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ROLE OF INTRAVENOUS HIGH DOSE METHYLPREDNISOLONE PULSE THERAPY IN PARAQUAT POISONING - A CASE REPORT

Medicine

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ABSTRACT

Paraquat is a rapidly acting, non-selective herbicide that is relative inexpensive. Paraquat self-ingestion remains a leading cause of pesticide-induced mortality[1]. After rapid absorption paraquat is concentrated inside many cells where it undergoes redox cycling leading to generation of reactive oxygen species and causes widespread inflammation affecting multiple organ primarily lungs and kidney. Treatment is usually conservative with antibiotics, anti-inflammatory, antioxidant, immunosuppressive agent and hemodialysis/hemoperfusion. There is no specific antidote. In our case, we have given iv methyl prednisolone 1gm for 5 days and observed decrease in the oxygen requirement of the patient as patient respiratory function improves and patient was shifted from bipap support to high flow nasal canula on day 5 and also there is improvement in bleeding manifestations on day 3. However, patient succumbed to death on day 9 due to persistently deteriorating liver and renal parameters.

KEYWORDS

Paraquat poisoning, Methyl prednisolone, ARDS, ROS

INTRODUCTION

Paraquat is a bipyridyl compound that after absorption in cell undergoes redox cycling leading to generation of superoxide radicals which can cause cellular damage. Redox cycle consumes NADPH, one of the cells key antioxidant defences. The resultant oxidative stress created causes cell damage via lipid peroxidation, mitochondrial dysfunction, necrosis and apoptosis and secondary inflammatory response. Corticosteroids are a group of natural and synthetic analogues of hormones secreted by the hypothalamic- pituitary-adrenocortical axis. These drugs are potent anti-inflammatory, antifibrotic and immunomodulatory agents. These drugs exhibit their anti-inflammatory activity through the following 3 independent mechanisms: induction and activation of annexin-I, induction of mitogen activated protein kinase Phosphate-I and repression of COX-2 resulting in blockage of various cytokines, chemokines and complement factor responsible for the development of ARDS. So steroids have a beneficial role in treating the ARDS if started early in the disease course and hence can improve respiratory damage and later onset fibrosis.

Case

A 35-year-old male came to the emergency department of our hospital with the history of ingestion of 100ml of of paraquat under the influence of alcohol 7 days back followed by patient is taken to a local clinic for the next 3 days where he was managed conservatively with iv fluids and antibiotics. Gastric lavage with activated charcoal was also done. After 3 days, patient develop swelling over face and has episode of hemoptysis for which he is taken to local hospital and managed conservatively for the next 3 days and then patient was referred our hospital. In our hospital, patient presented with the complaints of decrease urine output, black colour stools and shortness of breath since 3 days and nasal and oral bleed since 6 hrs. Clinically, he was restless and agitated but was conscious and oriented to time, place and person. His vitals were B.P- 90/60 mmHg, pulse- 96/min, SPO2- 49% on room air and afebrile to touch. In general, physical examination icterus and oronasal bleed was present. In systemic examination, mild tenderness was present all over the abdomen and bilateral crackles were present in the chest. Rest all examination was with in normal limits.

Laboratory investigation revealed leukocytosis, anemia, deranged LFT, RFT {Table 1}. ABG Suggestive of metabolic acidosis {table 2}. Patient was started with inj. Piperacillin tazobactam, inj. Sodium bicarbonate for metabolic acidosis, inj. Pantaprazole and inj. Trenexamic acid for bleeding manifestaion, inj. Methyl prednisolone as anti-inflammatory agent and inj. N-acetylcysteine as antioxidant to improve the acute liver failure. Alternate day hemodialysis was done because of worsening renal function and decrease urine output and fresh frozen plasma was given to improve the coagulation parameters. One unit PRBC was also transfused. Bipap support was given initially and patient was shifted to HFNC on day 5. However, renal and liver parameters were continuing deteriorating and patient succumbed to death on day 9 of admission.

Table 1- Haematological and biochemical parameters of the patient

Day	Hb (g/dl)	TLC (cumm)	Urea/creatinine(mg/dl)	AST/ALT (IU/L)	Platelets (cumm)	Serum bilirubin (mg/dl)	PT/INR	Others Viral marker
1.	8.9	14.4x1000	201/8.1	630/571	245x1000	28.8/19		Non-reactive
2.	9.1	17x1000	154/7.2	378/538		30/21.2	14.8/1.2	
3.	9.7	20.1x1000	227.3/9.8	356/545	242x1000	44/25		
4.		23.4x1000	208/7.43					
5.		20.3x1000	371/9.2	334/460		44.4/34		
6.	13.3	29.5x1000	333/8.18		259x1000			
7.		35.8x1000	353/10.4	554/441		74/37.8		
8.			247/8.5					
9.	10.0	33x1000	342/10.4	389/269	236x1000	51/33.1		

Table 2- ABG

Day	PH	HCO3(mmol/l)	PCO2(mmhg)	Lactate(mmol/l)
1.	7.24	11.3	24.2	1.2
2.	7.45	18.0	26.0	0.9
3.	7.39	17.5	29.0	0.8
4.				
5.	7.34	17.1	32.5	0.8
6.				
7.	7.42	12.0	54.3	1.4

DISCUSSION

Paraquat is an herbicidal agent widely in agriculture as it is easily accessible, cost effective and rapidly acting. It also got immediately inactivated on contact to the clay in the soil, leaving minimal residue. Paraquat is reasonably safe to use in agriculture because dermal or spray exposure generally causes only limited localized injury[2]. However, accidental and deliberate ingestion has an extremely high case fatality rate[3]. Minimal ingestion of 10-20ml of 20% paraquat is lethal.

Pathophysiology

The principal target organ for paraquat poisoning is the lung and kidney. Paraquat has a structural similarity to naturally occurring polyamines that are taken up by the alveolar cells and hence paraquat concentrates in alveolar type I and II cells. Paraquat is also actively secreted by the kidney leading to its accumulation in the proximal tubular epithelial cells at higher concentrations. On accumulation in the pulmonary alveoli and the nephrons, paraquat causes redox cycling

and production of toxic reactive oxygen species. This oxidative stress overwhelms the cellular defense mechanisms and leads to pulmonary damage (alveolitis and fibrosis)4. At moderate doses, the initial lung injury develops into pulmonary fibrosis. This occurs due to rapid and excessive proliferation and differentiation of fibroblasts, resulting in loss of pulmonary architecture. Paraquat causes vacuolation in the cells of the proximal convoluted tubules, thereby causing renal tubular necrosis. Hepatocellular injury occurs secondary to mitochondrial damage and endoplasmic reticulum degranulation[2]. Paraquat concentration in the lung is 10–20 times greater than in the plasma due to the energy-dependent uptake of the poison by the alveoli. The acute respiratory distress syndrome sets in after 24–48 hours of exposure[4].

Kinetics

Paraquat is highly polar and corrosive substance. Paraquat is rapidly but incompletely absorbed from the gut after ingestion. It then rapidly distributed into other tissues with maximum tissue levels 6 hr after ingestion. Paraquat does not undergo significant metabolism and eliminated primarily by kidneys.

Clinical feature

Oral and gastrointestinal symptoms are common. Patients usually have a painful mouth and pain with swallowing. Nausea, vomiting and pain abdomen are common. Respiratory complaints indicate systemic poisoning and are associated with fatal outcomes. Patient who ingest large doses present with fulminant multi-organ dysfunction (MODS), pulmonary edema, cardiac and renal hepatic failure and CNS system involvement with seizures. The pulmonary lesion has two phases: an acute alveolitis over 1-3 days followed by secondary fibrosis.

Management

The management of paraquat exposure is determined on an individual basis depending on the amount ingested and the time elapsed since exposure. Sign and symptom of paraquat poisoning usually appear with in 12hrs so patient should be monitored for at least this duration. However, a negative urinary dithionite test beyond 6 hr post ingestion suggests that exposure was minimal and patient can be medically cleared if asymptomatic.

Initial resuscitation of the patient follows standard guidelines except oxygen therapy should not be administered unless there is confirmed hypoxia, as oxygen may exacerbate the oxygen mediated cellular damage. Fluid losses are treated with 2-3L of isotonic crystalloid. Gastrointestinal decontamination is given with approximately 2 hr of ingestion with activated charcoal or fullers earth. Exposed skin should be washed thoroughly with soap and water as soon as possible for up to 15 minutes. Ocular exposure should be decontaminated by rinsing the eye with isotonic saline for a minimum of 30 minutes.

Anti-inflammatory agents such as dexamethasone, methylprednisolone usually given along with immunosuppressive agents such as cyclophosphamide but usually none has any proven benefit. In this case we have given a higher dose of steroid so that we can supress ongoing inflammation and cytokine storm which help in preventing the fibrosis later on and also our patient has shown clinical improvement and there is improvement in respiratory parameters, decrease in respiratory rate and decrease in the requirement of oxygen.

A range of antioxidant like acetyl cysteine, deferoxamine, vitamin c and vitamin E can be given. Extracorporeal therapy such as hemodialysis and hemoperfusion are effective in enhancing elimination because paraquat has low protein binding.

CONCLUSION

Although, none of the current treatments have proven effective for patients with severe poisoning and prognosis is uniformly poor in nearly all centres but we have seen started improvement in the respiratory parameters after starting high dose methylprednisolone pulse therapy. Hence, it is concluded that early starting of higher dose of steroids can be beneficial in supressing the cytokine storm and reducing inflammation and thereby preventing ARDS and later onset fibrosis. However, the clinical efficacy is still to determine at its best as patient presented to us 7 days after taking the poisonous substance.

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