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Review Article

One-lung circumvention, an interventional strategy for pulmonary salvage in acute paraquat poisoning: An evidence-based review

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ABSTRACT

Paraquat is highly toxic to humans. Peak plasma levels are reached within 1 hour after intentional ingestion of this poison, followed by a rapid decline because of its distribution to the extravascular compartment and renal elimination. It induces generation of free oxygen radicals and consumption of intracellular nicotinamide adenine dinucleotide phosphate in a cyclic single-electron reduction/oxidation reaction; consequently, cell death occurs because of lipid peroxidation of the cell membrane. Paraquat selectively accumulates in the lungs, resulting in pulmonary fibrosis, which can eventually lead to respiratory failure in many survivors of the acute phase. It is believed that charcoal hemoperfusion is the best modality for extracorporeal elimination in the acute phase. Afterward, anti-inflammatory and immunosuppressive treatment and even lung radiotherapy have been proposed to alleviate inflammation. Unfortunately, these protocols are unsuccessful in a majority of patients. Because the first hours are critical for treatment and the lungs are the target organs, pulmonary salvage is the aim of the toxicologist. Deep insertion of an endotracheal tube as the first treatment effort can produce alveolar collapse, as well as an arteriovenous pulmonary shunt in one lung. Decreased paraquat uptake, at least in one lung, leads to a reduced inflammatory process in the treated lung after the acute phase of toxicity. Furthermore, preserving a functioning lung is sufficient for life.

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1. Introduction

Paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride) is an herbicide used to destroy shallow-rooted vegetation on farms. Accidental or intentional ingestion when attempting suicide is the usual reason for toxicity [1]. Paraquat is rapidly absorbed after ingestion and peak plasma levels are reached within 1 hour, followed by a rapid decline because of its distribution to the

extravascular compartment. About 90% of the absorbed toxin is eliminated by renal excretion as the parent compound within the first 24 hours [2,3]. Unfortunately, renal cells are vulnerable to the toxic compound and paraquat-induced kidney injury leads to deterioration of renal function within the first few hours [2]. The toxin compound then accumulates in target organs. Paraquat selectively accumulates in the lungs through the polyamine uptake system [4]. It induces generation of free oxygen radicals as well as consumption of intracellular nicotinamide adenine dinucleotide phosphate in a cyclic single-electron reduction/oxidation (redox) reaction; consequently, cell death occurs because of lipid peroxidation of the cell membrane [2,5–7]. The parent toxic molecule reproduces in this redox reaction, resulting in a cascade of pulmonary cellular damage [8].

Conflict of interest: none.

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2. Factors related to prognosis

There is no specific antidote for paraquat poisoning. In moderate to severe poisoning, death occurs within the first few days because of multiorgan dysfunction [2,9]. The amount of ingested paraquat is the most important prognostic factor. Severe poisoning after ingestion of > 100 mL of a 20% product may result in cardiac arrest within the first 24 hours; ingestion of 50–100 mL may result in renal and respiratory failure, with death occurring within the first 7 days. By contrast, ingestion of 15–50 mL of a 20% product may result in gradual respiratory failure due to pulmonary fibrosis within the 1st month. However, corrosive effects may be the sole presentation after consumption of a small amount and complete recovery after ingestion of < 15 mL is conceivable [2,10].

In a study by Gil et al [11], no patient with a plasma paraquat level of 3.44 µg/mL 2 hours after ingestion survived despite aggressive treatment; however, the lowest plasma paraquat level in nonsurvivors was 0.92 µg/mL at 2 hours.

3. Current treatment protocols

Paraquat is a water-soluble salt, which has a relatively large volume of distribution (1.0–1.5 L/kg body weight) [2,12]. Charcoal hemoperfusion, especially in the first hours, increases the elimination rate of paraquat from the plasma [13]. Because the toxic effects of paraquat occur through production of reactive oxygen species (ROS) as well as depletion of glutathione, it is proposed that antioxidant therapy may alleviate subsequent tissue injury [14–17]. The alveolar oxygen pressure has an important role in ROS production within pneumocytes [18]. In moderate toxicity, gradual respiratory dysfunction is expected if the patient survives the initial insult. The main cause is pulmonary fibrosis due to the inflammatory process after alveolar cell damage. Hence, anti-inflammatory drugs such as high-dose steroids, immunosuppressive agents such as cyclophosphamide, and even lung radiotherapy have been applied in several studies with varying success rates [17,19–21]. Lung transplantation is the only curative strategy for pulmonary fibrosis [22]. However, transplantation is not readily available and prevention of lung fibrosis is still the main treatment by clinical toxicologists.

4. Lung circumvention

Because pulmonary scavenging of paraquat during the first hours of systemic hemoperfusion is not sufficient, an inflammatory process is predictable in moderate cases. In fact, the polyamine uptake system in the lungs continues competitive recruitment of paraquat against the plasma concentration gradient during hemoperfusion. Prompt accumulation of the parent toxin leads to steady alveolar cell damage despite a decrease in the plasma level

of the toxin after extracorporeal elimination. Therefore, engendering an iatrogenic pulmonary shunt before hemoperfusion may alleviate pulmonary uptake and enhance lung preservation. This is achieved by deep insertion of an endotracheal tube, which leads to alveolar collapse as well as an arteriovenous pulmonary shunt in one lung [23,24]. This blocks the uptake of more toxins (Figure 1). Furthermore, preserving a functioning lung is sufficient for life. A lung-separation technique was first reported by Geffin et al in 1969 [25]. They established intubation of one main bronchus for resection of distal tracheal and carinal tumors. Nowadays, lung-separation techniques are widely used for surgical operations on the pulmonary tree, to bypass a tracheobronchial injury site, and for protection against contralateral pulmonary secretions [26,27].

5. Evaluation of this therapeutic intervention

Selective recruitment of paraquat through the polyamine uptake system results in lung concentrations about 10-fold greater than that in the plasma compartment [4,28,29]. If the patient survives the acute phase, pulmonary fibrosis in relation to cellular oxidative damage is the main pathophysiological development after moderate paraquat intoxication. This condition represents a refractory hypoxemia [2,20]. In the literature, researchers have only focused on alleviation of toxin-induced oxidative stress or inflammatory processes following the acute phase [17,20,21,28–32]. Hoffer et al [14] indicated that *N*-acetyl-L-cysteine (NAC) has protective properties against the cytotoxicity of paraquat in alveolar type II cells in a rat model. Another study conducted by Hong et al [15] showed that 10 µmol of NAC suppressed ROS formation in paraquat poisoning. As the Haber–Weiss reaction is deemed to have a role in free radical-induced oxidative stress, iron-chelating therapy has been proposed as another treatment modality in acute paraquat intoxication [16]. In a series of studies, Lin et al [17,19,31] evaluated repeated pulse steroids and immunosuppressive agents and indicated improvement in the survival of their patients. Some authors have tried hypooxygenation to reduce ROS production [33,34]. Unfortunately, these protocols have been unsuccessful in a majority of patients [35]. We believe that if the treatment protocol focuses on the attenuation of pulmonary toxin recruitment during the acute phase, a reduced inflammatory process can be expected. We feel that circumvention of one lung before applying extracorporeal toxin removal methods can preferentially suppress paraquat uptake by lung cells. Much evidence shows that perfusion of non-ventilated parts of the lung will induce intrapulmonary arteriovenous shunting, which is associated with a ventilation–perfusion mismatch. This condition is tolerated by the patient and only some degree of hypoxia results [36].

So far, no study has investigated iatrogenic lung circumvention as a treatment protocol in any situation. Available information shows that after obstruction of the main bronchus, functional

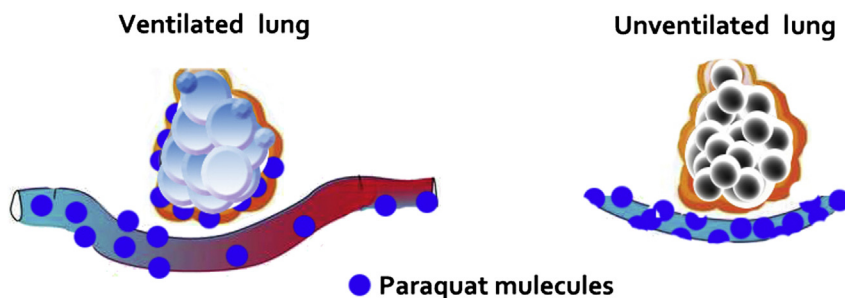


Figure 1. Deep insertion of the endotracheal tube can produce alveolar collapse, as well as arteriovenous pulmonary shunt in one lung, which is responsible for prohibition of more toxin reuptake.

intrapulmonary shunting and absorption atelectasis develop [37,38]. However, these studies do not prove that one-lung bypass enhances the elimination of pretreatment-absorbed toxins, or diminishes selective uptake of paraquat and increases wipe out of oxygen molecules in the treated lung. Gil et al [11] showed a progressive decrease in the plasma paraquat level during the first hours of intoxication. Proudfoot et al [39] showed a correlation between plasma paraquat levels over time and the survival of patients.

6. Conclusion

Patient deaths in moderate paraquat toxicity are directly related to pulmonary fibrosis. Less cellular damage and a reduced inflammatory process are related to a lower alveolar microcirculatory paraquat level. This condition is conceivable with intrapulmonary arteriovenous shunting. Furthermore, occasionally emergency charcoal hemoperfusion, which is thought to be the best modality for extracorporeal elimination, is not available promptly. Therefore, many patients do not receive appropriate treatment at the proper time. By contrast, endotracheal intubation is a relatively safe protocol, which is achievable in locations with trained emergency personnel. Deep endotracheal intubation as the first treatment effort can decrease paraquat uptake in at least in one lung; therefore, we can expect a reduced inflammatory process and diminished fibrotic changes in the treated lung after the acute phase of toxicity. All of this evidence could lead to a new treatment protocol in the management of acute paraquat toxicity. However, the ventilated lung will be sacrificed, preserving one functioning lung, which is sufficient for life.

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