantiate a cause-effect relationship.

Conclusion

Paraquat a widely used herbicide in India has high acute toxicity to humans. As little as mouth full of paraquat can be lethal. In spite of being commonly used for self poisoning very few studies are available. Oral mucosal ulcerations, acute renal failure and hepatitis forms the early triad of poisoning. Involvement of lung initially as alveolitis and later as fibrosis is hallmark of paraquat poisoning. Mortality ranges from 40 to 90% and depends on amount consumed. Most common cause of death is multiorgan failure. There is no antidote and treatment is mainly supportive. Delayed presentation has grave consequences. Activated charcoal and Hemoperfusion if performed should be done as soon as possible. Hemoperfusion has shown promising results when done early and with nonsevere dose of poisoning. Immunosuppressants and antioxidants have been tried with inconclusive results. Once the patients develop respiratory distress, conventional therapies cannot stop the pulmonary fibrosis. More trials are needed to prove the efficacy of newer drugs Edavarone and Perfenidone. Farmers buy and use paraquat in an unsafe manner which may lead to accidental exposure resulting in grave consequences. Appeal to ban paraquat in india is underway. Apart from 32 countries only one state in india has banned its use. Medicos witnessing substantial number of paraquat poisonings should conduct studies with a proper strategy and report their outcomes.

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