Review Paper

Paraquat: The Underestimated Lethal Pesticide

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ABSTRACT

Paraquat and diquat are popular herbicides which belong to the bipyridyl group. Paraquat was first synthesized in 1882, but began to be used as a herbicide only since the 1960s. It is available either in granular form or as water soluble concentrate which is an odourless brown liquid. The granular form is available as colourless crystals (dichloride salt) or a yellow solid [bis(methyl sulfate) salt]. In India, most of the concentrates of paraquat are available as 10-20% solutions. Paraquat is a rapidly acting herbicide and kills the tissues of green plants mainly by contact action with foliage. Ingestion of paraquat by humans is associated with high mortality, which is a fact that is not widely recognized. Estimated lethal dose is just 10 to 15 ml of the concentrate. Ingestion of 20 to 40 mg of paraquat ion per kg body weight results in death in most cases. It is important to treat all cases of paraquat ingestion as potentially fatal poisonings.

Key Words: Paraquat, Diquat, Herbicide

Introduction

Paraquat and diquat are widely used herbicides which belong to the bipyridyl group. Other bipyridyl herbicides which are rarely encountered include chlormequat, difenzoquat, and morfamquat. Paraquat is 1,1-dimethyl-4,4-bipyridylium dichloride, and was first synthesized in 1882, but began to be used as a herbicide only since the 1960s. It is available either in granular form (25-80 gm/kg), or as water soluble concentrate which is an odourless brown liquid (100-200 gm/L). The granular form is available as colourless crystals (dichloride salt) or a yellow solid (bis(methyl sulfate) salt). In India, most of the concentrates of paraquat are available as 10-20% solutions, and therefore 10 ml of a 20% solution can contain about 2 gm of paraquat.[1] Common brand names include *Weedol granules*, *Gramoxone solution, and Uniquat*.

Diquat is 1,1-ethylene-2,2-dipyridylium dibromide, and is less commonly used than paraquat. It has the same indications and mode of action as paraquat but produces much less severe pulmonary lesions.

Absorption through inhalation, skin contact, or eye contact is minimal, though prolonged contact can be hazardous. On ingestion, paraquat solution is much more rapidly absorbed than the granular form. After absorption it tends to accumulate in the lungs and kidneys. Paraquat has a large volume of distribution (1.2 to 1.6 L/kg). More than 90% of an absorbed dose is excreted by the kidneys as the parent compound within 12 to 24 hours.[2] Paraquat is distributed into all organs.

Highest concentrations are found in kidney and lung; paraquat also accumulates in muscle tissue, which may represent a reservoir, explaining prolonged detection of plasma or urine paraquat weeks or months following ingestion.[3]

Mode of Action & Toxicity

Paraquat is a rapidly acting herbicide. It kills the tissues of green plants by contact action with foliage and by some amount of translocation to the xylem.[4]

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Corneal injury and protracted opacification of the cornea may result following eye exposure to paraquat. Extensive loss of superficial areas of the corneal and conjunctival epithelium may occur.[5] Healing, although slow, is usually complete if given prompt medical care. Irritation of the skin and mucous membranes may be severe following paraquat exposure. After ingestion, sore throat and difficulty in swallowing can occur. Irritation of the gut including abdominal pain, nausea, vomiting, and diarrhoea may occur immediately following ingestion. Concentrated solutions of paraquat corrode the GI mucosa. Tachycardia, hypotension, and cardiorespiratory arrest can occur with large ingestions. Cerebral oedema may occur. Pancreatitis may develop in some cases of acute paraquat poisoning, and can cause severe abdominal pain.

The maximum damage is seen in the lungs where cellular injury is initiated by the NADPH-dependent reduction of paraquat to the monocation radical (PQ^+). Reaction with molecular oxygen yields the superoxide radical (O_2^-) and reforms the paraquat dication, ready to be reduced again. This process known as redox cycling is sustained by the extensive supply of electrons and oxygen in the lungs. This and the subsequent reactions explain why oxygen enhances the toxicity of paraquat, and paraquat enhances the toxicity of oxygen.[6] Two superoxide species form hydrogen peroxide in a reaction catalysed by superoxide dismutase. Superoxide and hydrogen peroxide undergo a series of iron-catalysed reactions to yield the hydroxyl radical (OH) which is thought to be the ultimate toxic element. The hydroxyl radical causes degradation of cell membranes through lipid peroxidation resulting in cellular death.

The estimated lethal dose is 10 to 15 ml of the concentrate. Ingestion of 20 to 40 mg of paraquat ion per kg body weight (7.5-15.0 ml of 20% (w/v) paraquat concentrate) results in death in most cases. Prudence requires that all cases of paraquat ingestion be treated as potentially fatal poisonings.

Clinical Features[7,8]

There are three types of clinical presentation -

I. Typical Form : (*ingestion of 30 to 50 mg/kg of paraquat*)
   a) Initial Phase – pain in the mouth, oesophagus, and stomach due to corrosion, vomiting, diarrhoea, dysphagia, aphonia. There may be gastric perforation/ gastrointestinal haemorrhage.
   b) Second Phase – begins after 2 to 5 days and is characterised by renal and hepatic toxicity, i.e., renal tubulopathy and centrilobular hepatic necrosis respectively. Although hepatic injury from exposure to paraquat may be quite severe, clinical outcome is generally not determined by hepatotoxic effects.
   c) Third Phase – begins after 5 days and is characterised by pulmonary fibrosis which leads to progressive respiratory failure.

II. Hyperacute Form : (*ingestion of more than 50 mg/ kg of paraquat*)
   There is rapid development of cardiogenic shock ending in death in 3 to 4 days. Renal and hepatic lesions are also common.

III. Subacute Form : (*ingestion of less than 30 mg/kg of paraquat*)
   This is characterised only by gastrointestinal manifestations.

Mortality in paraquat poisoning can be high and is related to two factors – concentration and quantity. Ingestion of 20% solution is associated with high mortality.[9] Swallowing more than a mouthful can cause death in 72 hours because it corresponds to ingestion of more than 50 mg/kg.[10] If it is less than a mouthful, death may be delayed upto 70 days and is usually due to pulmonary fibrosis. Pneumothorax, pneumopericardium and subcutaneous emphysema may develop in patients with paraquat induced lung injury.[11]

Yamamoto et al (2000) performed a prospective observational study of 43 patients with paraquat poisoning to evaluate the effects on haemodynamics and oxygen metabolism for the first 96 hours after admission.[12] Patients were divided into three groups based on the severity index of paraquat poisoning (SIPP = serum level on presentation in mg/l multiplied by the time since ingestion in hours). All patients with an SIPP of more than 50 died within 125 hours of ingestion of circulatory failure. These patients had lower cardiac index, decreased left ventricular stroke work index, decreased systemic vascular resistance, and increased oxygen extraction ratio. Only one of 13 patients with an SIPP of 10 to 50 survived, the rest died between 115 and 960 hours after ingestion of respiratory failure. This group had increased cardiac index, initially increased left ventricular stroke

work index, decreased systemic vascular resistance, increased oxygen delivery index and oxygen consumption index, and increasing oxygen extraction ratio. All patients with an SIPP of less than 10 survived.

Survivors of severe paraquat poisoning often develop progressive pulmonary fibrosis within 5 to 10 days or longer after exposure. Continued survival is dependent on the extent of lung involvement.

Occupational exposure to paraquat can cause a dry, cracking dermatitis and nail atrophy.

Diagnosis of a case of paraquat poisoning can be aided by the following -

1. X-ray of the chest may reveal patchy infiltration in the early stages, and opacification of one or both lung fields in later stages. However if death is due to the hyperacute form of presentation, no abnormalities may be noted on the chest x-ray.
2. Plasma paraquat level can be assayed by spectroscopy, radioimmunoassay, or HPLC. Serum levels greater than 0.2 mg/ml at 24 hours, and 0.1mg/ml at 48 hours are asociated with high mortality.[13]
3. Urine can be tested for gross amounts of paraquat by alkalizing 3 to 5 ml with a few mg of sodium bicarbonate, then adding a few mg of sodium dithionite. An intense blue-green color is a positive test.[14]
4. Urine paraquat level can be assayed by spectrophotometry. Survival is usually associated with levels less than 1mg/ml, while mortality is high when the level exceeds 10 mg/ml.
5. Monitor renal and liver function tests carefully. Obtain baseline urinalysis and monitor urine output.
6. Obtain baseline pulmonary function tests, chest x-ray, and ABGs and monitor serially for several days.

When submitting samples for chemical analysis it must be ensured that only plastic containers are used, since paraquat binds to glass.

Treatment Measures

All cases of paraquat ingestions should be considered as medical emergencies even if the patient is asymptomatic.

It is recommended that upper gastrointestinal endoscopy is done early to identify the extent and severity of corrosion. Stomach wash may be beneficial only if done within 1 hour of ingestion. Emesis and cathartics are contraindicated. Activated charcoal is of doubtful value. Pain due to corrosion may be relieved by ice-cold fluids (e.g., ice cream), mouthwashes, local anaesthetic sprays, and lozenges. Opiates may be required in some cases. Haemodialysis or haemoperfusion may be beneficial if undertaken within the first 10 to 12 hours.[15]

Supportive measures form the mainstay of treatment : protection of airway, maintenance of circulation, treatment of secondary infection, prevention or treament of renal failure, and treatment of complications. Oxygen must not be administered as far as possible since it enhances lung damage. Allow additional oxygen only in victims considered beyond rescue to relieve air hunger and terminal disease.

N-acetylcysteine may be of value. There are indications that if intravenous n-acetylcysteine and early haemodialysis (within 4 hours of ingestion) are undertaken, survival rate may improve. The combination of corticosteroids and cyclophosphamide has shown promise in reducing paraquat mortality, although efficacy has not been proven in prospective controlled clinical trials. Usual dose of cyclophosphamide is 15 mg/kg or maximum of 1 gm/day in 200 ml of 5% dextrose saline infused for 2 hours/day for two days.[16] Nonsteroidal anti-inflammatory agents, colchicine, collagen synthesis inhibitors, desferrioxamine, or total exclusion from external respiration may prevent lung fibrosis. However, the efficacy of these treatments has yet to be established in the treatment of human paraquat poisonings.

Pulmonary damage may be ameliorated by radiotherapy. However the current consensus is NOT to undertake radiotherapy because of lack of clinical evidence of efficacy.[17] Lung transplantation has not met with success in most cases where it was attempted, though some recent reports indicate that it could be beneficial.[18,19] Nitric oxide inhalation to maintain tissue oxygenation in anticipation of lung transplantation once all absorbed paraquat has been eliminated, is recommended by some investigators.[20]

Autopsy Features[21,22]

Ulceration is a common finding around lips and mouth. Oral and oesophageal mucosa appear reddened or desquamated, while ther may be erosion and patchy haemorrhages in the stomach. Liver may show pallor or

mottled fatty change; centrilobular necrosis has been described. Lungs often appear stiffened. There may be evidence of proliferative pulmonary fibrosis, fibrinous pleurisy, or scanty blood-stained pleural effusion. Cut surface reveals oedema. Kidneys may reveal evidence of tubular damage.

Conclusion

Up until now, bipyridyl herbicides such as paraquat have not received the importance they deserve. Since these compounds are commonly available in India, and are used quite indiscriminately, cases of accidental and suicidal exposure are being reported with increasing frequency. As these pesticides are among the most lethal, it is important to be familiar with the clinical presentation and treatment measures. This paper is an attempt at highlighting these aspects.

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