EDITORIAL

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Cyclophosphamide dose: how much is needed to win the war against paraquat poisoning?

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See Article on Page 420-427

Paraquat (PQ; 1,1′-dimethyl-4,4′-bipyridinium) dichloride is a nonselective herbicide that has been used in many countries since the 1960s because of its strong activity against weeds and rapid deactivation upon soil contact [1]. However, it is highly toxic to humans, and there is no specific antidote or effective treatment. Self-poisoning with PQ is a major public health problem associated with high mortality (> 50%) in developing countries in Asia, the Pacific Islands, and the Caribbean, where its use is regulated less strictly than in Europe or the United States [2].

PQ poisoning can cause severe multiple-organ failure of the kidneys, liver, lungs, adrenal glands, and central nervous system. Ingestion of more than 20 mL of a 20% preparation is likely to cause death from multiorgan failure and cardiogenic shock within 1 to 4 days, while smaller quantities (10 to 20 mL) can initiate irreversible lung fibrosis and renal failure that result in death within several weeks [3]. PQ is rapidly distributed in the body, accumulating at the highest concentrations within the lung and kidney [1]. Kidneys exposed to PQ demonstrate the development of large vacuoles in the proximal convoluted tubules, leading to necrosis and a decline in renal function [2]. In addition, because PQ is primarily excreted unchanged via the kidney, the reduction in renal function also leads to an increased plasma concentration, which contributes to its toxicity in other nonrenal organs, especially the lungs. Respiratory failure in the presence of PQ-induced acute kidney injury is responsible for most PQ-associated deaths. The toxic effect of PQ on the lung results in pulmonary edema, hypoxia, respiratory failure, and pulmonary fibrosis [1].

The mechanism of PQ-induced organ injury is thought to be production of reactive oxygen species by enzymatic one-electron reduction of PQ, followed by one-electron transfer to dioxygen with the generation of the superoxide anion [1]. PQ-induced lung injury consists of two phases: an early destructive period when the alveolar epithelial cells are damaged, and a late proliferative period characterized by infiltration of inflammatory cells, alveolitis, pulmonary edema, and finally pulmonary fibrosis [1]. Cytokines such as tumor necrosis factor-α, interleukin (IL)-1, and IL-6 are involved in PQ-induced acute lung injury, whereas transforming growth factor (TGF)-β1 functions primarily in fibrogenesis, stimulating collagen deposition by newly replicated myofibroblasts [4].

Several parameters—such as liver enzymes, serum creatinine, potassium, arterial blood bicarbonate, the re-

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spiratory index, and plasma and urinary PQ concentrations—have been proposed as prognostic indicators [1]. Measurement of the plasma PQ concentration is useful for assessing the severity and predicting the outcome of PQ poisoning. PQ concentration-time data have been used to predict prognosis for three decades. Proudfoot et al. [5] presented a nomogram of the relationship between outcome and the plasma PQ concentration on admission and the time interval between ingestion and blood collection. Hart et al. [6] created six plasma PQ concentration-time curves representing estimates of the probability of survival, which ranged from 10% to 90%. Sawada et al. [7] developed a severity index for paraquat poisoning to predict patients' prognosis. More recently, the Acute Physiology and Chronic Health Evaluation II system was applied in predicting the mortality of these patients [8]. All of these curves and formulae have been used to predict outcomes with acceptable performance, but none have been validated independently and prospectively [3]. Recently, biomarkers such as pentraxin-3 or neutrophil gelatinase-associated lipocalin were used to predict prognosis in patients with PQ poisoning [9,10].

The management of PQ intoxication involves removal of PQ from the gastrointestinal tract (preventing absorption), increasing its removal from the blood, and preventing pulmonary damage with antioxidants and anti-inflammatory agents. Gastric lavage has been recommended for patients presenting within 1 to 2 hours of ingestion, and activated charcoal or Fuller's earth has been used to prevent PQ absorption; however, neither procedure has been proven beneficial in PQ poisoning [1,3]. Extracorporeal elimination through hemoperfusion or hemodialysis is performed to remove PQ from the circulation and prevent its uptake by pneumocytes and Clara cells of the lungs. Commencing charcoal hemoperfusion at an early stage (within 2 to 4 hours of ingestion), when PQ is concentrated in the central compartment, can remove PQ from the plasma but does not reduce PQ uptake by the lungs sufficiently to change the overall outcome [1]. Because the main biochemical mechanism of the lung injury is initiated by oxygen free radicals produced by peroxidation, a number of antioxidants—such as vitamins C and E, xanthine oxidase inhibitors, deferoxamine, N-acetylcysteine, and superoxide dismutase—have been evaluated to determine whether they interfere with the process. Unfortunately, none of these treatments has been proven effective [1,2]. In addition, anti-inflammatory and immunosuppressive agents such as cyclophosphamide (CP) and glucocorticoids (dexamethasone and methylpredisolone) have been used to reduce the extent of pulmonary inflammation and fibrosis [1,2].

CP, which has a wide range of immunomodulatory actions that affect virtually all components of the cellular and humoral immune response and decrease the severity of inflammation, has been used since the 1980s. However, the adequate dose for treatment of patients with PQ poisoning has not been determined. Some studies used a CP dose of 5 mg/kg, whereas others administered CP at a dose of 15 mg/kg [1]. In addition, fatal lung injuries developed when high doses of CP (200 mg/kg) were administered in an adult rat model [11]. In the present issue of *The Korean Journal of Internal Medicine*, Choi et al. [12] reported that a CP dose of > 15 mg/kg was effective in reducing the severity of PQ-induced lung injury in a rat model. They also suggested that reduction of the severity of PQ-induced lung injury was possibly due to modulation of antioxidant enzymes and TGF-β1. The authors also used microtomography to determine the size of the lung lesions and demonstrated the effectiveness of 15 mg/kg CP. This article is notable because no other study has compared the effectiveness of various CP doses on the severity of lung lesions in PQ intoxication.

Recently, a new antifibrotic agent, pirfenidone, was reported to decrease pulmonary fibrosis following PQ poisoning in a rat model [13]. However, no clinical trial has shown that pirfenidone is effective in human PQ poisoning. Therapeutic approaches such as mechanical ventilation with additional inhalation of nitric oxide, induction of P-glycoprotein, and sodium salicylate have been proposed based on the pathologic mechanism of toxicity [1], but further studies are needed to demonstrate their clinical efficacy. Furthermore, although a CP dose of 15 mg/kg was effective in reducing the severity of PQ-induced lung injury, further studies are required to determine whether a CP dose of 15 mg/kg is also effective when combined with a glucocorticoid.

Respiratory failure is a frequent cause of death in moderate-to-severe PQ poisoning, and various therapeutic approaches have been used to prevent lung dam-

age [1]. Of these, CP and steroids are the primary agents used to reduce the inflammatory process. Although an adequate dose of CP was determined in a PQ rat model [12], there have been no controlled trials of human poisoning. Moreover, although immunosuppressive medications (CP and glucocorticoids) and antioxidants (N-acetylcysteine, vitamin C and E, salicylate) appear to be effective to counter the PQ poisoning, more evidence is needed to guide the choice of dose, duration, and combination.

In conclusion, well-designed controlled trials with multidisciplinary "cocktail" approaches that combine these agents, preferably with prognostic parameters such as PQ concentration-time data, should be conducted and their efficacy should be validated to win the war against PQ poisoning.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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