REVIEW ARTICLE

An Overview of Paraquat Poisoning: A Review

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Abstract

Poisoning by pesticides is the major public health problem in low-income and middle-income countries, and it is responsible for almost 20% of global suicides in the last decade. Paraquat (PQ) is a toxic bipyridyl compound commonly used in agriculture and it has potential ill-effects with high fatality if ingested even in very small amounts. The mode of poisoning is usually suicidal or accidental. Paraquat poisoning is still a nuisance faced in the rural and semiurban areas, attributable to wide availability and easy access to the poison as well lack of knowledge among the common people regarding its life-threatening effects. Paraquat is partially absorbed from the gastrointestinal tract and the toxic effects are mainly mediated by the production of reactive oxygen species (ROS) causing cell damage. It acts as a corrosive and erodes the gastrointestinal tract but majority of deaths occur due to acute lung injury (ALI). Renal failure and consequent multiorgan dysfunction are also common. The mainstay of management is supportive with paucity of human data on role of antioxidants and immunosuppressives. This review gives a comprehensive outlook on PQ poisoning, the probable mechanisms, available treatment options, and plausible recommendations while managing PQ toxicity.

Keywords: Acute lung injury, Free radicals, Nuclear factor kappa B, Paraquat, Pesticides poisoning.

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Introduction

Pesticide poisoning is a major public health problem worldwide. It is estimated that 385 million cases occur annually, with around 11,000 fatalities, with the greatest proportion occurring in southern and South-Eastern Asia.[1] Organophosphates and carbamates are the most common culprit agents used. Paraquat (PQ) (1,1′-Dimethyl-4,4′-bipyridinium dichloride), a rapidly acting, contact nonselective herbicide, is the leading cause of fatal poisoning and a major health problem in many countries, especially in the Indian subcontinent. Ingestion is by far the commonest route of poisoning. Topical (dermal/mucous membrane), inhalational, and intravenous routes have also been reported. Paraquat poisoning is a grave concern in many developing countries, predominantly due to the lack of specific antidote or effective treatment; and high mortality (over 50% case fatality) due to multiorgan involvement.[2] Moreover, most of these poisonings occur in resource poor rural settings with delayed access to appropriate treatment. The goal of this review is to provide an overview on the mechanism and clinical manifestations of PQ poisoning, treatment modalities available in the literature and attempt to devise a rational protocol for early patient evaluation, diagnosis, and management for best long-term outcomes.

Mechanism of Toxicity

Paraquat exerts its toxic effects by the following interconnected mechanisms:[2–7]

- **Oxidative injury:**
  - *Generation of superoxide and other free radicals* – Paraquat is metabolized by various enzyme systems (cytochrome P450 reductase, ubiquinone oxidoreductase, xanthine oxidase, and nitric oxide synthase) to generate a PQ+ radical, which undergoes a redox cycling, depleting the cell of NADPH and glutathione, while generating superoxide, hydroxyl, and peroxynitrite radicals.
  - *Lipid peroxidation* – Free radicals extract hydrogen atoms from fatty acids, causing lipid peroxidation which damages cell membranes and may trigger apoptosis.
  - *Mitochondrial damage* – Calcium dependent damage of inner mitochondrial membrane has been noted to occur in the presence of PQ, leading to membrane depolarization, uncoupling of the electron transport system, and matrix swelling.
  - *Altered cellular metabolism* – Secondary to mitochondrial damage and depletion of NADPH (which also impairs innate defenses against oxidative injury).
- **Inflammation:** Activation of nuclear factor kappa B (NF-kB) due to reactive oxygen species (ROS), leads to induction of the inflammatory cascade facilitating the synthesis of inflammatory mediators, cytokines, and chemokines. This leads

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to aggregation of platelets and fibroblasts, which is thought to be responsible for the rapid pulmonary fibrosis characteristic of PQ poisoning.

- **Pneumotoxicity:** Acute lung injury (ALI) is especially severe in PQ poisoning since it is actively uptake in an energy-dependent manner into type 1 and type 2 pneumocytes, as well as Clara cells. The process is mediated by a polyamine uptake system, and paraquat competes with endogenous polyamines like putrescine, cystamine, spermine, spermidine, and others for uptake into pneumocytes.[8] Once inside the lung cells, PQ damages the cell by the mechanisms described above.

Toxokinetics

Paraquat is generally poorly absorbed across intact skin and mucosa. Gastrointestinal absorption is also low (5–10% of ingested dose) but rapid, with peak plasma concentration being reached within 2 hours of ingestion. It is widely distributed to tissues, with estimates of volume of distribution ranging from 1.2 to 2.75 L/kg. Paraquat exhibits rapid endogenous clearance, with 80–90% of the dose removed via urine within 12–24 hours. However, the remaining dose and the amount distributed into tissues are eliminated very slowly due to rapidly declining renal function attributable to PQ toxicity. Hence, while initial elimination half-life is around 6 hours, the terminal half-life can be up to 120 hours and beyond.[9,10] These toxicokinetics may be advantageous to consider rapid gastrointestinal decontamination and assisted elimination therapies (hemodialysis/hemofiltration/hemoperfusion) may be effective if initiated within the first 2–4 hours of ingestion. Hereafter, elimination therapies are useless as very little PQ remains in circulation.

Clinical Manifestations

Three degrees of severity of PQ poisoning may be encountered. Mild poisoning refers to very small doses of PQ ingestion that initially leads to inflammation of the oral mucosa and posterior pharyngeal wall, esophagitis, and gastritis followed by eventual complete remission. Patients who ingest slightly larger quantities, classified as moderate severity, tends to develop acute renal failure and pulmonary fibrosis. Mortality in moderate poisoning exceeds 50% in 2–3 weeks.[2] Patients who ingest large doses (50–100 mL of 20% w/v) present with fulminant multiorgan dysfunction syndrome (MODS) which ultimately lead to death in a few hours to days.[2,11–16]

The amount of ingested poison and quick access to healthcare are of two most important factors that affect the prognosis of PQ poisoning. In patients not presenting with severe poisoning with large doses, the manifestations evolve in roughly the following order:

Gastrointestinal/cutaneous (point of entry) toxicity: Mucosal lesions of the mouth and the tongue are almost universal when ingested ("paraquat tongue") (Fig. 1). Inflammation and corrosive action in the esophagus, stomach, and small intestine lead to vomiting, diarrhea, and abdominal pain. The vomitus may be brightly colored, as dyes are often added to PQ formulations to make it look distinctive and prevent accidental ingestion. Patients who have been exposed topically via sprays/liquid spills develop erythema and blistering over contaminated skin, which may progress to burn injuries.[17]

Renal: Acute renal failure with hiking serum creatinine and declining urine output develop approximately 24–48 hours following ingestion. However, there is paucity of contribution of

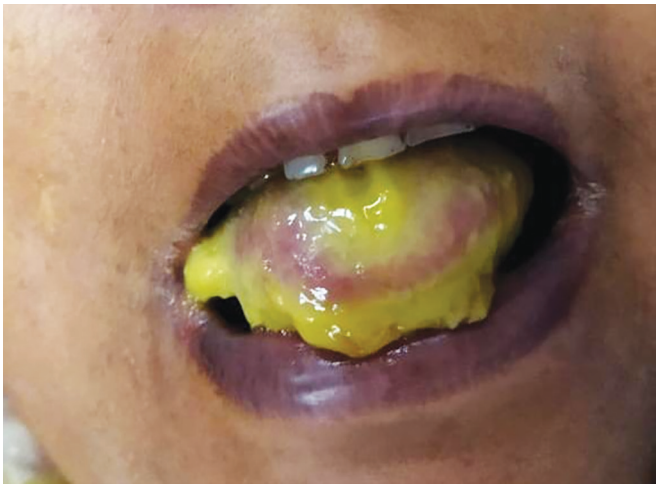

Fig. 1: Ulcerated and coated tongue with slough formation (paraquat tongue)

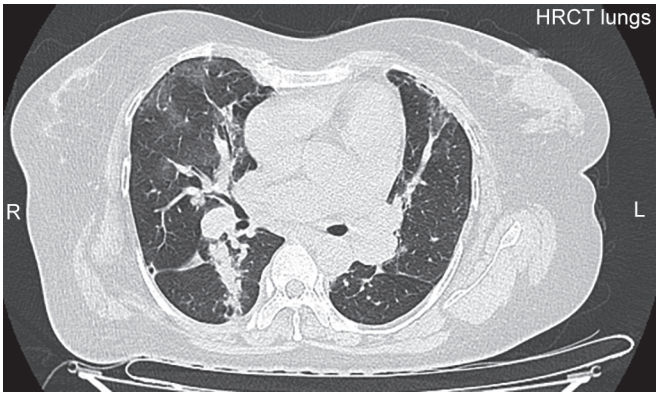

Fig. 2: High-resolution computed tomography of the thorax showing bilateral ground glass opacities with fibrosis in a patient of paraquat poisoning (2 weeks after ingestion)

renal failure to mortality in PQ poisoning as there is limited data on long-term renal damage in survivors.[2,18]

Hepatobiliary: Acute hepatitis with transaminitis and hyperbilirubinemia may be seen. Similar to renal failure, there is no significant impact on mortality, and there is no lasting impairment in survivors.[2]

Pulmonary: Pulmonary involvement is biphasic leading to an acute alveolitis with sloughing of epithelial cells and pulmonary edema over 1–3 days, followed by a secondary fibrosis over the next few weeks (Fig. 2).[2,11–16,19] Death in PQ poisoning has been attributed mainly to respiratory failure secondary to ALI.[20–22] Hypoxemia secondary to rapidly developing pulmonary fibrosis has also been implicated to contribute to mortality in patients with PQ poisoning.[23]

Laboratory Assessment

Analytical methods for qualitative and quantitative confirmation of the poison can be done to predict prognosis of patients. Urine dithionite test is used to detect PQ levels semiquantitatively. It is a urine spot test which when positive gives a blue color to indicate urine PQ concentration >1 mg/L (which by itself indicates a likely

fatal prognosis). Light blue or colorless test result indicates PQ concentration <1 mg/L.[24,25] A 4-hour post ingestion plasma sample is used for quantitative levels. A plasma concentration of >5 mg/L at any time from the time of PQ ingestion indicates a fatal outcome.[25] Paraquat levels can also be quantified in samples by spectrophotometry, high-performance liquid chromatography (HPLC) with fluorescence detection and liquid chromatography with mass spectrometric detection analysis.[26] Plasma PQ levels seem to be the greatest predictor of mortality in patients, and can be used to guide therapeutic goals.[27] Liu et al. also illustrated that the dose of poison and arterial blood lactate was sensitive in predicting the mortality risk of PQ poisoning.[28] Zhou et al. stated that neutrophil lymphocyte ratio (NLR), leukocyte, and neutrophil counts might be useful and simple parameters in predicting the prognosis of PQ poisoning.[29] Markers of renal function, i.e., creatinine, cystatin-C, and neutrophil gelatinase-associated lipocalin (NGAL) have also been studied by Roberts et al. as predictors of outcome.[30] It must be emphasized that most of these laboratory assessment tools are beyond the scope of the resource-poor settings where majority of PQ poisoning occur. Rapid and accurate history and physical examination are essential for timely identification of patients. Measurement of the above described serum markers is largely of academic interest, as they have very little implications for management.

Treatment Protocol

Since no specific antidote exists, treatment is largely symptomatic/supportive. A summary of the available treatment options has been described in Table 1. Approach includes:

- **Resuscitation:** For patients with severe poisoning who present with fulminant multiorgan failure, almost all measures are likely to be futile. However, standard resuscitative measures such as securing airway, maintaining breathing, and circulation by volume replacement ("checking ABCs") should be followed. Hypoxia should not be aggressively treated with oxygen support as that worsens oxidative damage.[31] Hypotension should be treated with fluids and vasopressors as per routine protocols. Fluid replacement should initially be targeted to achieve a brisk diuresis for the first 24 hours, as that may help in clearing PQ from the circulation. However, beyond 24 hours, with renal function deteriorating, fluids should be given judiciously to avoid overload.
- **Gastrointestinal decontamination:** Paraquat is rapidly absorbed from the GI tract, hence early GI decontamination (within 2–4 hours) is of paramount importance. Adsorbents used are mainly activated charcoal, bentonite or Fuller's earth. While it was previously believed that Fuller's earth is superior to the other agents (clay *in vivo* inactivates PQ), studies have now demonstrated non-inferiority of activated charcoal compared to Fuller's earth and bentonite.[32] Gastric lavage, though widely used in Asia for various pesticide poisonings, has no proven benefit, and may actually be detrimental due to the caustic nature of PQ.[33]
- **Enhanced elimination:** Hemodialysis or hemoperfusion are used in equipped centers to enhance the elimination of PQ from the circulation. Hemoperfusion appears to clear PQ from the circulation more rapidly and completely than hemodialysis.[34] However, since early endogenous clearance is very high and uptake into lung tissue is active, these techniques are of limited utility in preventing mortality.[35] Pond et al. demonstrated in an animal model that hemoperfusion was ineffective in reducing pulmonary concentrations unless initiated within 2 hours of ingestion.[36] Koo et al. compared hemoperfusion alone with hemoperfusion followed by prophylactic continuous venovenous hemofiltration (CVVH) in a group of 80 cases of poisoning. The CVVH prolonged survival in those patients, despite the absence of any mortality benefit.[37]
- **Immunosuppression:** Since hyperinflammation is a sinister mechanism of PQ toxicity, several trials have studied regimens of immunosuppressive agents. Most have focused on combinations of cyclophosphamide, methylprednisolone, and dexamethasone.[38–40] In addition to anti-inflammatory effects, these drugs also work by other mechanisms. Dexamethasone in particular has been shown to induce the expression of P-glycoprotein and hence reduce accumulation of PQ in lung tissue when given within 2-hours of ingestion in rats.[41] Human studies are promising but are limited by significant heterogeneity of results and lack of randomized controlled trials.[42]
- **Antioxidants:** This approach targets the other pillar of PQ toxicodynamics, i.e., oxidative damage. A variety of antioxidants has been studied, most prominent of which are vitamins C and E, N-acetylcysteine, salicylic acid, and iron chelators like deferoxamine.[43–49] While Block showed that rats deficient in Vit E have significantly reduced duration of survival and higher mortality following PQ intoxication, other studies failed to show any survival benefit.[43,44] Vitamin C has an interesting role, as it can exert both anti- and pro-oxidant effects. The pro-oxidant effects are seen when vitamin C is given after tissue damage has already started, by accelerating the Fenton reaction. If given before the onset of tissue damage, it acts as an antioxidant. Administration of deferoxamine completely blocked the pro-oxidant effect.[45] However, these studies were all conducted in animals and are largely of research interest.

  Important human trials on management of PQ poisoning have been described in Table 2.[38–40,50]

Prevention

Paraquat is banned in 32 countries across the world. In India, it is banned in the state of Kerala. Due to the lack of an antidote and the very high mortality, prevention of poisoning by banning use of PQ seems the only fool-proof solution.

Recommendations

Paraquat seems to be a very effective pesticide and its benefits may outweigh the associated risks as far as agricultural industries are concerned, hence banning of PQ may be of limited interest to the policymakers. Paraquat poisoning is extremely fatal, claiming lives within hours of ingestion in severe poisoning and associated with high long-term morbidity in survivors. The efficacies of the available treatment strategies are limited in absence of concrete evidence, as the majority of studies have been conducted in animal models. The laboratory assessment of severity and degree of PQ poisoning are suitable for research interest and barely accessible in resource limited setups. The management of patients accessing a healthcare facility shall encompass basic resuscitation and securing a nasogastric/orogastric tube within early hours of ingestion, which may increase the chances of injury and perforation if attempted late. Hypoxemia if severe must be addressed with adequate oxygenation on invasive/non-invasive ventilation as per the requirement of the patient. Antioxidants and immunosuppressive agents may be used

Table 1: Summary of the available treatment options in paraquat poisoning

Treatment options	*Mechanism*	*Implications*
Intubation and mechanical ventilation	To overcome lung toxicity causing respiratory failure. The standard principles of resuscitation—management of airway, breathing, and circulation followed as per routine guidelines.	Mechanical ventilation does not meaningfully change the prognosis of lung injury. It should be used only if airway protection is needed and in overt respiratory failure.
Gastric decontamination with activated charcoal or Fuller's earth (*Multani Mitti*)	They act as adsorbents.	Recommended if the patient presents within 2–4 hours.
Nasogastric tube	Must be inserted early since it can cause swallowing difficulties/edema.	Gastric lavage is not recommended as PQ is corrosive.
Elimination of the toxin	Hemodialysis (HD) and hemofiltration (HF). Hemoperfusion with activated charcoal also has superior clearance compared to HD. Hemodialysis can also treat metabolic acidosis and acute renal failure induced by PQ. Unfortunately, mortality still remains over 50% even with these interventions.	The window available for elimination is very short (within 2–4 hours of ingestion) as PQ is quickly removed from circulation (high endogenous clearance) and deposited in organs. Hemodialysis in patients who have developed renal failure, may not change outcome with dialysis as organ deposition has occurred. Hemodialysis and HF may not be easily available in rural centers where PQ poisoning is common.
Immunosuppression	Acute inflammatory response to the poisoning eventually leads to lung fibrosis. Glucocorticoids such as methylprednisolone and dexamethasone and chemotherapeutic agents such as cyclophosphamide are used. Dexamethasone increases the expression of glycoprotein P receptors, resulting in reduction in PQ deposit in the lung and increased excretion in the urine.	Randomized controlled trials in comparing dexamethasone, methylprednisolone, and cyclophosphamide vs standard treatment have shown mortality benefit in the treatment arm. Limited by lack of follow-up and sample size calculation, and plasma PQ level measurements.
N-acetylcysteine (NAC)	N-acetylcysteine suppresses superoxide production and replenishes cysteine which is the rate-limiting step in the generation of glutathione.	No prominent human studies.
Vitamin C	Vitamin C donates electrons to free radicals and hence neutralizes them.	Promising results in rats, but no human studies.
Vitamin E	Reduction in lipid peroxidation and thereby lung toxicity.	No human studies
Desferrioxamine	Iron enhances the toxicity of PQ and the use of desferrioxamine is protective but does not reduce mortality.	To date, there are no studies with desferrioxamine in human subjects.
Salicylic acid	Inhibits cyclooxygenase. Scavenges hydroxyl radicals also inhibiting their production.	There are no human studies on salicylic acid till date but studies done on rats have shown that salicylic acid treated rats showed improved survival while the untreated group had 100% mortality.
Lung transplantation	In cases where it is feasible, this is an option for permanent lung damage caused by PQ.	

Table 2: Important clinical trials on the management of paraquat poisoning

Study	*Population*	*Drugs*	*Findings*
Lin et al.[38]	50 patients; RCT	Pulse dose methylprednisolone + cyclophosphamide	Lower incidence of renal failure, milder hypoxia in study group. 100% mortality in both control and study groups
Addo et al.[50]	72 patients, uncontrolled	High-dose dexamethasone + cyclophosphamide; potassium and magnesium supplementation	52 patients (72%) survived
Lin et al.[39]	23 patients; RCT	Pulse methylprednisolone + cyclophosphamide followed by daily dexamethasone till $PaO_2 > 80$ mm Hg, then repeat initial pulse	ARR for mortality in study group 54.4%, $p = 0.0272$
Afzali et al.[40]	20 patients; RCT	Pulse methylprednisolone + cyclophosphamide	ARR for mortality in study group 49.5%, $p < 0.05$

ARR, absolute risk reduction; RCT, randomized controlled trial

as per discretion of the clinician despite low strength of evidence in an attempt to curb the hyperinflammation and oxidative damage. In absence of any specific antidote, the patients must be managed meticulously even in presence of guarded prognosis and dismal outcome.

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