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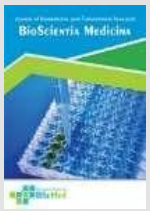

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Diagnosis and Management of Paraquat Intoxication

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A B S T R A C T

Paraquat poisoning is a clinical toxicological emergency due to the active ingredient of this type of herbicide, gramoxone, with a high mortality rate due to high toxicity, and no antidote has yet been found. Paraquat intoxication can cause multi-organ failure if ingested accidentally or spontaneously because paraquat quickly produces ROS (reactive oxygen species), which causes cell damage through lipid peroxidation, NF-kB activation, mitochondrial damage, and apoptosis in many organs. This results in rapid nephrotoxic and hepatotoxic as well as pulmonary fibrosis. Clinical manifestations depend on the level of paraquat ingested, which can be in the form of local toxicological and systemic toxicological effects. Laboratory tests for diagnosing paraquat toxicity can be used for toxicological analysis of plasma and urine. Management of paraquat intoxication is primarily to remove paraquat from the gastrointestinal tract (prevent absorption) by using activated charcoal, changing the toxicokinetics of the herbicide (increasing serum paraquat elimination) by hemoperfusion and hemodialysis, as well as modifying its toxicodynamics with anti-inflammatory drugs such as immunosuppressants (corticosteroids and cyclophosphamide) and antioxidants (N -acetylcysteine and vitamin C).

1. Introduction

Paraquat (1,1-dimethyl,4,4-bipyridyl) is one of the active ingredients of a type of herbicide, gramoxone, which works fast are widely used for chemical weed control on agricultural land around the world, including in Indonesia. Paraquat is highly toxic to the human body and can cause acute poisoning if accidentally or spontaneously ingested.[1,2] The World Health Organization (WHO) reports that every year there are 1-5 million cases of pesticide poisoning in farmers, 80% of which occur in developing countries. Worldwide, paraquat causes 20 deaths per million people, and it is the cause of death in more than 100,000 suicides each year. Paraquat poisoning is associated with a high mortality rate (50-90%) and is a serious public health problem, especially in Asian countries. Sri Lanka reports around 3–4 people poisoned by herbicides per 100,000 population annually. The death rate for paraquat poisoning is 61% in South India. Paraquat poisoning does not only occur in developing countries, but paraquat also occurs in developed countries such as the UK, which causes 56% of all deaths due to pesticides. The incidence rate is 3.8 cases/100,000 population/year. European Union countries report that French Guiana has the highest rate of paraquat poisoning, with a fatality rate of 52%.[3-7]

The incidence of paraquat poisoning is 65% of men and 35% of women. The mean age for adults is 31 years and for children it is 13.4 years. The mortality

rate ranges from 35-62% in the world. The highest mortality occurred in the adult population (65%) and in children (22%). Most cases of paraquat intoxication occur due to suicide attempts (84%). The cause of death of paraquat poisoning patients was 82.3% of deaths due to multi-organ failure and 17.7% of patients died due to acute lung injury (ALI).[5,8] Paraquat intoxication causes multi-organ failure, causing increased morbidity and mortality. Paraquat enters the body in various ways, whether oral, local contact, or injection, after contact it will be quickly absorbed and causes an acute poisoning reaction that damages the digestive tract, kidneys, liver, lungs, heart, suprarenal glands, central nervous system, muscles, and spleen, resulting in multi-organ failure, up to 50-80% of deaths. Paraquat is highly toxic to humans after consumption. Early clinical manifestations of paraquat consumption can include mouth ulcers, nausea, vomiting and diarrhea. After ingestion, some paraquat is absorbed rapidly and within 12-24 hours is mostly excreted in the urine without further metabolism. Acute systemic effects may include pulmonary edema, convulsions, cardiac, renal and hepatic failure. Causes of death are multi-organ failure, such as metabolic acidosis, depression of myocardial function and respiratory failure due to pulmonary fibrosis, and renal or hepatic failure.[9-12]

Paraquat poisoning can cause organ failure, where the lungs are the main target organ can be acute or chronic. Exposure to herbicide class paraquat dichloride concentrates in lung tissue and causes progressive and irreversible damage (pneumonitis and fibrosis) causing death within 5 - 31 days after lung injury. This is because lung damage occurs due to alveolar damage due to ingestion oral and upper respiratory tract damage due to inhalation. Toxicity in the lungs is marked by the appearance of pulmonary edema, damage to the alveoli membranes of the lungs, and then develops into pulmonary fibrosis.[2,9,13,14] Paraquat death depends on the dose ingested. Patients who ingest large doses (50-100 ml) cause severe poisoning and show fulminant multiple organ dysfunction syndrome (MODS) with clinical features of pulmonary edema, hepatic and renal failure, heart, and central nervous system involvement with seizures, severe poisoning, and in this group death will occur within a few days due to MODS. Patients who ingested smaller amounts showed predominant involvement of the two organs – the kidneys and lungs (renal failure and pulmonary fibrosis). Although classified as moderate severity, mortality in this group is still above 50%. Paraquat accumulates in the lungs with damage to lung cells causing decreased gas exchange and respiratory distress. The pulmonary lesion has two phases: acute alveolitis for 1-3 days followed by secondary fibrosis. Gastrointestinal toxicity often presents as lesions of the oral mucosa and tongue (paraquat tongue).[15,16]

The mortality rate due to paraquat toxicity is still high, in intensive care centers that often treat >50% paraquat intoxication because of its direct toxicity and the absence of effective treatment. Currently there are no standard guidelines for the management of paraquat poisoning. Current treatments for poisoning include preventing paraquat absorption with activated charcoal or gastric lavage, increasing paraquat elimination by hemodialysis, and administering glucocorticoids, immunosuppressants, and oxidants. This approach is of limited benefit in preventing the toxic effects of paraquat.[4,5,18,19] Paraquat poisoning is a clinical toxicological emergency, which needs to be diagnosed, treated quickly and appropriately.[12] Considering the large number of herbicide users, especially the paraquat dichloride class in Indonesia, the poisoning and death rates due to paraquat toxicity are very high due to the fact that no antidote for paraquat toxicity has been found.[2,9]

Paraquat chemistry

Paraquat (1,1-dimethyl4, 4'bipyridylium chloride), Bipyridyl compound, is one of the active ingredients of the herbicide class bipyridilium type gramoxone, bipyridylium group. The chemical composition of paraquat is C12H14N2 which is a type of herbicide the most widely used in agricultural land in the world, including in Indonesia. Characteristics of paraquat

have a molecular weight of 186.3 (ion), 257.2 (dichloride) with a specific gravity (20°C) of 1,240–1,260 g/cm^3. A synonym for paraquat is methyl viologen. The physical state of paraquat is white (pure salt), yellow (technical product) crystalline, odorless, hygroscopic powder. The melting point of paraquat dichloride melts by decomposition at 340°C to form a toxic vapor. Paraquat is very soluble in water, slightly soluble in alcohol, and insoluble in organic solvents. Paraquat is non-explosive and non-flammable in liquid formulations.[13,20] Paraquat is corrosive to metals and incompatible with alkyl aryl sulfonate wetting agents and strong oxidizing agents, stable in acid solutions but easily hydrolyzed by alkaline solutions (at pH > 12). Paraquat can withstand long-term storage and is also stable at room temperature.[13,20]

Paraquat toxicokinetics

Absorption

Paraquat is very quickly absorbed after inhalation and ingestion through the intestines, about 10% of which is swallowed is absorbed. Paraquat is absorbed orally (10 – 30%), about 1% -5% is absorbed in the intestine. The main site of absorption of paraquat is in the small intestine, and small amounts are absorbed in the stomach. Due to the erosive nature of paraquat, which causes gastrointestinal erosion, absorption increases by 10% to 90%. The absorption system uses a carrier-mediated transport system on the brush border membrane. After being swallowed, paraquat is absorbed quickly but incompletely. Only 10-30% of paraquat is not absorbed. Oral paraquat bioavailability varies, also estimated to be below 5-10% within one to six hours.[6,20-22]

Most paraquat poisoning is caused by accidental or intentional oral ingestion. Jejunum is the main pathway for the absorption of paraquat after oral ingestion. The three main transporter systems in the absorption process are choline, polyamines, and amino acid transport systems. The choline transport system, the polyamine transport system, and the amino acid transport system are related to the transporters involved in the toxicokinetic process of intestinal absorption of paraquat through the epithelial cells of the small intestine. Paraquat has an important role as an endogenous absorption compound in quaternary ammonium compounds (QACs) such as choline, namely as a facilitator and a diffuse component in the absorption process in the intestine. Therefore Paraquat has chemical properties similar to choline. The choline transporter system is mediated by a carrier-mediated transport system expressed on the membrane brush border in small intestinal epithelial cells and is associated with the absorption of paraquat into the systemic circulation. Paraquat interferes with cholinergic transmission by reducing acetylcholine levels and blocking acetylcholinesterase in nerve cells and pneumocytes. The researchers found that the pump Na+/Ca2+ influx, pH, and temperature mediated paraquat absorption.[4,13]

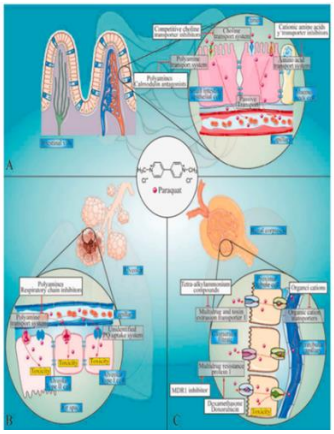

Figure 1. Paraquat toxicokinetic transporter.[4]

The polyamine transport system was the first to be identified in paraquat adsorption because of the structural similarities between paraquat and the natural substrate polyamines. Polyamines are mainly derived from the decarboxylation of several amino acids, especially cationic amino acids such as lysine and arginine. Because polyamines are essential for cell proliferation, this transporter system exists in the body, including in intestinal epithelial cells, and is involved in the active accumulation of paraquat. In intestinal epithelial cells, structural similarities allow the absorption of polyamines and these amino acids to be common transporters, suggesting that several amino acid transporters are involved in paraquat absorption. Paraquat absorption via polyamine transporters is an ATP-dependent process regulated by the Ca2+/calmodulin complex. The total absorption of paraquat through the small intestine is around 1%-5%, whereas 1-6 hours after ingestion is the window period to prevent accumulation of paraquat throughout the body.[4,23]

Absorption through intact skin is approximately 0.5%, increases if the skin is broken, and can cause death. Once ingested, paraquat has high concentrations in highly perfused tissues such as the lungs, brain, heart, liver, and kidneys. Plasma concentrations are relatively stable for 30 hours. Peak concentration (Cmax) in plasma will be reached within 4 hours and sometimes 2 hours after poisoning, detected in the urine as early as an hour after ingestion. The concentration in the human bloodstream decreases rapidly in the first 15 hours after peak plasma time (Tmax) to much lower levels.[1,13,21] The half-life of paraquat is 5 hours, with a lethal dose of 50%. The lethal dose in humans is estimated to be 3-5 mg/kg, if converted to about 10-15 mL in 20% paraquat solution. Paraquat is 90% absorbed and excreted in a fixed form in the urine within 12-24 hours. After 1 hour of digestion, paraquat can already be detected in the urine.[13,15] Paraquat concentrations in the lungs increase progressively several times compared to plasma concentrations. In the first 30 hours, plasma paraquat concentrations are markedly reduced by decreased absorption of the herbicide from the gastrointestinal tract. Food consumption may decrease the amount of systemic absorption or increase its elimination by extracorporeal techniques from plasma and lethal concentrations will not reach the lungs. Several studies have concluded that what is responsible for determining the level of lung levels is the Cmax plasma level of paraquat. The use of an effective adsorbent to prevent paraquat from entering the blood should be administered within a few hours, or within the first few minutes after taking paraquat.[13,15]

Distribution

After absorption, the plasma paraquat concentration reaches a peak, and paraquat is distributed rapidly to highly perfused tissues such as the kidney, liver, muscle, heart, and highly vascularized tissues such as the lungs, especially type I and II pneumocytes, and Clara cells in the bronchioles, some remain are in the intravascular space which has a volume of distribution between 1.2-1.6 L/kg. Paraquat accumulates a lot in the lungs because of the polyamine transport system (PTS). Morphological and autoradiographic studies found that the transporter responsible for the distribution of this paraquat was localized in alveolar type I, type II, and Clara bronchioles but not in alveolar endothelium or macrophages.[4,6,13] Plasma paraquat concentrations showed an average half-life distribution (t1/2α) of 5 hours and an average elimination half-life (t1/2β) of 84 hours. Paraquat binds weakly to serum proteins, is rapidly distributed to all tissues with a distribution half-life of four to six hours, and accumulates in alveolar cells. Peak concentrations in the blood occur within about six hours after ingestion. After several hours, renal clearance decreases rapidly in severe poisoning. This causes a small portion of paraquat which is distributed to deeper tissues, to be eliminated slowly by the kidneys for days to weeks.[6,13,22]

Paraquat accumulates in the lungs mainly through active transfer and polyamine transporters. These polyamine transporters are mainly involved in the

transport of polyamines such as spermine, spermidine, and putrescine. The concentration of paraquat in the lungs is ten times higher than that in plasma. Cellular uptake in the lungs is carried out by alveolar epithelial cells and via polyamine uptake pathways. Cellular absorption of paraquat occurs because of the structural similarities between paraquat and androgen diamines and polyamines, including putrescine and spermidine. Studies have shown that paraquat selectively accumulates in lung tissue and results in severe tissue damage and fibrosis in the lungs.[4,6,23]

Peak concentrations in the lungs occur 4-5 hours after intravenous administration, and 5-7 hours after ingestion, under conditions of normal renal function. Lethal concentrations in the lungs can be reached within 6 hours after ingestion of 35 mg/kg. The initial T1/2 of paraquat in the lungs is much higher than the t1/2 in the tissues of other organs (e.g., kidney, liver, muscle, adrenal, spleen, heart, testes). This proves that the accumulation of paraquat in the lungs is higher.[13,15]

Immunohistochemical studies used to demonstrate the distribution and localization of paraquat in several organs using a mouse model showed that paraquat was localized in the skin in the ducts of the sweat glands and sebaceous glands between 3 - 10 days after paraquat injection and was found to be weakly positive in the eyes in the retinal nerve fibers between 3 -10 days after injection, paraquat is localized in the corneal epithelial cells within the first 3 hours and between 3 - 10 days after paraquat administration. [13,15]

Paraquat is also found in the immune system and the hematopoietic system. In the bone marrow, paraquat is found in several types of blood cells (granulocytes, erythrocytes, and megakaryocytes) in its precursors between 24 hours and 7 days after injection. Paraquat is mainly localized in the thymus in the medulla between 12 hours to 7 days after administration, whereas in the spleen, it is localized mainly in the red pulp within 12 hours to 10 days after paraquat administration. In the stomach, paraquat localized to epithelial cells between 24 hours and 10 days after injection, whereas in the esophagus, paraquat localized to epithelial cells and the mucosal lamina propria between 12 hours and 10 days after administration. In the intestine, paraquat localized in epithelial cells 3 hours after injection. Three hours after injection, paraquat localized in hepatocytes and in the kidney in distal tubular epithelial cells. Jaiswal et al. (2002) demonstrated the binding of paraquat to plasma albumin using fluorescence techniques.[4,24]

Metabolism

Paraquat is not actively metabolized in the body. More than 90% is excreted unchanged by the kidneys.[21] Apart from being an important place for enzymatic metabolism and detoxification, the liver is also responsible for metabolizing some of the paraquat in blood circulation. Paraquat induces toxicity due to its ability to affect redox cycles and form reactive oxygen species (ROS). Paraquat is metabolized by several enzyme systems, such as nicotinamide adenine dinucleotide phosphate (NADPH), Cytochrome p450 reductase, xanthine oxidase, NADH, and ubiquinone oxidoreductase, and nitric oxide synthase.[1,6,8,25] Paraquat metabolism through this enzyme system causes the formation of paraquat mono-cation radical (PQ+) in the cell. PQ+ is rapidly reoxidized to PQ2+, and this process triggers the formation of superoxide (O_2-). O_2 acts as an electron receptor, and NADP acts as an electron donor in this reaction. This reaction further forms hydroxyl free radical (HO). Nitric oxide (NO) combines with O_2 to form peroxynitrite (ONOO-), which is a very strong oxidant. NO is enzymatically produced from L-arginine by NO synthase, and paraquat also directly or indirectly induces NO synthase, which mediates nitric oxide production. The formation of ROS and nitrites causes multi-organ toxicity, but the most serious toxicity is found in the lungs according to the concentration gradient. Only a small part of paraquat for oral consumption is metabolized, and a large part is excreted without metabolism in the urine. Of the total oral dose of paraquat, 30% is a product of

metabolism in the intestine, then excreted in the urine.[1,6,8,13]

Elimination

Paraquat is quickly excreted and eliminated by the kidneys, by elimination in two ways, namely glomerular filtration and tubular secretion, and minimal tubular reabsorption, then 90% of the absorbed paraquat is excreted within 12 to 24 hours if the kidney function is normal. Paraquat filtration in the glomerulus involves two steps: the first step enters cations from the blood into the basolateral membrane of the proximal tubular cells, while the second step exits the apical membrane into the urine. There are three transporters that play a role in the excretion process of paraquat in the kidneys, namely organic cation transporters (OCTs), multidrug and toxin extrusion (MATE) transporter, and multidrug resistance protein 1 (MDR1).[4,13,22] Paraquat is actively excreted and can be detected in the urine one hour after ingestion. In normal kidney function, clearance paraquat (CLPQ) is much greater than creatinine clearance (CLCr), which allows the excretion of high concentrations of large amounts of the herbicide within the first few minutes after ingestion. The CLPQ (28 ml/min) is greater than the glomerular filtration rate (GFR), indicating an active secretory process, which can exceed 200 ml/min when renal function is normal. High doses of paraquat cause tubular necrosis with reduced GFR and rapid tubular secretion, and increased t1/2 elimination. After administration of large doses of Paraquat (20 mg/kg), CLPQ and CLCr decreased, due to renal tubular necrosis, causing a decrease in urine output and CLPQ 10 to 20 times after the first few hours. As a result, the urine t1/2 is increased (beyond 120 hours), even without renal failure. In humans, excretion of paraquat has been shown to be slower than in animals since it was detected in the urine, 7 days to 26 days after ingestion.[13,22]

Biliary elimination may also represent an important excretory pathway due to the strong expression of P-glycoprotein (P-gp) in the hepatocyte canalicular membrane. Studies show that paraquat is secreted from the liver into the duodenum, then reabsorbed into the intestinal epithelial cells. Small amounts of paraquat were found in postmortem bile. Thus enterohepatic recirculation may also be present in humans.[13,26]

Mechanism of paraquat toxicity

Paraquat induces toxicity due to its ability to affect the redox cycle and form ROS. Paraquat, during the redox cycle process, forms more toxic ROS anions such as hydrogen peroxide and hydroxyl radicals, which are formed in the presence of NADPH and cytochrome P450 reductase. If protective mechanisms such as catalase and glutathione peroxidase are reduced, the resulting oxidative stress will lead to cellular damage. Hydroxyl radicals formed in the presence of iron are stronger oxidants and can induce lipid peroxidation, which causes damage to cell membranes and cell death.[27,28]

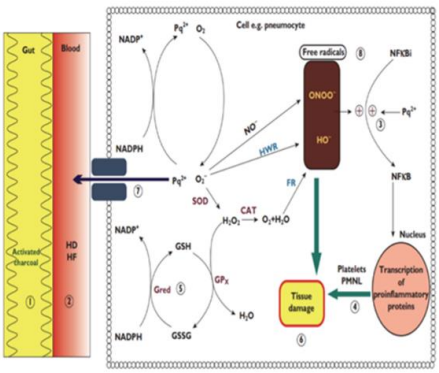

Figure 2. Paraquat toxicity.[6]

In essence, paraquat is an alternative reduction agent and repeated re-oxidation which will cause the formation of oxygen free radicals such as superoxide, hydrogen peroxide, and hydroxyl radicals, which cause oxidation damage to fats, proteins, and DNA. The redox cycle also causes a decrease in the amount of NADPH and cellular thiol (SH). Lipid peroxidation is formed from electrophilic free radicals that extract hydrogen atoms from polyunsaturated fatty acids. Paraquat can induce lipid peroxidase. Lipid peroxidation disrupts cell membrane function and triggers apoptosis. Lipid peroxidation is considered by some experts to be the main key to the initial pathophysiological process of paraquat intoxication.[6,20]

Paraquat causes mitochondrial toxicity in various cell lines. Mitochondrial toxicity is due to reduced NADH-ubiquinone oxidoreductase complex resulting in the formation of superoxide. Paraquat is reduced primarily by NADH ubiquinone oxidoreductase in mitochondria. Paraquat induces Ca^{2+}, which results in increased permeability of the inner mitochondrial membrane (due to lipid peroxidation), leading to membrane depolarization, uncoupling, and swelling of the mitochondrial matrix.[6,8]

Reactive oxygen activates nuclear factor kappa B (NF-kB) from its inactive form. In normal cells, NF-kB is bound to inhibitory protein (IkBA). IkBA is rapidly phosphorylated by NF-kB inducers. Once activated, NF-kB is translocated into the nucleus and binds to the promoter region, and induces target genes involved in inflammation. Consequently, NF-kB induces the transcription of inflammatory enzymes, cytokines, and chemokines. This causes platelet aggregation and fibrogenesis and triggers inflammatory cells. Paraquat-induced apoptosis due to ROS production and NF-kB activation. This causes DNA fragmentation. Peroxynitrite also reacts with proteins, lipids, and DNA so that it interferes with pathway enzymes and causes impaired hemostasis and apoptosis.[6,28,29]

Paraquat toxicodynamics

Pulmonary toxicity

After ingestion, paraquat concentrations are found in the lungs, and peak concentrations in 5 - 7 hours. In the lungs, it causes pulmonary congestion, edema, hemorrhage, diffuse alveolitis, and extensive pulmonary fibrosis. Acute respiratory distress may occur 24 - 48 hours after ingestion. Paraquat selectively accumulates in capillary endothelial cells and lung epithelium and causes diffuse alveolitis followed by extensive pulmonary fibrosis in about 3-14 days. In all fatal cases, the lungs are usually involved with features of pulmonary edema and pulmonary fibrosis. This is due to the rapid and excessive proliferation and differentiation of fibroblasts, which results in loss of lung architecture.[22,24]

The main pathogenesis of lung damage is the result of the formation of free radicals with oxidative damage to lung tissue. Acute pulmonary edema and lung damage occur within hours due to heavy exposure. Lung damage then progresses to pulmonary fibrosis, which is the most common cause of death with paraquat, and usually on days 7−14 after paraquat ingestion. In patients who consume large amounts, some will die earlier (48 hours) due to circulatory failure. Toxicity is characterized by the occurrence of pulmonary edema, pulmonary alveolar membrane damage, and pulmonary fibrosis. Death occurs from respiratory failure due to pulmonary edema or pulmonary fibrosis. The toxic dose of paraquat dichloride that can cause pulmonary fibrosis in humans is 20−40 mg/kgBW.[13,14]

The main organs affected by paraquat are the lungs. Paraquat selectively accumulates in alveolar cells and induces the production of many toxic free radicals, such as ROS, which cause cell membrane lipid peroxidation, a decrease in nicotinamide adenine dinucleotide phosphate, and cell necrosis.[25,27] Paraquat concentrations in the lung parenchyma are very high due to active and energy-dependent uptake of paraquat by type 1 and type 2 alveolar epithelium via the polyamine uptake. Both types of pneumocytes

are type I and type II. appear to selectively collect or accumulate paraquat. Paraquat biotransformation In pneumocytes, this causes the formation of lipid peroxidase and cell damage. Edema and hemorrhagic fluid and infiltration of leukocytes into the alveolar space, accompanied by a proliferation of fibroblast tissue, further disruption of arterial oxygen exchange and CO_2 diffusion will occur, which causes impaired gas exchange and progressive proliferation of fibrous connective tissue in the alveoli and results in tissue asphyxia and anoxia. Fibrotic changes in the alveoli result in impaired gas exchange in the lungs and develop into acute respiratory distress syndrome (ARDS).[6,13]

Toxicological effects on the lungs begin with the destruction phase marked by the destruction of type I and type II alveolar epithelial cells, which occurs within 1-3 days. The speed of occurrence depends on the dose given and the route of administration. The main function of type I alveolar cells is gas exchange between the air spaces and capillaries. While the main functions of type II epithelial cells are surfactant secretion, active transport of water and ions, and epithelial regeneration. The destruction of type II cells causes an increase in surface tension in the alveoli. Fluid is pulled from the capillaries resulting in edema. Entry of inflammatory cells, neutrophils, macrophages, and eosinophils into the interstitial and alveolar spaces occurs during this destructive phase and is maintained throughout the proliferative phase. Therefore alveolitis, pulmonary edema, acute pneumonitis, and bleeding occur.[13,20]

Initial lung damage caused by paraquat occurs in type I alveolar epithelial cells in the form of swelling, mitochondria, and ribosomes are also found, and increased metabolism, followed by cell degeneration and cytoplasmic edema, which eventually causes protrusion of the cytoplasm into the alveolar space, and further rupture of type I cells to the basement membrane. In the acute destructive phase, pulmonary edema may occur due to acute alveolitis, diffuse alveolar collapse, vascular congestion, and adherence of polymorphic nuclear leukocytes and activated platelets to the vascular endothelium.[5,13]

The second phase of pulmonary toxicity is the proliferative phase. In this phase, mononuclear pro-fibroblasts fill the alveolar space, for several days to weeks, transform into fibroblasts and cause pulmonary fibrosis. Extensive fibrotic proliferation in the lung, which may be a compensatory repair mechanism in alveolar epithelial cells damaged during alveolitis. If the exposure level of the lungs to paraquat is high, the alveolitis will be more extensive and severe, resulting in contracted fibrosis and severe anoxia. Fibroblast proliferation and collagen deposition are very rapid, resulting in loss of normal alveolar architecture, impairing the effectiveness of gas exchange and reducing it, and subsequently causing death due to anoxia. Severe pulmonary fibrosis ensues, resulting in dyspnea, cyanosis, and finally, death from respiratory failure. Paraquat poisoning causes lung stiffness and a tendency to barotrauma. After the alveoli are ruptured, free air can travel to the hilus of the lung through the peribronchial vascular sheaths and then diffuse proximally into the mediastinum, resulting in a pneumomediastinum. Zhou et al. (2015) reported that pneumomediastinum occurred in 21.3% of their paraquat poisoning patients. 13% of these patients developed a pneumomediastinum within three days of taking paraquat, and 15 died within three days of the onset of the pneumomediastinum.[6,11,13]

Kidney toxicity

Damage to the proximal renal tubules may occur, which is more reversible than damage to the lung tissue. Impaired kidney function plays an important role in determining the prognosis of paraquat poisoning. Paraquat is mainly eliminated unchanged by the renal system via glomerular filtration and active tubular secretion. This results in acute tubular necrosis, hypoperfusion due to hypovolemia/hypotension, and immediate glomerular injury after poisoning, which can lead to acute kidney injury. More than 90% of paraquat is excreted in the urine in the first 24 hours of poisoning if the kidney

function is normal. Renal impairment prolongs the elimination of paraquat, causing high mortality.[13,20]

Paraquat can accumulate in the kidney tubule cells, causing reduction and oxidation cycles, producing ROS, and finally damaging the proximal tubules. Since the kidney is the main organ for the excretion of paraquat, kidney injury can reduce paraquat elimination and increase its toxicity to other organs. Kidney tubular cells actively excrete paraquat in the urine, efficiently clearing paraquat from the blood. Very high levels of paraquat in the blood will cause tissue damage.[1,11] Paraquat toxicity in the kidney causes vacuolation of the proximal convoluted tubular cells, thus causing renal tubular necrosis and kidney failure. Acute tubular necrosis, glomerular and tubular hemorrhage, and proximal tubular dysfunction may be present.[10,19,30]

Consumption of large doses of paraquat causes tubular necrosis with reduced GFR and accelerated tubular secretion. After administration of large doses of paraquat (20 mg/kg), CLPQ and CLCr decreased, due to renal tubular necrosis, reducing urine output and CLPQ 10 to 20 times after the first few hours. Renal failure (which usually occurs when paraquat consumption is more than 20 mg/kg) precludes the elimination of paraquat in its normal route. Impaired renal function of at least 5% results in a fivefold higher herbicide concentration in plasma. In renal failure, peak lung concentrations are not reached for 15-20 hours and can reach very high values (120 hours or more).[13,14]

Gastrointestinal toxicity

The gastrointestinal tract is the initial site of damage which is characterized by damage to the surface of the intestinal mucosa by paraquat. This toxicity is manifested by mucosal edema, swelling, and ulceration of the mouth, pharynx, esophagus, stomach, and intestines, which are very painful. Paraquat is corrosive, and almost all patients with paraquat poisoning have corrosive esophageal injuries. Corrosive esophageal injury can also stimulate salivary gland secretion, leading to increased serum amylase levels. Higher levels of paraquat cause gastrointestinal, hepatocellular toxicity, which causes increased levels of bilirubin, and hepatocellular enzymes such as AST, ALT, and LDH.[1,13,33]

Hepatocellular congestion and injury occur due to mitochondrial damage and endoplasmic reticulum degranulation for hours to days after paraquat ingestion. The liver is a major reservoir source of intrinsic antioxidants, and is considered a major target of xenobiotic-mediated oxidative stress. Paraquat will increase ALT and AST levels and induce other clinical manifestations including jaundice and histopathological changes. Metabolic disorders or insufficient antioxidants caused by liver injury will have an unavoidable impact on paraquat poisoning patients. It is characterized by jaundice and elevated transaminases on liver function tests. Centrilobular hepatic necrosis and cholestasis may also be seen. Ingestion of large amounts of paraquat liquid concentrate causes edema, resulting in renal, hepatic, and cardiac failure. Patients with fulminate organ failure suffer from hypoxia, shock, and metabolic acidosis. Death occurs within hours to several days.[19,25,32]

Muscle toxicity

Focal necrosis of the myocardium and skeletal muscle is the main feature of paraquat-induced muscle tissue toxicity compared to other muscle tissues. Muscle represents an important reservoir that explains the persistence of paraquat in plasma and urine for several weeks or months after poisoning. Prolonged paraquat poisoning has toxic effects on striated and smooth muscles in the form of myopathy due to type I muscle fiber degeneration.[6,33] It has also been reported that paraquat causes cerebral edema and brain damage. Paraquat death depends on the dose ingested. Patients ingesting large doses (50-100 ml) show fulminant MODS, pulmonary edema, hepatic and renal failure, and cardiac and central nervous system involvement with seizures.[15,16]

Diagnosis of paraquat intoxication

Clinical manifestations

Clinical manifestations of paraquat intoxication range from local irritation to multi-organ failure and death. Symptoms in paraquat poisoning patients include local and systemic toxicological effects. Local clinical presentation of paraquat oral poisoning may include mouth ulcers, hemoptysis, and gastrointestinal (GI) symptoms such as nausea, vomiting, diarrhea, and GI bleeding. These symptoms are caused by direct mucosal irritation. Systemic toxicological effects, such as liver or lung and kidney damage, occur later than local effects and depend on the lethal dose consumed.[13,26]

According to Rahmani et al. (2015) study in Iran, the order of the most frequent clinical findings in paraquat-intoxicated patients was vomiting (69%), respiratory disorders (47.6%), kidney dysfunction (45.2%) and liver dysfunction (38.1%). Meanwhile, according to Narendra et al. (2015), in an Indian study, the most common symptom was vomiting (100%), followed by changes in sensorium (69%), mouth ulceration or dysphagia (60%), dyspnoea (51%) or diarrhea (34%).[34,35]

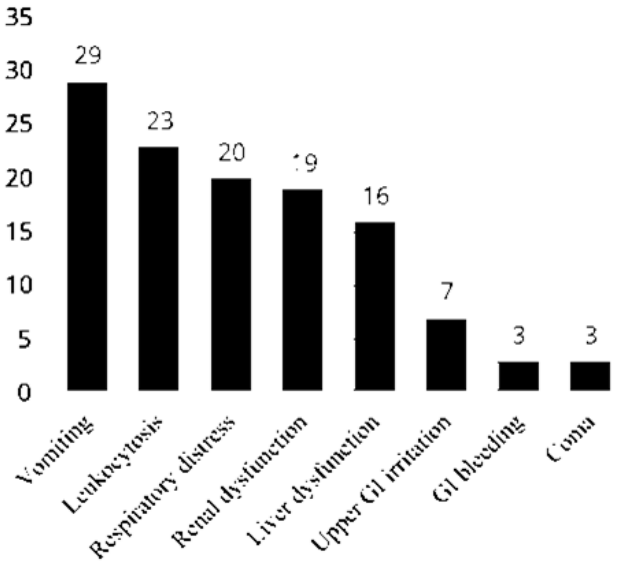

Figure 3. Clinical findings of paraquat intoxication.[34]

The clinical picture of acute paraquat poisoning is characterized by high mortality, rapid progression, and frequent injuries to the lungs and kidneys. Acute paraquat intoxication is usually asymptomatic in its early stages. Irritation and numbness of the tongue and oral mucosa are common complaints in the first few days. Shortness of breath, increased respiratory rate (tachypnea), lethargy, and confusion appear within 3 to 4 days after taking paraquat because lung injury (consolidation on imaging) develops in cases of moderate to severe poisoning. Hiccups generally occur when consumption is > 100 ml. Confusion is usually followed by death within a few days.[19,36] The results of research by Oghabian et al. (2019) in Iran found that the highest mortality rate in paraquat-intoxicated patients was respiratory distress, followed by mouth ulceration and excess saliva. In all paraquat poisoning patients, doses greater than 2250 mg were predicted to die with a specificity of 86.2% and a sensitivity of 75.7%. The mortality rate in paraquat poisoning patients depends on the dose of poison, blood sugar levels, and aspartate transaminase levels. This parameter has excellent prognostic value for predicting mortality.[19,36] Gastrointestinal toxicity is common in patients who ingest paraquat concentrate. Lesions of the oral mucosa and tongue (paraquat

tongue) begin to appear within the first few days and may become ulcerated with bleeding. Mucous lesions of the pharynx, esophagus, and stomach are also very common and far more dangerous. This can lead to perforation, mediastinitis, and/or pneumomediastinum.[6,30]

Ingestion of large quantities of liquid concentrates (>50-100 mg/kg) results in fulminant organ failures such as pulmonary edema, cardiac, renal, and hepatic failure, and seizures due to central nervous system involvement. Clinical manifestations of these patients occur in hypoxia, shock, and metabolic acidosis. Death occurs from multiple organ failure within hours to days. Ingestion of smaller amounts usually causes toxicity to the two main target organs (kidneys and lungs) that develops over the next 2-6 days. This is often referred to as 'moderate to severe' poisoning in the clinical literature.[6,13] In contrast, patients with intravenous paraquat poisoning do not experience direct mucosal irritation, but they may have some GI symptoms, such as nausea and vomiting, which may be explained by paraquat's systemic effects on the central nervous system. Patients with intravenous poisoning have skin or local vascular symptoms. Skin presentation may be explained by local reactions due to extravasation of paraquat solution into adjacent soft tissues and/or by local vascular injury, such as phlebitis, associated specifically with paraquat injection. Systemic toxicological effects are also thought to have a more rapid onset in patients with intravenous poisoning than in patients with oral ingestion.[12,13] The main effect of this amount of paraquat follows its accumulation in the lungs with damage to lung cells resulting in decreased gas exchange and respiratory distress. The pulmonary lesion has two phases: acute alveolitis for 1-3 days followed by secondary fibrosis. Patients usually experience increasing signs of respiratory involvement over 3-7 days and eventually die of severe anoxia due to rapidly progressive fibrosis up to 5 weeks later. Some liver toxicity (jaundice, increased transaminases) is also common in these patients.[5,13,26]

Classification

Acute paraquat poisoning is mostly caused by the consumption of concentrated liquid herbicide formulations. Symptoms of human paraquat poisoning can be divided into three different toxicities depending on the amount ingested, namely mild or asymptomatic toxicity, moderate to severe toxicity, and severe toxicity or acute fulminant.[13,26,29]

Mild or asymptomatic toxicity

The patient has ingested less than 20 mg of paraquat ion per kilogram of body weight (mg/kg). The patient is asymptomatic or has vomiting and diarrhea. Kidney and liver toxicity is low and resolves within a few days. Lung injury would be similar to restrictive airway disease.[13,26,29]

Moderate-severe toxicity

The patient has ingested 20 to 40 mg/kg of paraquat ion. They may suffer from vomiting, diarrhea, and general symptoms such as lethargy, widespread burning sensation, myalgias, general weakness, dizziness, headache, anorexia, and fever. Fear, dread, and anxiety are sometimes observed. After a few days, dyspnea occurs in the majority of cases as a result of pulmonary fibrosis. Occasionally, kidney failure and/or liver dysfunction may occur. Generally, death occurs in most of them within 2 or 3 weeks.[19,29]

Acute toxicity or acute fulminant

Acute fulminant occurs after ingestion of more than 40 mg/kg of paraquat. Oropharyngeal ulceration, nausea, vomiting, general symptoms, and dyspnea occur early. Dyspnea can develop into respiratory distress syndrome. Pneumothorax (mediastinitis), pleural effusion, and iatrogenic pulmonary edema can precipitate dyspnea. Death can occur within 24 hours after poisoning from cardiac, respiratory, renal, hepatic, adrenal, pancreatic and neurological failure.[24,29]

Laboratory examination

Paraquat poisoning is mainly associated with pulmonary toxicity, while various extrapulmonary effects have been reported, including nephrotoxicity and hepatotoxicity, which are considered to be the main clinical manifestations of paraquat poisoning. Liver and kidney, as key organs for the detoxification and elimination of paraquat. Injury to these organs can suppress toxin excretion and increase paraquat toxicity in other organs and worsen the prognosis. According to Shashibushan et al. (2015), laboratory tests on paraquat poisoning showed increased blood urea, serum creatinine, and increased total bilirubin.[13,14,25,26]

According to Chen et al. (2021), predictors of mortality from paraquat poisoning are serum creatinine and serum paraquat concentration. Overall sensitivity and specificity were 81.5% and 94.8%. In line with the study, Lee et al. (2002) identified significant prognostic factors for paraquat poisoning based on initial blood and urine samples obtained in the emergency room and patient demographics. Age, amount of ingested paraquat, plasma paraquat concentration, leukocyte count, blood urea nitrogen, serum creatinine, uric acid, aspartate aminotransferase, alanine aminotransferase, and amylase are significant prognostic factors for paraquat poisoning. Severe paraquat toxicity can occur within 24 hours, oliguria or non-oliguric renal failure resulting in increased BUN and creatinine as well as proteinuria, glycosuria, microscopic haematuria, phosphaturia, and aminoaciduria. In renal impairment and muscle damage, there is an increase in serum creatinine activity. Damage to the liver from paraquat can be severe and can cause jaundice, which is a sign of severe liver damage.[37,38]

Based on research by Zhang et al. (2021) that the ALT and BUN values in the death group were higher than the survivor group. The prediction of death in acute paraquat poisoning in ALT had a sensitivity of 56.67%, a specificity of 89.57%, while BUN had a sensitivity of 96.67%, a specificity of 100%, while the ratio of plasma/urine paraquat had a sensitivity of 88.89%, a specificity of 100%. In accordance with the research of Kang et al. (2015) found a low survival rate in patients with a history of paraquat having incidents, toxic hepatitis, and hypoxemia. Significantly increased levels of BUN, SCr, AST, ALT, total bilirubin, and direct bilirubin in patients with low survival rates. Functional markers such as serum creatinine can predict death after paraquat intoxication. Increased serum creatinine after paraquat poisoning is one of the causes of decreased kidney function. During severe oxidative stress, to meet the increased energy requirements, there is an increase in serum creatinine.[11,25,39]

Kim et al. (2011) reported that hyperuricemia increased the risk of death 3.7-fold and increased the risk of kidney failure 3.3-fold (adjusted for age, gender, and estimated intake of paraquat) and suggested that serum uric acid level was a predictor of mortality for paraquat toxicity. Theoretically, renal failure reduces uric acid elimination resulting in increased serum uric acid levels.[11,40]

Leukocyte count is a strong predictor of survival in patients with acute paraquat poisoning, according to Feng et al. (2018). Recent research by Chen et al. (2021) validates that the APPM (acute paraquat poisoning mortality) score is a score in predicting the mortality of available paraquat poisoning based on three simple parameters when the patient is admitted, namely serum glucose concentration, leukocytes, and urine paraquat concentration. Where the three parameters that contributed to the 28-day mortality were urine paraquat concentrations >10ppm, leukocytes >13.0 G/L, and blood glucose >140mg/dL. In applying this score to the validation cohort, patients could be grouped into low (4%), moderate (47%), high (95%), and very high (100%) mortality groups.[40,41]

Li et al. (2015) reported increased serum amylase levels to predict prognosis and demonstrated that leukocytes, amylase levels, neutrophil percentage, and CO_2 pressure were risk factors for death. In line with the study by Huang et al. (2020) that the paraquat poisoning group who had elevated serum amylase (>250 U/L) had a much higher mortality rate (91.8%)

compared to those in the serum amylase group who did not increase (35.6%). The incidence of elevated serum amylase levels caused by paraquat poisoning ranges from 20.6% -58.5%. Serum amylase levels had a sensitivity value of 70.4% and a specificity of 74.0% for predicting the prognosis of the severity of paraquat poisoning. Oxidative stress is the main mechanism for increased serum amylase caused by paraquat poisoning. The patient with the highest serum amylase level died within 3 days. Hyperamylasemia is strongly associated with the severity of paraquat-induced hepatotoxicity and nephrotoxicity. The risk of nephrotoxicity, hepatotoxicity, and lung toxicity occurred in the serum amylase group, which increased compared to the serum amylase group, which did not increase.[31,42]

Tachypnea with low $PaCO_2$ indicates hypoxia. Based on research by Kang et al. (2015), pH and PaO_2 were significantly lower than the non-surviving group. PaO_2 decreased progressively during lung injury and paraquat-induced lung volume restriction. Notably, in cases of PaO_2 < 60 mmHg, there was a significant increase in morality. Pulmonary fibrosis develops in the advanced stages of lung injury.[19,30,39]

Dithionite test examination

Detection of paraquat in body fluids (e.g., serum, plasma, urine) is necessary and sufficient to confirm paraquat poisoning. The urine test was used as a paraquat screening test, whereas a confirmatory diagnosis of paraquat poisoning was only possible through blood paraquat concentration analysis (spectrophotometry, Hitachi, Tokyo, Japan). There is a correlation between serum paraquat concentration and risk of death. SIPP score (severity index of paraquat poisoning) is a prognostic indicator after paraquat poisoning, calculated by multiplying the serum paraquat concentration at admission (mcg/mL) by the time at the time of poisoning (hours). SIPP value < 10 indicates a high survival rate, whereas SIPP value > 10 is usually associated with a high mortality rate. Conversely, those with a SIPP between 10 and 50 often die from interstitial pulmonary fibrosis secondary to paraquat poisoning, and those with a score greater than 50 die rapidly from circulatory collapse. SIPP proved to be superior in predicting prognosis.[3,11,13]

The mortality of patients with SIPP < 10, SIPP 10-50, and SIPP > 50 were 33.8%, 96.9%, and 98.6%, respectively. Longer time to hospital admission and SIPP score were found to predict AKI (acute kidney injury) after paraquat intoxication. This suggests that blood paraquat concentrations and the time between paraquat consumption and arrival at the hospital are significant determinants of AKI.[3,11,13] The reaction of the urine sodium dithionite screening test depends on the reduction of paraquat by sodium dithionite under alkaline conditions to form a stable blue radical ion. The appearance of a strong dark blue color generally indicates significant consumption of paraquat and often indicates a poor prognosis. At some health centers, test colorimetric Simple methods can be used to identify paraquat in the urine and provide an indication of the range of absorbed paraquat doses. This is done by adding 0.5 cc of fresh urine with 1% sodium dithionate (sodium hydrosulfite) dissolved in sodium hydroxide (1.0 N NaOH). Then observe the color that is formed after 1 minute. The blue color indicates that more than 0.5 μg/liter of paraquat was found. When urine is collected over 24 hours, the dithionite test can have prognostic value: concentrations less than 1 μg/L (colorless to light blue) may reflect patient survival, whereas concentrations greater than 1 μg/L/day (navy blue to dark blue) usually have a poorer prognosis and is fatal. Paraquat can also be measured in blood and urine using spectrophotometric, gas chromatographic, liquid chromatographic, and radioimmunoassay methods.[1,11,13,15]

Seok et al. (2012) described the diagnostic potential of the urine dithionite test, an indicator of plasma paraquat levels, to determine the severity of paraquat poisoning. The first step of the dithionite test is the addition of dithionite to a fresh urine sample in a colorless vessel, followed by alkalization with a weakly alkaline agent such as sodium bicarbonate. The principle behind the dithionite test is that the

absorbance of the paraquat changes as a result of the blue color produced in the reaction with dithionite. The lowest paraquat detection rate with high-performance liquid chromatography (HPLC) is 0.01 µg/mL, and by paraquat dithionite detection test, about above 1 µg/mL.[19,39] A sequential dithionite urine test is performed every 3-4 hours after the second dithionite urine test until the result is negative. The time to achieve a negative urine dithionite test is a marker for predicting death and/or essential organ failure. The sensitivity and specificity for mortality were 71.4% and 75.0%, respectively, with a cut-off value of 34.5 hours for the negative conversion time of the urine dithionite test. The incidence of acute kidney injury and respiratory failure with a time >34.5 hours was 100% and 85.0%, respectively.[19,39] Based on the results of the research by Shashibushan et al. (2015), compared with other studies, from the autopsy results of patients with a history of consuming paraquat in India, erosion of the esophagus and stomach was found. Histopathological findings of lung, liver, and kidney on biopsy showed diffuse alveolar hemorrhage, loss of centrilobular hepatocytes, and renal parenchymal congestion.[27,28] The main imaging modalities of choice are chest X-ray and CT scan. scan thorax. According to Chan et al. (2009) that from the thoracic radiograph of the patient, a history of intravenous paraquat taken on the 3rd day of hospitalization showed unclear alveolar infiltration dominant in the lower lung fields bilaterally with patch consolidation in the right middle lobe of the lung. Whereas the 10th day of hospitalization showed diffuse fibrotic rapid changes and reticulonodular opacities in the lungs bilaterally.[11] Simple chest radiography has poor sensitivity and specificity for evaluating paraquat-induced lung injury. Gill et al. (2014) recommended high-resolution computed tomography (HRCT) of the lungs on day 7 after consuming paraquat. HRCT is the best modality in fully evaluating the extent of acute paraquat lung injury.[17,39]

Management of paraquat intoxication

Initial therapy for paraquat poisoning consists of gastrointestinal decontamination to prevent further absorption for oral exposure using activated charcoal. This is followed by supportive treatment measures, including increased elimination of serum paraquat by hemoperfusion and drugs that inhibit the inflammatory response, such as immunosuppressants (corticosteroids and cyclophosphamide) and antioxidants (N-acetylcysteine and vitamin C). Every patient who presents to the hospital with paraquat poisoning is treated with a standard detoxification protocol, including charcoal hemoperfusion and methylprednisolone therapy. pulse doses, cyclophosphamide, as well as follow-up treatment with dexamethasone. The therapy can normalize respiratory function and blood oxygen concentration within three to six months. This protocol has been researched and recommended by the Cochrane injuries group, useful in cases of pulmonary fibrosis caused by paraquat.[2,5,11]

Management of paraquat intoxication has been directed primarily at eliminating paraquat from the GIT (preventing its absorption), increasing its excretion from the blood, and measures aimed at preventing lung damage with anti-inflammatory agents and some supportive therapy. According to Iyyadurai et al. (2019), The management of herbicide poisoning is mainly supportive because there is no effective treatment. The standard principles of resuscitation covering the assessment and management of the airway, breathing, and circulation should generally be followed as per routine guidelines. Chart monitoring of intake - daily output, cardiac status, respiratory status, and level of consciousness can predict the occurrence of organ failure. Fluid resuscitation with 15-20 ml/kg is important because hypotension is common in paraquat poisoning due to hypovolemia.[13,17]

Preventing paraquat absorption

The key to successful treatment of acute paraquat exposure depends almost entirely on aggressive early

decontamination measures to limit absorption. If direct skin exposure has occurred or is secondary to contact with contaminated vomit, the cloth should be removed immediately, and the skin should be washed gently but thoroughly with soap and water to prevent transdermal abscesses. Hard scrubbing should not be done because the skin abrasion that occurs can actually increase the transdermal absorption of paraquat. Eyes exposed to paraquat should be irrigated with large amounts of lukewarm water or normal saline for at least 15 to 20 minutes.[13,15]

Decontaminate with activated charcoal or Fuller's Earth (Multani Mitti) is recommended if the patient arrives within 2-4 hours. According to Elenga et al. (2018), the most common gastric decontamination method for patients was gastric lavage with charcoal in 44 cases (71%). According to the literature, the use of activated carbon significantly reduces mortality compared with Earth Foulon or Bentonite. In fact, the activated carbon absorbs paraquat best. It is recommended to use it as soon as possible after consuming paraquat within the first hour after consumption. contact with Fuller's earth disable paraquats.[6,8]

The paraquat detoxification protocol included gastric lavage with large amounts of 0.9% saline, followed by 1 g/kg of activated charcoal and 250 mL of magnesium citrate via a nasogastric tube. Gastric lavage is not recommended because paraquat is corrosive. A nasogastric tube should be placed early because paraquat is corrosive and can cause difficulty swallowing during hospitalization.[11,19]

Increases paraquat elimination

In cases of poisoning by ingestion of paraquat, after GIT decontamination has been performed, there are still two additional treatment strategies. The first is to try to change the toxicokinetics of the herbicide (i.e., its distribution in the body after ingestion). The second is to try to modify its toxicodynamics (i.e., the effect of the herbicide on target organs).[13,15]

Extracorporeal elimination

Elimination of paraquat by hemoperfusion (HF) and hemodialysis (HD). The goal of the extracorporeal elimination procedure is to remove paraquat from the circulation and prevent its uptake by pneumocytes and Clara cells. The only method that has been shown to be efficient and to improve the elimination of extracorporeal paraquat is charcoal hemoperfusion (CHP). Most toxicologists currently recommend rapid initiation of CHP to lower plasma paraquat levels and to limit absorption of paraquat in the lungs and other organs. The best modality for the elimination of extra-corporeal paraquat is HF. The rate of reduction of plasma paraquat levels by HP was higher than that of HD. Charcoal hemoperfusion with a charcoal-containing dialysis machine (Adsorba, Gambro, Germany) (Surdial, Nipro, Japan) was started if the urine paraquat concentration was > 5 ppm. The second hemoperfusion session was arranged if the urine paraquat concentration was > 5 ppm 4 hours after the first hemoperfusion.[11,13,18,19]

Hemoperfusion is the most effective modality for clearing paraquat and detoxifying poisons. The survival rate was around 57% in the hemoperfusion group, compared to the group that did not receive hemoperfusion (8%), indicating that hemoperfusion improves the survival rate in paraquat poisoning patients, according to a study conducted by Hsu et al. (2012). Initial charcoal hemoperfusion < 5 hours significantly reduces the risk of death in paraquat-poisoned patients. In the study, Rao et al. (2017) found that early hemoperfusion (≤ 6 hours) increased survival rates compared to those who received late hemoperfusion (> 6 hours). The peak time of paraquat in plasma is 1-3 hours, whereas, in lung cells, it is 4-5 hours. Almost 9% of paraquat is lost in plasma 5-6 hours after ingestion. Therefore, patients who receive early hemoperfusion will most likely benefit due to the removal of significant amounts of paraquat from the blood.[5,11]

A recent meta-analysis of 1041 patients with paraquat poisoning has shown that hemoperfusion in combination with continuous venovenous

hemofiltration (CVVH) within 24 hours of ingestion reduced overall 4-day mortality and circulatory failure compared with hemoperfusion alone but had no significant impact on long-term mortality. Taken together, early hemoperfusion combined with CVVH can be considered a last resort to improve outcomes in paraquat-poisoned patients.[45,46]

Diuresis and dialysis

Furosemide to maintain an adequate urine flow (achieving a urine output of 1 to 2 ml/kg/hour) is important because the kidneys are the main physiological pathway for paraquat excretion. Rapid urine flow supports both glomerular filtration and tubular secretion of paraquat and delays the onset of acute renal failure and oliguria. Paraquat can cause peripheral vasodilation and intrarenal vasoconstriction. This mechanism explains the early stages of paraquat-induced renal failure, which is mostly reversible.[13,15]

There are two problems faced by paraquat poisoning, and firstly, paraquat is quickly removed from circulation because endogenous clearance is very high. Second, the initiation time of HD will have a very short impact on paraquat levels stored in the lungs. Therefore, the time available for elimination is very short. Studies conducted in animal models have shown that when hemodialysis is performed within 2-4 hours after ingestion of paraquat, it is effective in reducing paraquat plasma levels but does not reduce paraquat-induced lung damage. Therefore, HD can reduce paraquat plasma load but not reduce its toxic effect on target organs. Comparative studies from various parts of the world show that there is no difference in outcome in patients with paraquat poisoning who are managed with early dialysis compared to those who are managed without dialysis or who are initiated on dialysis only when kidney failure occurs. HD should be suggested to patients who have already developed renal failure, but because of lung involvement, there may be no change in outcome with dialysis.[17,18]

Measures to prevent lung damage

Immunosuppressants

Immunosuppressants are often used in the management of paraquat poisoning. Paraquat induces an acute inflammatory response which eventually leads to pulmonary fibrosis, so intervention at an early stage and stopping the inflammatory response can inhibit the process of pulmonary fibrosis and mortality. Pathophysiology relevant to high-dose immunosuppression will be effective in paraquat poisoning in humans because paraquat quickly produces ROS, which causes cell damage through lipid peroxidation, NF-kB activation, mitochondrial damage, and apoptosis in many organs. This leads to the rapid deterioration of kidney and liver function and the development of acute alveolitis.[2,4,47]

The drugs most widely used are glucocorticoids such as methylprednisolone and dexamethasone and chemotherapeutic agents such as cyclophosphamide. According to research by Xu et al. (2019) that therapy pulse dose Immunosuppression with glucocorticoids and cyclophosphamide for paraquat poisoning significantly reduced mortality (59.3%) compared to the control group. Therefore, pulse dose Immunosuppressive drugs can efficiently reduce paraquat poisoning mortality and are relatively safe. The immunosuppressive therapy protocol consisted of the administration of corticosteroids, starting with methylprednisolone (1 g/day for three days) followed by dexamethasone (20–40 mg daily) or administration of cyclophosphamide, initially 15 mg/kg/day for two days.[2,3,6,11]

According to Oghabian et al. (2019), Management of paraquat poisoning with anti-inflammatory methylprednisolone succinate 15 mg/kg intravenous infusion every day after hemodialysis for three times, followed by intravenous dexamethasone 8 mg/three times daily for 1 week, cyclophosphamide 15 mg/kg intravenous infusion every other day after hemodialysis for three times, and mercaptoethanesulfonate 15 mg/kg continuous intravenous infusion daily after cyclophosphamide to prevent side effects of cyclophosphamide such as

hemorrhagic cystitis. The protocol included cyclophosphamide therapy pulse dose (15 mg/kg/day) for two days and methylprednisolone (1 g/day) for three days. Intravenous dexamethasone (20 mg/day) was given for 11 days after the methylprednisolone therapy pulse dose. Cyclophosphamide and methylprednisolone are given after extracorporeal treatment because they are potentially released during charcoal hemoperfusion. Pulse dose therapy with cyclophosphamide and methylprednisolone is repeated if PaO_2 <60 mmHg for more than two weeks after initial treatment unless the patient has leukopenia (leukocytes < 3000/m^3).[6,11,17,36]

According to Chen et al. (2021), Methylprednisolone has better survival and is effective in severe cases. Therapy pulse dose with methylprednisolone can prevent the release of certain factors from lymphocytes which will stimulate the formation of superoxide anions by macrophages and neutrophils. Steroid therapy can also reduce superoxide production in the arachidonic acid cascade. Hence therapy pulse dose Repeat with methylprednisolone can stop superoxide, thereby preventing further lung inflammation. Human experimental studies have demonstrated that prolonged methylprednisolone therapy (3 days at 15 mg/kg/day followed by every 2 days halved and discontinued at 0.47 mg/kg/day) can significantly reduce mortality in moderate to severe paraquat poisoning. compared to treatment pulse dose (3 days 15 mg/kg/day).[11,17,36,37,39,48]

Dexamethasone is a high-dose immunosuppressant, low toxicity, cheap, and easy to administer, showing better results. Dexamethasone has two mechanisms of action. Namely, in addition to anti-inflammatory effects, and also induces transporters and increases the expression of glycoprotein receptors which can reduce the accumulation of paraquat in the lungs and increase its excretion in the urine. Further studies in Wistar rats have shown that dexamethasone can improve the histological and biochemical changes in paraquat poisoning and also reduce lipid peroxidation, thereby increasing the survival rate in Wistar rats. Prednisone, a synthetic corticosteroid, is very effective as an immunosuppressant drug and is used to treat certain inflammatory diseases. It has also become a treatment for patients with acute paraquat poisoning. In addition to these general anti-inflammatory effects, recent in vitro experiments demonstrated that methylprednisolone attenuates the cell cycle-induced paraquat cytotoxicity via transporter induction and P-glycoprotein expression.[6,16,44,47]

The rationale for using cytotoxic drugs in the treatment of paraquat poisoning is that paraquat induces inflammatory cell infiltration in the lungs. Cyclophosphamide is recommended for short courses in the first 3-4 days. This is because the cardinal pathological changes are complete within the first few days of poisoning, and prolonged use of these drugs can exacerbate opportunistic infections. However, until now, cyclophosphamide has had inconsistent treatment effects for paraquat poisoning. Some reports show positive effects, while others have negative effects. Administration of cyclophosphamide was more or less effective in suppressing inflammatory cell infiltration in the lungs due to paraquat. However, to achieve this effect, early administration of cyclophosphamide, at least 2-3 hours after paraquat exposure, is important because cyclophosphamide is not effective after cells have been infiltrated with inflammatory cells.[18,44,49]

Antioxidant

There are currently no pharmacological antagonists or antidotes for paraquat poisoning. However, because paraquat induces its toxic effects through mechanisms mediated by oxidative stress, innovations in the management of paraquat poisoning are directed at providing antioxidants. The antioxidant therapy protocol consisted of the administration of N-acetylcysteine at an initial dose of 140 mg/kg, then 70 mg/kg for three days, and vitamin C (200-400 mg daily).[3,18,19] N-acetylcysteine (NAC) is a precursor of glutathione and exhibits antioxidant properties. In addition, NAC can reduce inflammatory cell infiltration

during paraquat poisoning. NAC increases glutathione levels in type 2 pneumocytes in mice. NAC reduces paraquat-induced apoptosis. NAC suppressed the production of malondialdehyde and superoxide, and there was an increase in glutathione levels in all tissues in experimental animals.[16,17,50]

Glutathione depletion (GSH) reduces paraquat toxicity. By adding GSH to type-II alveolar cells, it protects against paraquat toxicity. In experimental animal studies, that GSH peroxidase plays a key protective role against paraquat toxicity was demonstrated in transgenic mice where deletion of this enzyme increased toxicity while the addition of GSH provides some protection to reduce hydrogen peroxide to HO, then oxidize it to its disulfide (GSSG). Most of the GSSG is immediately reduced back to GSH via GSH reductase with the cofactor NADH. NAC is a precursor of GSH. Several studies by incubating NAC with type-II alveolar cells will show an increase in GSH content and prevention of paraquat-induced cytotoxicity.[18,19]

Mechanism of action vitamin C can donate electrons to free radicals and, therefore, can neutralize free radicals. Vitamin C acts as a powerful free radical scavenger and is believed to reduce levels of pro-inflammatory and profibrotic molecules, such as IL-6, IL-17, and TGF-β, in lung tissue. Human studies have shown that high doses of Vitamin C and antioxidants reduced death in a case series of ten paraquat poisoning patients. Animal models poisoned by paraquat showed reduced lung toxicity and reduced lipid peroxidation when treated with Vitamin E. Similarly, vitamin E can ameliorate the oxidative stress caused by paraquat. Vitamin E can also inhibit ferroptosis, which has been illustrated to contribute to the development of cell injury in paraquat poisoning. Lipophilic antioxidants such as vitamin E have an inhibitory effect on ferroptosis through scavenging free radicals to suppress lipid peroxidation. According to Oghabian et al. (2019), for the treatment of paraquat poisoning, apart from that, antioxidant therapy was given with vitamin C 1500 mg/intravenous infusion twice a day (q12 hours) given for 1 week, as well as Vitamin E 2 international units (IUs)/kg intramuscularly three times a day (q8 hours). For 1 week, and N-acetylcysteine 150 mg/kg/day by continuous intravenous infusion for 1 week.[17,23,36,51,52]

Salicylic acid inhibits cyclooxygenase and can inhibit the production of hydroxyl radicals. Studies conducted on mice showed that the mice given salicylic acid showed increased survival, while the untreated group had a mortality rate of 100%. There are no human studies of salicylic acid to date. Studies in bacteria and mice have shown that iron increases paraquat toxicity and that use of desferrioxamine is protective but does not reduce mortality. To date, there are no studies with desferrioxamine in human subjects.[17,36]

Supportive therapy

The current management of paraquat poisoning patients is more supportive than curative. Paraquat poisoning patients are always dehydrated to some extent due to the loss of GIT fluids. In addition to maintaining renal perfusion, administration of fluids and electrolytes is also important for dehydration. Administration of oxygen should be avoided until the patient exhibits persistent hypoxemia.[11,13,48] Reduction of O_2 supply (hypooxygenation) has been shown to have a relationship between increased FiO_2 and the severity of lung damage. Similarly, poisoned animals kept in a hypoxic atmosphere had a lower mortality rate than animals kept in room air. Oxygen can increase lung injury by providing additional substrates for O_2 generation. In humans, O_2 also appears to accelerate lung damage, and thus artificial ventilation of low O_2 concentrations (<21%) in respiratory mixtures with NO ventilation is recommended to limit inhaled O_2 concentrations for as long as possible unless the PaO_2 falls below 40 mm Hg. The rationale for normal-inspired oxygen therapy is that increased FiO2 can increase oxidative stress, and the production of free radicals and superoxide can exacerbate acute lung injury and systemic toxicity. Supplemental O_2 is given when needed for symptomatic relief, but mechanical ventilation would

not be recommended as a treatment option for patients with respiratory failure due to pulmonary fibrosis.[11,13,48]

Based on the research by Lin et al. (2021), it was found that the mortality rate was higher in the liberal oxygen therapy group (87.8%). That is, patients who received oxygen therapy before being marked hypoxic had mortality at 28 days. Oxygen therapy should be avoided because it is associated with increased mortality unless hypoxia is proven (SpO_2 <90%). In accordance with the research of Khazraei et al. (2019), The mortality rate was higher in the high FiO_2 group (96.1%) compared to the low FiO_2 group of 89.6%.[20,53] Role Palliative care in cases of paraquat poisoning is very important. Because medical therapy is very insufficient in the recovery of moderate to severe poisoning, consumption of paraquat. The arts of medicine are important here as a multi-disciplinary support and palliative care role. Honesty about the prognosis, without losing hope, and emphasizing what can be done (i.e., alleviating pain and anxiety as well as psychosocial) are key approaches to the terminal situation of paraquat poisoning.[13,14]

2. Conclusion

Paraquat poisoning is a clinical toxicological emergency with a high mortality rate due to high toxicity, and no antidote has been found. The clinical picture depends on the level of ingested paraquat, which can be in the form of local toxicological effects and systemic toxicology. Mild paraquat toxicity at levels <20 mg/kg, moderate to severe toxicity at levels of 20-30 mg/kg. Fulminant Severe or acute toxicity when level >40-55 mg/kg. Laboratory tests for diagnosing paraquat toxicity can be used for toxicological analysis of plasma and urine. Management of paraquat toxicity is by early decontamination, modifying the toxicokinetics and toxicodynamics of paraquat. Early hemoperfusion therapy <6 hours is the golden hour for the management of paraquat poisoning.

The immunosuppressive therapy protocol consisted of the administration of corticosteroids with methylprednisolone (3 days at 15 mg/kg/day followed by every 2 days halved and discontinued at 0.47 mg/kg/day) followed by dexamethasone (20–40 mg daily) for 11 weeks. day. Or administration of cyclophosphamide, the initial dose of 15 mg/kg/day for two days, recommended 2-3 hours after paraquat exposure, after extracorporeal treatment. The protocol for administering antioxidants to paraquat intoxication is recommended with vitamin C 1500 mg/iv infusion 2x daily for 1 week, as well as Vitamin E 2 (IUs)/kg intramuscularly 3x daily for 1 week, and N-acetylcysteine 150 mg/kg/day intravenous infusion for 1 week. 1 week. High-concentration oxygen therapy in paraquat intoxication should be avoided because it can increase mortality. Unless proven hypoxic (SpO_2<90%).

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