Tzu Chi Medical Journal 27 (2015) 99–101

Contents lists available at ScienceDirect

Tzu Chi Medical Journal

journal homepage: www.tzuchimedjnl.com

Review Article

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

Sayed Mahdi Marashi [a], Hojatollah Raji [b], Zeynab Nasri-Nasrabadi [b,*], Mohammad Majidi [c], Maryam Vasheghani-Farahani [d], Abdollah Abbaspour [e], Ahmad Ghorbani [f], Shayesteh Vasigh [e]

[a] Trauma Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[b] Department of Pediatrics, Children's Medical Center, Pediatric Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Forensic Medicine and Clinical Toxicology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran
[d] AJA University of Medical Sciences, Tehran, Iran
[e] Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran
[f] Ahvaz Jondishapour University of Medical Sciences, Ahvaz, Iran

ARTICLE INFO

Article history:
Received 3 March 2015
Received in revised form
27 May 2015
Accepted 3 June 2015
Available online 28 July 2015

Keywords:
Fibrosis
Lung
Paraquat
Poisoning
Prevention

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.

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.

* Corresponding author. Department of Pediatrics, Children's Medical Center Hospital, Tehran University of Medical Sciences, 62, Gharib Street, Tehran, Iran. Tel.: +98 9179167438.
E-mail address: drmr44@yahoo.com (Z. Nasri-Nasrabadi).

http://dx.doi.org/10.1016/j.tcmj.2015.06.002

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 nonventilated 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

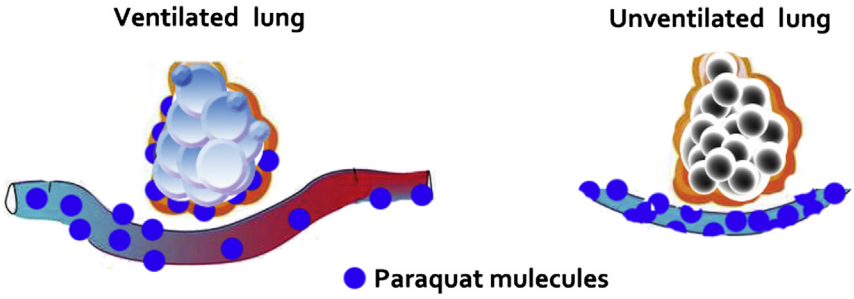

Figure 1. Deep insertion of the endotracheal tube can produce alveolar collapse, as well as arteriovenous pulmonary shunt in one lung, which is responsible for prohibition of more toxin reuptake.

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.

References

[1] Czarniewska E, Kasprzyk A, Ziemnicki K. Effect of paraquat and metoxychlor on antioxidant enzymes in frog *Rana esculenta* L. liver. Biol Lett 2003;40:125–33.

[2] Gil HW, Hong JR, Jang SH, Hong SY. Diagnostic and therapeutic approach for acute paraquat intoxication. J Korean Med Sci 2014;29:1441–9.

[3] Hoffman RS, Nelson LS, Howland MA, Levin NA, Flomenbaum NE, Goldfrank LR. Goldfrank's manual of toxicologic emergencies. New York: McGraw Hill Publishing; 2007.

[4] Dinis-Oliveira R, Duarte JA, Sánchez-Navarro A, Remião F, Bastos ML, Carvalho F. Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. Crit Rev Toxicol 2008;38:13–71.

[5] Shi Y, Bai Y, Zou Y, Cai B, Liu F, Fu P, et al. The value of plasma paraquat concentration in predicting therapeutic effects of haemoperfusion in patients with acute paraquat poisoning. PLoS One 2012;7:e40911.

[6] Tsai HL, Chang JW, Yang HW, Chen CW, Yang CC, Yang AH, et al. Amelioration of paraquat-induced pulmonary injury by mesenchymal stem cells. Cell Transplant 2013;22:1667–81.

[7] Yeh ST, Guo HR, Su YS, Lin HJ, Hou CC, Chen HM, et al. Protective effects of N-acetylcysteine treatment post acute paraquat intoxication in rats and in human lung epithelial cells. Toxicology 2006;223:181–90.

[8] Pasi A. The toxicology of paraquat, diquat and morfamquat. Bern, Switzerland: Hans Huber Publishers; 1978.

[9] Serra A, Domingos F, Prata MM. Paraquat intoxication. Acta Med Port 2003;16:25–32 [In Portuguese].

[10] Chen HH, Lin JL, Huang WH, Weng CH, Lee SY, Hsu CW, et al. Spectrum of corrosive esophageal injury after intentional paraquat or glyphosate-surfactant herbicide ingestion. Int J Gen Med 2013;6:677–83.

[11] Gil HW, Kang MS, Yang JO, Lee EY, Hong SY. Association between plasma paraquat level and outcome of paraquat poisoning in 375 paraquat poisoning patients. Clin Toxicol (Phila) 2008;46:515–8.

[12] Lee HL, Kan CD, Tsai CL, Liou MJ, Guo HR. Comparative effects of the formulation of glyphosate-surfactant herbicides on hemodynamics in swine. Clin Toxicol (Phila) 2009;47:651–8.

[13] Hong SY, Yang JO, Lee EY, Kim SH. Effect of haemoperfusion on plasma paraquat concentration *in vitro* and *in vivo*. Toxicol Ind Health 2003;19:17–23.

[14] Hoffer E, Baum Y, Tabak A, Taitelman U. N-acetylcysteine increases the glutathione content and protects rat alveolar type II cells against paraquat-induced cytotoxicity. Toxicol Lett 1996;84:7–12.

[15] Hong SY, Gil HW, Yang JO, Lee EY, Kim HK, Kim SH, et al. Effect of high-dose intravenous N-acetylcysteine on the concentration of plasma sulfur-containing amino acids. Korean J Intern Med 2005;20:217–23.

[16] Jomova K, Valko M. Importance of iron chelation in free radical-induced oxidative stress and human disease. Curr Pharm Des 2011;17:3460–73.

[17] Lin JL, Lin-Tan DT, Chen KH, Huang WH. Repeated pulse of methylprednisolone and cyclophosphamide with continuous dexamethasone therapy for patients with severe paraquat poisoning. Crit Care Med 2006;34:368–73.

[18] Hoet PH, Demedts M, Nemery B. Effects of oxygen pressure and medium volume on the toxicity of paraquat in rat and human type II pneumocytes. Hum Exp Toxicol 1997;16:305–10.

[19] Lin JL, Lin-Tan DT, Chen KH, Huang WH, Hsu CW, Hsu HH, et al. Improved survival in severe paraquat poisoning with repeated pulse therapy of cyclophosphamide and steroids. Intensive Care Med 2011;37:1006–13.

[20] Weng CH, Hu CC, Lin JL, Lin-Tan DT, Hsu CW, Yen TH. Predictors of acute respiratory distress syndrome in patients with paraquat intoxication. PLoS One 2013;8:e82695.

[21] Savy FP, Duval G, Her B, Canu P, Fintelz P. Failure of chemotherapy and radiotherapy in pulmonary fibrosis caused by paraquat. Ann Fr Anesth Reanim 1988;7:159–61 [In French].

[22] Licker M, Schweizer A, Hohn L, Morel DR, Spiliopoulos A. Single lung transplantation for adult respiratory distress syndrome after paraquat poisoning. Thorax 1998;53:620–1.

[23] Campos JH. Lung isolation techniques. Anesthesiol Clin North America 2001;19:455–74.

[24] Campos JH. Progress in lung separation. Thorac Surg Clin 2005;15:71–83.

[25] Geffin B, Bland J, Grillo HC. Anesthetic management of tracheal resection and reconstruction. Anesth Analg 1969;48:884–90.

[26] Campos JH, Hallam EA, Van Natta T, Kernstine KH. Devices for lung isolation used by anesthesiologists with limited thoracic experience: comparison of double-lumen endotracheal tube, Univent torque control blocker, and Arndt wire-guided endobronchial blocker. Anesthesiology 2006;104:261–6.

[27] Hartigan PM. Practical handbook of thoracic anesthesia. 1st ed. New York: Springer; 2012. p. 142–3.

[28] Yao R, Zhou Y, He Y, Jiang Y, Liu P, Ye L, et al. Adiponectin protects against paraquat-induced lung injury by attenuating oxidative/nitrative stress. Exp Ther Med 2015;9:131–6.

[29] Wu WP, Lai MN, Lin CH, Li YF, Lin CY, Wu MJ. Addition of immunosuppressive treatment to hemoperfusion is associated with improved survival after paraquat poisoning: a nationwide study. PLoS One 2014;9:e87568.

[30] Chen GH, Lin JL, Huang YK. Combined methylprednisolone and dexamethasone therapy for paraquat poisoning. Crit Care Med 2002;30:2584–7.

[31] Lin NC, Lin JL, Lin-Tan DT, Yu CC. Combined initial cyclophosphamide with repeated methylprednisolone pulse therapy for severe paraquat poisoning from dermal exposure. J Toxicol Clin Toxicol 2003;41:877–81.

[32] Ghaffari AR, Noshad H, Ostadi A, Hasanzadeh N. Effect of pulse therapy with glucocorticoid and cyclophosphamide in lung fibrosis due to paraquat poisoning in rats. Saudi Med J 2011;32:249–353.

[33] Rhodes ML, Zavala DC, Brown D. Hypoxic protection in paraquat poisoning. Lab Invest 1976;35:496–500.

[34] Huh JW, Jegal Y, Hong S-B, Oh YM, Shim TS, Lim C-M, et al. Efficacy of deferoxamine on paraquat poisoning. Tuberc Respir Dis 2007;62:113–8.

[35] Sanaei-Zadeh H. Can pirfenidone prevent paraquat-induced pulmonary fibrosis?—a hypothesis. Tzu Chi Med J 2012;4:223 [Letter to the Editor].

[36] Braunwald E. Hypoxia and cyanosis. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al., editors. Harrison's principles of internal medicine. 17th ed. New York: McGraw-Hill; 2008. p. 229.

[37] Kolettas AA, Tsaousi GG, Grosomanidis V, Karakoulas KA, Thomareis O, Kotzampassi K, et al. Influence of apneic oxygenation on cardiorespiratory system homeostasis. J Anesth 2014;28:172–9.

[38] Shih WJ, Bognar B. Reverse mismatched ventilation-perfusion pulmonary imaging with accumulation of technetium-99m-DTPA in a mucous plug in a main bronchus: a case report. J Nucl Med Technol 1999;27:303–5.

[39] Proudfoot AT, Stewart MS, Levitt T, Widdop B. Paraquat poisoning: significance of plasma-paraquat concentrations. Lancet 1979;2:330–2.