Paraquat & Diquat

HIGHLIGHTS

Toxic doses are life threatening

Impacts GI tract, kidney, lungs, liver, heart, other organs

Pulmonary fibrosis is the usual cause of death in paraquat poisoning

Diquat has greater renal activity

Can be measured in blood and urine by spectrophotometric, gas chromatographic, liquid chromatographic and radioimmunoassay

SIGNS & SYMPTOMS

Ingestion (either): burning pain in mouth, throat, chest, upper abdomen; pulmonary edema, pancreatitis, renal & CNS effects

Dermal (paraquat): dry and fissured hands, horizontal ridging or loss of fingernails, ulceration, abrasion

Diquat: CNS toxicity as nervousness, irritability, combativeness, disorientation, diminished reflexes

CHAPTER 12

Paraquat and Diquat

Paraquat and diquat are identified chemically as dipyridyls.

Paraquat is a synthetic, non-selective contact herbicide, marketed as paraquat, paraquat dichloride salt and bismethylsulfate salt. Liquid technical products range from 20% to 50% concentration, but the formulations used in the field range from 0.07% to 0.14%. It is a restricted use pesticide.

Diquat is usually prepared as the dibromide monohydrate salt, 15%-25% in liquid concentrates, but the formulations in the field are usually 0.23%. Diquat dibromide is a non-selective contact herbicide, desiccant and plant growth regulator for use as a general herbicide for control of broadleaf and grassy weeds in terrestrial non-crop and aquatic areas; as a desiccant in seed crops and potatoes; and for tassel control and spot weed control in sugarcane. Unlike paraquat, it is not registered as a restricted use pesticide.

PARAQUAT

Toxicology

When a toxic dose is ingested (see below), **paraquat** has life-threatening effects on the gastrointestinal tract, kidney, liver, heart and other organs. The LD_{50} in humans is approximately 3-5 mg/kg, which translates into as little as 10-15 mL of a 20% solution.[1,2] In spite of the fact that the lung is the primary target organ, toxicity from inhalation is rare.

Although pulmonary toxicity occurs later in paraquat poisoning than other manifestations, it is the most severe and, therefore, mentioned first. Pulmonary effects represent the most lethal and least treatable manifestation of toxicity from this agent. The primary mechanism is through the generation of free radicals with oxidative damage to lung tissue.[1,2] While acute pulmonary edema and early lung damage may occur within a few hours of severe acute exposures,[3,4] the delayed toxic damage of pulmonary fibrosis, the usual cause of death, most commonly occurs 7-14 days after the ingestion.[5] In those patients who ingest a very large amount of concentrated solution (20%), some have died more rapidly from circulatory failure (within 48 hours) prior to the onset of pulmonary fibrosis.[5]

Both types I and II pneumatocytes appear to selectively accumulate paraquat. Biotransformation of the paraquat in these cells results in free-radical production with resulting lipid peroxidation and cell injury.[1,2,3] Hemorrhagic proteinaceous edema fluid and leukocytes infiltrate the alveolar spaces, after which there is rapid proliferation of fibroblasts. There is a progressive decline in arterial oxygen tension and CO_2 diffusion capacity. Such a severe impairment of gas exchange causes progressive proliferation of fibrous connective tissue in the alveoli and eventual death from asphyxia and tissue anoxia.[6] One study of survivors suggests that some of the fibrous toxic damage may be reversible, as evidenced by markedly improved pulmonary function tests 3 months after survival.[7]

Local skin damage includes a contact dermatitis. Prolonged contact will produce erythema, blistering, abrasion, ulceration and fingernail changes.[8,9] Although absorption across intact skin is slow, abraded or eroded skin allows efficient absorption.

The gastrointestinal (GI) tract is the site of initial or Phase 1 toxicity to the mucosal surfaces following ingestion of the substance. This toxicity is manifested by swelling, edema and painful ulceration of the mouth, pharynx, esophagus, stomach and intestine. With higher levels, other GI toxicity includes centrizonal hepatocellular injury that can cause elevated bilirubin, and hepatocellular enzymes such as AST, ALT, LDH and alkaline phosphatase.

Damage to the proximal renal tubule occurs and is often more reversible than the destruction to lung tissue. However, impaired renal function may play a critical role in determining the outcome of paraquat poisoning. Normal tubule cells actively secrete paraquat into the urine, efficiently clearing it from the blood; but high blood concentrations poison the secretory mechanism and may destroy the cells. Diquat poisoning typically results in greater renal injury than paraquat.[10]

Focal necrosis of the myocardium and skeletal muscle are the main features of toxicity to any type of muscle tissue and typically occurs following the Phase 1 gastrointestinal toxicity.

Ingestion has been reported to cause cerebral edema and brain damage. At necropsy, brain damage was found in the form of moderate neuronal depletion, probably secondary to anoxia, and damage to the central white matter and particularly the brain around the lateral and third ventricles. Examination of the brain by electron microscopy showed edema and destruction of myelin, with abundant myelin breakdown products, and astrocytic fibrous gliosis.[11]

Although much concern has been expressed about effects of smoking paraquat-contaminated marijuana, toxic effects by this mechanism have been either very rare or nonexistent. Most paraquat that contaminates marijuana is pyrolyzed to dipyridyl during smoking, which is a product of leaf (including marijuana) combustion and presents little toxic hazard.

Signs and Symptoms of Poisoning

Initial clinical signs depend upon the route of exposure. Early symptoms and signs of poisoning by ingested paraquat are burning pain in the mouth, throat, chest and upper abdomen, due to the corrosive effect of paraquat on the mucosal lining. Diarrhea, which is sometimes bloody, can also occur. Giddiness, headache, fever, lethargy and coma are other examples of CNS and systemic findings. Pancreatitis may cause severe abdominal pain. Proteinuria, hematuria, pyuria and azotemia reflect renal injury. Oliguria/anuria indicates acute tubular necrosis. Because the kidneys are almost the exclusive route of paraquat elimination from body tissues, renal failure fosters a buildup of tissue concentration, including the very important concentration in the lung.

Unfortunately, this pathogenic sequence may occur in the first several hours following paraquat ingestion, generating lethal concentrations of paraquat in lung tissue before therapeutic measures to limit absorption and enhance disposition have taken effect. It is probably for this reason that methods for enhancing paraquat disposition several hours following ingestion have had little effect on mortality.[9]

Cough, dyspnea and tachypnea usually appear 2-4 days following paraquat ingestion but may be delayed as long as 14 days. Progressive cyanosis and dyspnea reflect deteriorating gas exchange in the damaged lung. In some cases, the coughing up of frothy sputum (pulmonary edema) is the early and principal manifestation of paraquat lung injury.[9]

Dermal signs are common among agriculture workers with acute skin exposure to paraquat. Particularly in concentrated form, paraquat causes localized injury

Paraquat & Diquat
TREATMENT

Immediate GI decontamination with Bentonite, Fuller's Earth or activated charcoal

Maintain urinary output by administering IV, but monitor fluids in case of renal failure

Decontaminate eyes and skin

CONTRAINDICATED

Supplemental oxygen (unless patient develops hypoxemia)

Paraquat
COMMERCIAL PRODUCTS

Bonfire
Firestorm
Gramoxone
Helmquat
Para-Shot
Parazone
Quik-Quat

Diquat
COMMERCIAL PRODUCTS

Chemsico
Rapid Kill
Razor Burn
Reglone
Touchdown
Weedtrine-D

to tissues with which it comes into contact. Fatal poisonings are reported to have occurred as a result of protracted dermal contamination by paraquat, but this is likely to occur only when the skin's barrier integrity is impaired due to abrasion, erosion or other pathologic processes. In these cases, more efficient systemic absorption can occur. With an intact dermal barrier, paraquat leaves the skin of the hands dry and fissured, and causes horizontal ridging of the fingernails. Chronic exposure may even result in the loss of fingernails. Prolonged contact with skin will create ulceration and abrasion sufficient to allow systemic absorption.[9]

In addition, some agriculture workers can be exposed through prolonged inhalation of spray droplets and develop nosebleeds because of local damage. However, inhalation has not resulted in systemic toxicity because of the low vapor pressure and lower concentration of paraquat field formulations.

Eye contamination with paraquat concentrate or higher concentration diluted solutions results in severe conjunctivitis and sometimes protracted corneal opacification.[12,13]

The hepatic injury from paraquat may be severe enough to cause jaundice, which signifies severe injury. However, hepatotoxicity is rarely a major determinant to clinical outcome. No hepatic signs or symptoms are present other than the abnormal laboratory values mentioned under the toxicology section.

Clinical experience has offered a rough dose-effect scale on which to base prognosis in cases of paraquat ingestion[9]:

1. Less than 20 mg paraquat ion per kg body weight (less than 7.5 mL of 20% [w/v] paraquat concentrate). No symptoms or only gastrointestinal symptoms occur. Recovery is likely.

2. Twenty to 40 mg paraquat ion per kg body weight (7.5-15.0 mL of 20% [w/v] paraquat concentrate). Pulmonary fibroplasia ensues. Death occurs in most cases, but may be delayed 2-3 weeks. Multiple organ damage will occur.

3. More than 40 mg paraquat ion per kg body weight (more than 15.0 mL of 20% [w/v] paraquat concentrate). Multiple organ damage occurs as in Class 2 but is more rapidly progressive. The gastrointestinal effects are often characterized by marked ulceration of the oropharynx. Mortality is essentially 100% in 1-7 days.

DIQUAT

Toxicology

Diquat poisoning is less common than paraquat poisoning, thus the human reports and animal experimental data for diquat poisoning are less extensive than for paraquat. Systemically absorbed diquat is not selectively concentrated in lung tissue, as is paraquat, and pulmonary injury by diquat is less prominent. In animal studies, diquat causes mild, reversible injury to type I pneumatocytes but does not injure the type II cells. No progressive pulmonary fibrosis has been noted in diquat poisoning.[14,15]

However, diquat has severe toxic effects on the central nervous system that are not typical of paraquat poisoning.[14,15] While laboratory experimentation has suggested that diquat is not directly neurotoxic, there have been relatively consistent pathologic brain changes noted in reported fatal cases of diquat poisoning. These consist of brain stem infarction, particularly involving the pons.[16] It is not clear whether these postmortem changes represent direct toxicity or secondary effects related to the systemic illness and therapy. (See *Signs and Symptoms* section below for CNS clinical effects.)

Signs and Symptoms of Poisoning

In many human diquat poisoning cases, clinical signs of neurologic toxicity tend to be the most important. These include nervousness, irritability, restlessness, diminished reflexes, combativeness, disorientation, nonsensical statements and inability to recognize friends or family members. Neurologic effects may progress to coma, accompanied by tonic-clonic seizures, and result in the death of the patient.[14,15] Parkinsonism has also been reported following dermal exposure to diquat.[17]

Except for the CNS signs listed in the preceding paragraph, early symptoms of poisoning by ingested diquat are similar to those from paraquat, reflecting diquat's corrosive effect on tissues. They include burning pain in the mouth, throat, chest and abdomen; intense nausea and vomiting; and diarrhea. If the dosage was small, these symptoms may be delayed 1-2 days. Blood may appear in the vomitus and feces. Intestinal ileus, with pooling of fluid in the gut, has characterized several human poisonings by diquat.[10]

The kidney is the principal excretory pathway for diquat absorbed into the body. Renal damage is, therefore, an important feature of poisonings. Proteinuria, hematuria and pyuria may progress to renal failure and azotemia. Elevations of serum alkaline phosphatase, AST, ALT and LDH reflect liver injury. Jaundice may develop.

If the patient survives several hours or days, circulatory function may fail because of dehydration. Hypotension and tachycardia can occur, with shock resulting in death. Other cardiorespiratory problems may develop such as toxic cardiomyopathy or a secondary infection such as bronchopneumonia.

Diquat is somewhat less damaging to the skin than paraquat, but irritant effects may appear following dermal contamination with the concentrate. There is probably significant absorption of diquat across abraded or ulcerated skin.

The great majority of poisonings by paraquat and diquat (discussed below) have been caused by ingestion with suicidal intent, particularly in Japan[16] and many developing countries. Since 1987, there has been a decline in most countries in the total numbers of suicidal deaths attributed to paraquat and diquat. Nearly all of the relatively few occupationally related poisonings have been survived, but the mortality rate among persons who have swallowed paraquat or diquat remains high.[2,5] Avoidance of this mortality will probably have to rely on preventive strategies or on stopping gastrointestinal absorption very soon after the toxicant has been ingested.

Even though intestinal absorption of dipyridyls is relatively slow, lethal uptake by critical organs and tissues apparently occurs within 18 hours, possibly within 6 hours, following ingestion of toxic quantities of paraquat or diquat. Dipyridyls have large volumes of distribution. Once distribution to tissues has occurred, measures to remove dipyridyls from the blood are very inefficient in reducing the total body burden.

Several strategies are being tested to reduce the frequency of these occurrences. These include the addition of emetics, stenching agents, gelling substances and bittering agents such as sodium denatonium.

Confirmation of Poisoning

At some treatment facilities, a simple colorimetric test is used to identify paraquat and diquat in the urine and give a rough indication of the magnitude of absorbed dose. To one volume of urine is added 0.5 volume of freshly prepared 1% sodium dithionite (sodium hydrosulfite) in one normal sodium hydroxide (1.0 N NaOH). The color is observed after 1 minute. Development of a blue color indicates the presence of paraquat in excess of 0.5 mg per liter. Both positive and negative controls should be run to ensure that the dithionite has not undergone oxidation in storage.

When urine collected within 24 hours of paraquat ingestion is tested, the dithionite test appears to have some approximate prognostic value: concentrations less than 1 milligram per liter (no color to light blue) generally predict survival, while concentrations in excess of 1 milligram per liter (navy blue to dark blue) often foretell a fatal outcome. Analysis of serum by a sodium dithionite test has been reported to predict outcome in paraquat exposures. In one center a positive test was associated with 100% mortality, while negative or equivocal tests resulted in a 68% survival rate.[18]

Diquat in urine yields a green color with the dithionite test. Although there is less experience with this test in diquat poisonings, the association of bad prognosis with intense color is probably similar.

Paraquat and diquat can be measured in blood and urine by spectrophotometric, gas chromatographic, liquid chromatographic and radioimmunoassay methods. These tests are available in numerous clinical reference laboratories and sometimes by the manufacturing company. Paraquat poisonings in which plasma concentrations do not exceed 2.0, 0.6, 0.3, 0.16 and 0.1 mg per liter at 4, 6, 10, 16 and 24 hours, respectively, after ingestion are likely to survive.[19] A comparison of several methods of measuring plasma paraquat levels revealed comparable results. However, while the positive predictive value for death was quite high, the ability to predict survival was much lower.[20]

Lung Imaging

It has been reported that high-resolution computerized tomography of the lungs may be of predictive value in acute paraquat poisoning. A calculation is made of areas of ground glass opacities (GGOs) on tomography. In one study no patient survived when the area was greater than 40% and all survived when the area was less than 20%.[21] This study may be useful in evaluating newer therapeutic approaches.

Treatment of Paraquat and Diquat Toxicosis

1. Flush skin immediately with copious amounts of water to decontaminate. Irrigate the eyes with clean water for a prolonged period to remove material splashed in the eyes. Eye contamination should thereafter be treated by an ophthalmologist. Mild skin reactions usually respond to simple avoidance of further contact, but the irritation may take several weeks to resolve. Severe dermatitis with inflammation, cracking, secondary infection or nail injury should be treated by a dermatologist.

2. If paraquat or diquat has been ingested in any amount, immediately administer an adsorbent. This is the one therapeutic measure most likely to affect the outcome of paraquat or diquat ingestion favorably. Bentonite (7.5% suspension) and Fuller's Earth (15% suspension) are highly effective but sometimes not available.

Dosage of Bentonite and Fuller's Earth

- ***Adults and children over 12 years: 100-150 gm***
- ***Children under 12 years: 2 gm/kg body weight***

CAUTION: ***Hypercalcemia and fecaliths have sometimes occurred following administration of Fuller's Earth.***

Activated charcoal is nearly as effective, and is widely available. This treatment is discussed in **Chapter 3, *General Principles***.

3. Secure a blood sample as soon as possible for paraquat analysis and urine samples for either paraquat and/or diquat. Serial samples of urine for either agent and plasma for paraquat may be followed for prognostic information.

4. Do not administer supplemental oxygen until the patient develops severe hypoxemia. High concentrations of oxygen in the lung increase the injury induced by paraquat and possibly by diquat as well. There may be some advantage in placing the patient in a moderately hypoxic environment, *i.e.,* 15%-16% oxygen, although the benefit of this treatment has not been established empirically in human poisonings. Inhalation of nitric oxide has been suggested as a method to maintain tissue oxygenation at low inspired oxygen concentrations but is of unproven efficacy. When the lung injury is so far advanced that there is no expectation of recovery, oxygen may be given to relieve air hunger.

5. In serious poisonings, provide care in an intensive care setting to allow proper monitoring of body functions and skilled performance of necessary invasive monitoring and procedures.

6. As it is essential to maintain adequate urinary output,[3] administer intravenous fluids: isotonic saline, Ringer's solution or 5% glucose in water. This is highly advantageous early in poisonings as a means of correcting dehydration, accelerating toxicant excretion, reducing tubular fluid concentrations of paraquat and correcting metabolic acidosis. However, fluid balance must be monitored carefully to forestall fluid overload if renal failure develops. Monitor the urine regularly for protein and cells to warn of impending tubular necrosis. Intravenous infusions must be stopped if renal failure occurs, and extracorporeal hemodialysis is indicated. Hemodialysis is not effective in clearing paraquat or diquat from the blood and tissues.

7. Consider hemoperfusion over cellophane-coated activated charcoal. The procedure has been used in many paraquat poisonings because the adsorbent does efficiently remove paraquat from the perfused blood. However, recent reviews of effectiveness have failed to show any reduction in mortality as a result of hemoperfusion.[2,3,22] The apparent reason for this is the very small proportion of paraquat body burden carried in the circulating blood even when only a few hours have elapsed after ingestion. Theoretically, a patient who can be hemoperfused within 10 hours of paraquat ingestion may derive some marginal benefit, but this has not been demonstrated. If hemoperfusion is attempted, blood calcium and platelet concentrations must be monitored. Calcium and platelets must be replenished if these constituents are depleted by the procedure.

8. Control seizures following procedure in **Chapter 3**.

CAUTION: ***Be prepared to assist ventilation mechanically if respiration is depressed, to intubate the trachea if laryngospasm occurs and to counteract hypotensive reactions.***

9. Consider administering cyclophosphamide and methylprednisolone. Many drugs have been tested in animals or given in human dipyridyl poisonings without clear evidence of benefit or harm: corticosteroids, superoxide dismutase,

propranolol, cyclophosphamide, vitamin E, riboflavin, niacin, ascorbic acid, clofibrate, desferrioxamine, acetylcysteine, terpin hydrate and melatonin.[23] However, recent evidence regarding the use of cyclophosphamide and methylprednisolone shows that they may be effective in reducing the mortality associated with moderate-to-severe paraquat poisoning. Two studies found a reduced mortality associated with the treatment, while one study found no difference.[24] The dosages used for cyclophosphamide and methylprednisolone were 1 gram daily for 2 days and 1 gram daily for 3 days, respectively, given after the hemoperfusion. Each drug was administered as a 2-hour infusion; white cell counts, serum creatinine levels, chest radiography and liver function tests were monitored.[24] Two controlled trials seem to have confirmed benefit from cyclophosphamide and methylprednisolone therapy with reduction of mortality from 81% to 33% in one study and 86% to 31% in another.[24,25] The protocols for administration of the drugs were similar but not identical.

10. Manage pain with morphine sulfate. Morphine sulfate is usually required to control the pain associated with deep mucosal erosions of the mouth, pharynx and esophagus, as well as abdominal pain from pancreatitis and enteritis.

Dosage for Morphine Sulfate

- ***Adults and children over 12 years: 10 - 15 mg subcutaneously every 4 hours.***
- ***Children under 12 years: 0.1 - 0.2 mg /kg body weight every 4 hours.***

Mouthwashes, cold fluids, ice cream or anesthetic lozenges may help to relieve pain in the mouth and throat.

With severe pulmonary toxicity, recovery of the patient may only be accomplished by lung transplantation. However, the transplanted lung is susceptible to subsequent damage due to redistribution of paraquat.[26]

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