

Case Report

The successful treatment of systemic toxic induced paraquat poisoning by skin absorption: case reports and a literature review

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Abstract: Paraquat (PQ) poisoning is life-threatening, can cause acute organ damage, and has a high mortality. However, cases of skin absorption induced by PQ poisoning are rare. This report describes a case where PQ was absorbed by the patient's skin, causing severe organ damage. Having accidentally touched PQ on his skin, the patient, whose skin festered, became damaged, red, and swollen, developed serious systemic toxic symptoms. The patient recovered after systemic treatment. Generally speaking, being poisoned by PQ through skin absorption is rare. By analyzing the reported PQ poisoning through skin absorption and by reviewing the relevant literature, this paper aims to explore successful treatments for PQ poisoning through skin absorption and to provide treatment guidance for physicians encountering such cases.

Keywords: Paraquat poisoning, skin absorption, systemic toxic, successful treatment

Introduction

Paraquat, the chemical name of which is known as 1-1-dimethyl-4-bipyridine cationic salt, is soluble in water but insoluble in most organic solvents. In China, it is the most commonly-used agricultural chemical when people attempt to commit suicide [1]. To make it worse, the number of patients poisoned by PQ is growing linearly. According to the slightly-varied reports both from home and abroad, the lethal rate of PQ poisoning can reach approximately 80%-90% [2]. In most cases, the PQ poison enters patients' bodies orally, but skin absorption is quite rare [3]. The authors will discuss two cases of PQ poisoning through skin absorption in the main body of the paper. Both cases are related to an accidental touching of PQ by patients who later suffered from skin chemical burns and serious inflammation symptoms throughout their entire bodies, but fortunately their health was finally restored. In this paper, the authors refer to and gather up relevant material about the cases and discuss the successful treatments of PQ poisoning.

Case presentation

Case 1: The patient was a twenty-one-year-old man who got poisoned on July 11th, 2016 when he was spraying PQ in the field and stayed in the field for 11 hours. On July 12th, he found his whole body was covered with itchy red patches. Part of his skin hurt with a burning pain but was not swollen. Meanwhile, he was nauseous and had no appetite and had a sense of pressure in the chest and shortness of breath. On the night of July 13th, he began to vomit. The vomitus had gastric contents. The local hospital received him and determined he was poisoned by PQ. Due to his rare medical condition, he was transferred to a higher level hospital for better treatment. On July 14th, he was received by the Emergency Department of the First Affiliated Hospital Guangxi Medical University, which performed a physical examination on him. The examination result was as follows: T: 36.6°C, pulse (P): 69/min, respiratory rate (R): 20/min, blood pressure: 129/76 mmHg. The patient was alert, and red maculae had covered the burned area. The total body



Figure 1. A. Recorded on the day of admission, on July 14, 2016. B. Recorded on the 13th day of hospitalization, on July 26, 2016. C. Patient reviewed for the first time after discharge, on August 24th, 2016.

surface area (TBSA) burned by the PQ was 8%, and the ranking was shallow: II degree to deep II (Figure 1A). A routine blood examination revealed that his leucocyte count was $14.71 \times 10^9/L$, the renal function test showed his blood urea nitrogen (BUN) was 12.53 mmol/L, his serum creatinine (SCr) concentration was $462 \mu\text{mol/L}$, the liver function and PT, APTT, TT and FIB were normal, and CT (computed tomography) scanning was also preliminarily normal. The patient then immediately received symptomatic treatments, including anti-inflammatory therapy, anti-infection, scavenging oxygen free radicals, and organ function protection. On July 15th, the patient was suffer-

ing from burning pain of the entire affected skin area, he had hot pain in both eyes but without nausea and vomiting, but his mind was clear. The doctors found that his face was normal, his pharynx flushed, and he had bilateral conjunctival congestion. Several blisters, pustules, and festering areas appeared in some parts of his back, shoulder, bilateral axilla, buttocks, thighs, inguinal region, and scrotal skin. The temperature in some parts of his skin increased. A routine blood examination indicated that his leucocyte count was $11.58 \times 10^9/L$ and his percentage of neutrophils was 0.76. A renal function test showed his BUN was 11.19 mmol/L and his SCr concentration was $412 \mu\text{mol/L}$. On July 18th, the patient told doctors he had floaters in his eyes but without blurred vision. His leucocyte count was $14.00 \times 10^9/L$, his BUN was 14.53 mmol/L, and his SCr concentration was $327 \mu\text{mol/L}$. A second CT test showed there was a new effusion of the lesions in the patient's bilateral pleura (Figure 2A). On July 23rd, scabs began to appear on his back, shoulder, bilateral axilla, buttocks, thighs, and inguinal

region, but there was no effusion or bleeding. There was damage in the patient's scrotal skin, and a black scab began to appear with reduced effusion. The leucocyte count was $18.08 \times 10^9/L$, BUN 16.21 mmol/L and the SCr concentration was $146 \mu\text{mol/L}$. On July 26th, the burning sensation on his back decreased, and the patient's scrotal skin, but he had no symptoms of fever, cough, sputum, chest tightness, shortness of breath or dyspnea. After an examination, the doctor found that his life signs were stable, his mind clear, but his eyelid were swollen, he had bilateral conjunctival congestion, and edematous, white pseudomembranous attachments were visible. On his back, shoulders, bilateral

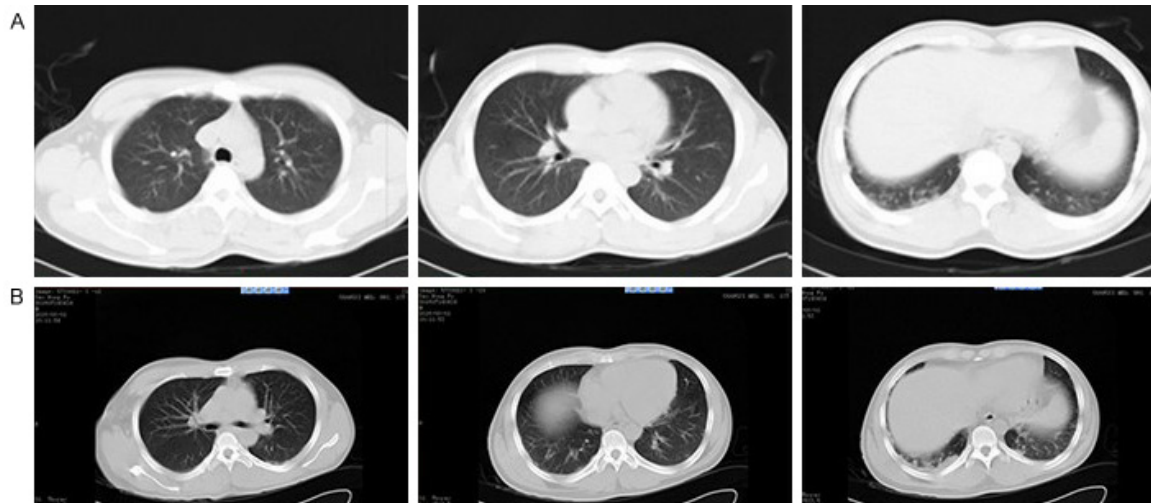


Figure 2. A. Computed tomography (CT) examination on the 5th day of hospitalization, on July 18th, 2016. B. Computed tomography (CT) examination as an outpatient, on August 1th, 2016.

axilla, buttocks, thighs, inguinal region, and scrotal skin, there was partial skin exfoliation in the burned areas with little effusion, no bleeding and changes in the dark red schistose burned areas. The effusion at the scrotum was clearly decreased (**Figure 1B**). A routine blood examination showed that his leucocyte count was $25.59 \times 10^9/L$. Given that there was a possibility of the infection becoming worse, the patient continued to be treated with the anti-infective drug cefoxitin. His BUN was 14.68 mmol/L, and his SCr concentration was 111 $\mu\text{mol/L}$, which was lower than before. The urinary output of the patient stayed within the normal range, which illustrated the improvement of his kidney function. On August 1st, the patient had no discomfort, his spirit, appetite, and sleep were good, and his urination and defecation were normal. A body check showed his life signs were stable, his mind clear, the swelling in eyes and faces subsiding, his bilateral conjunctiva were mildly congested, and his vision normal. There were scabs on his shoulder, bilateral axilla, buttocks, thighs, and inguinal region, where there was no effusion. On his back, a bright red granulation was growing around the skin paddles on the edge of which new skin was growing. The temperature of his skin was slightly higher. There was damage in his scrotal skin which changed to dark red with little effusion, and less than before. An examination of his body showed his leucocyte count was decreasing and his kidney function was becoming normal. A CT test showed no pulmonary fibrosis without new exudative lesions

compared with the previous CT (**Figure 2B**). The patient was discharged from the hospital the next day. He rechecked his body on August 24th, finding his spirit and appetite indicators were good, there was no congestion in his bilateral conjunctiva, and his vision normal. There were red dark burned scars on his shoulders, bilateral axilla, arms, thighs, and inguinal area with no effusion, where newly grown skin was covering the wound (**Figure 1C**). The CT recheck in the lungs demonstrated post-poisoning changes without pulmonary fibrosis and the effusions of inflammation stopped. Finally, the patient had recovered. The patient's general blood routine indicators were attached during the hospitalization (**Table 1**).

Case 2: The patient was a 45-year-old man who was sent to the hospital by ambulance on August 5th, 2015 after suffering from dizziness, cough, and shortness of breath for ten days and dyspnea for three days. The patient's scrotum had touched some plants sprayed with PQ fluid one week earlier. In the following three days, the patient had trouble breathing and then sought help at the Emergency Department of the Affiliated Hospital of Guangxi Medical University. A general medical examination on the patient in the hospital showed a certain part of the skin mucosa at the penis and scrotum was damaged, and there was festering and swelling, and part of it was purple black. A blood gas analysis of the patient showed: PH: 7.48, PaCO_2 : 37 mmHg, PaO_2 : 64 mmHg, SaO_2 : 94%. A check on his kidney function showed:

Table 1. General clinical data during hospitalization

General Clinical data during hospitalization	2016-07-14	2016-07-15	2016-07-18	2016-07-20	2016-07-23	2016-07-26	2016-07-30
BUN (mmol/L)	12.53	11.19	14.53	15.06	16.21	14.68	10.86
SCr (μmol/L)	462	412	327	222	146	111	105
Leukocyte count (10 ⁹ /L)	14.71	11.58	14.00	15.31	18.08	25.59	24.01
Percentage of neutrophils (%)	0.738	0.760	0.776	0.722	0.741	0.835	0.915

BUN = blood urea nitrogen; SCr = serum creatinine.

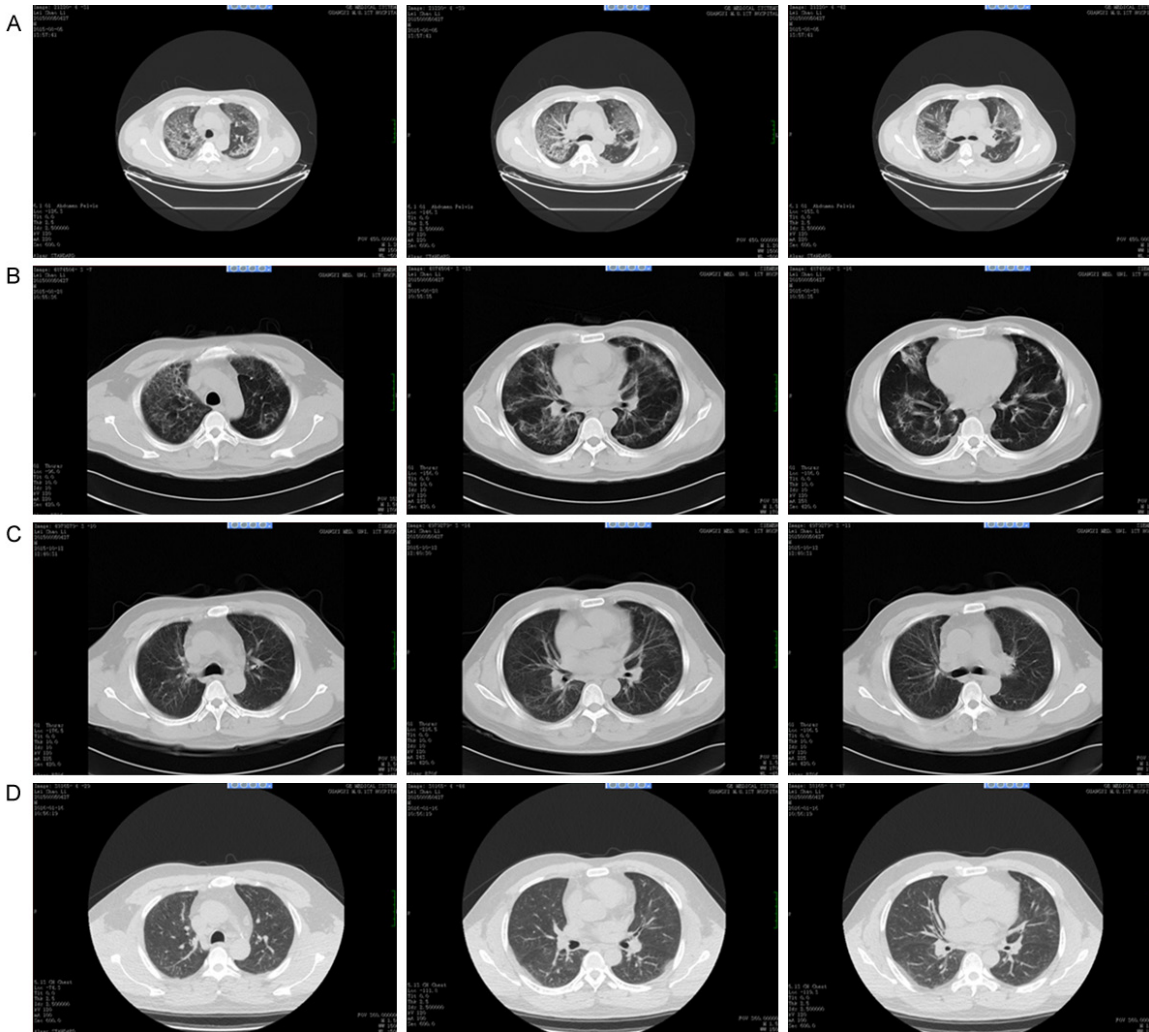


Figure 3. A. First computed tomography (CT) examination, on August 5th, 2015. B. Computed tomography (CT) examination on the 21st day of hospitalization, on August 25, 2015. C. The patient's first review of computed tomography (CT), on October 12th, 2015. D. Second computed tomography (CT) review after discharge, on January 16th, 2016.

BUN: 27.4 mmol/L, Cr: 652.6 μmol/L, CT test showed: diffuse exudation of both lungs and bilateral pleural effusion (**Figure 3A**). The doctors immediately dressed the wounds on the scrotum and used silver sulfadiazine cream combined with semi-exposed therapy. After the necrotic tissue dissolved, the cream was replaced with mupirocin ointment and recombi-

nant human epidermal growth factor derivative (rhEGF) to promote wound healing. In addition, doctors administered other treatments, such as hemoperfusion (HP) working with continuous renal replacement therapy (CRRT), guarding against infection with cefoperazone tazobactam, pulse immunosuppressive therapy with glucocorticoid and cyclophosphamide for

antitoxicity, massive transfusions to promote toxic excretion, protecting the stomach and liver, and scavenging oxygen free radicals. On August 10th, the patient's dyspnea was slightly eased, but he still had a cough, sputum, and scrotum pain. The blood gas analysis showed: PH: 7.40, PaCO₂: 47 mmHg, PaO₂: 70 mmHg, SaO₂: 94%. A check on his body showed: BUN was 20.40 mmol/L and SCr concentration 251 μmol/L. On August 11th, the doctor found that a certain part of the skin mucosa on the patient's penis and scrotum of the patient were damaged, festering, and swelling, part of it was purple black, and there was a purulent secretion on it. A routine blood examination showed: leukocyte count was 15.60*10⁹/L and C-reactive protein 60.46 mg/L, which could be a result of the use of the glucocorticoid or the infection of the penis and scrotum. A CT test showed: diffuse exudation of both lungs and bilateral pleural effusion increasing. On August 15th, the patient felt better in terms of chest tightness and dyspnea due to the systemic therapy for five days, his BUN was reduced to 8.55 mmol/L and his SCr concentration was 144 μmol/L. Scabs began to appear in over most of his scrotum and penis with little effusion and without a purulent secretion. On August 28th, a CT examination on the patient revealed that inflammatory lesions appeared in both lungs and the pleural effusion had shrunk (**Figure 3B**). The patient was in good spirits and had no dyspnea or other discomfort, a purple-black eschar was generated and covered the major burn wound area with little exudation, then the patient was discharged. The patient received two follow-up examinations, one on October 12th, 2015 and one on January 16th, 2016. They found his eschar had fallen off; his skin ulcers were healing at the scrotum and penis without effusion and were significantly improved. The healed parts had also returned to their original colors. A CT test on his lungs showed the lesions had stopped and the patient had finally recovered (**Figure 3C and 3D**).

Discussion

PQ is a highly toxic compound. It has a high lethal rate due to the lack of specific antidotes after poisoning [4], but it is still widely used in many countries in the world because of its low cost and high efficiency. In case 1, the herbicide worker was exposed to PQ spraying with-

out proper protective measures, causing his eyes, back, buttocks, thighs, inguinal area, and scrotum to be hurt by PQ chemical burns. The skin showed patchy red maculae changes, local blisters and pustules, and a small amount of ulceration. Severe congestion and edema of his eyelid bulbar conjunctiva were observed in all his conjunctiva. Characteristic gray-white pseudomembranes were covered, and entire organs, including pulmonary and renal insufficiency, were damaged. After the patient received systematic treatment, his pulmonary and renal functions gradually returned to normal. The patient was eventually cured. In case 2, the patient had itching, redness, and swelling after his scrotum and glans skin touched PQ, followed by difficulty breathing and dyspnea. After general treatment and symptomatic support, the patient felt better in terms of dyspnea. A CT test showed the progression of the pulmonary inflammation in the patient's lungs was stopped, and the patient was finally cured. The PQ poisoning mechanism is still unclear. It is widely thought to be related to oxidative stress and excessive inflammation, as PQ enters the blood through skin absorption, and large quantities of nicotinamide adenine dinucleotide phosphate (NADPH) are consumed, produce a large number of superoxide anions (O²⁻), hydroxyl free radicals (HO[•]), hydrogen peroxide (H₂O₂), and other reactive oxygen species (ROS), cause lipid peroxidation and result in blocking breathing and the normal electron transport chain lead to mitochondria damage, and causes tissues and cells to continue to die. After PQ enters the lungs, inducing the activation of the NF-κB factor, the effector cells release a large number of inflammatory factors, which amplify the inflammatory response through the "cytokine cascade effect" [5]. A large number of inflammatory factors, such as IL-1, IL-6, TGF-1, and TNF-α, are released to cause a systemic inflammatory response. After entering the blood circulation, PQ easily accumulates in tissues and organs, blood flows to the concentration gradient of the reversible storage in the lung, even after renal excretion quickly reduces the PQ concentration in the blood within 24 hours. However, the PQ concentration in lung tissue is maintained at 10-90 times the circulating PQ concentration [6], so the prognosis of patients with oral exposure leads scholars to believe that it is directly associated with the circulating blood concentrations of PQ. Some scholars have set the lethal dose

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of PQ poisoning by oral administration at 40-160 mg/kg. Skin absorption of PQ has been reported as a polarization. Due to the limited skin absorption of PQ, Peiró reported that the skin absorption of PQ did not show any severe systemic inflammatory reaction symptoms. But Soloukides and others reported fatal cases of skin contact with PQ [7, 8]. The lethality of PQ skin absorption poisoning may be related to the skin contact site, the exposure dose, the burn area, and the residence time of the poison. Other researchers found that PQ-burned corneas may absorb PQ and cause a systemic toxic reaction apart from the characteristic pseudomembrane formed by simple eye burns and chronic conjunctivitis [9]. However, PQ burns the eyes, and almost no severe visual impairment or damage to the conjunctiva has a good prognosis. Probably due to the fact that the perineum and axilla skin are more fragile and possess more small fragile blood vessels, studies such as those by Tungsanga also support the theory that PQ uptake in the perineum and axilla is more likely to cause systemic reactions than normal skin absorption [10]. The chemical properties of PQ have obvious stimulating effects on the skin and mucosa. It can cause severe local damage to burned skin and systemic inflammation through skin damage and small wound absorption, leading to multiple organ damage. This suggests that due attention should be paid to toxicity absorbed by PQ affected skin. Early identification and active treatment can play positive roles in the prognosis of PQ patients. Therefore, we advocate that PQ skin absorption poisoning should be treated in following way based on our experience of successful treatment and study of the literature:

The source to prevention

Teach workers exposed to PQ environment to work by means of compulsory training and compulsory protective measures. Strict controls of plants sprayed with PQ should be put into place to prevent the contact of uninformed persons. More laws and regulations should be enacted and enforced to regulate the use of PQ [11]. In addition, many businessmen also mix cheap PQ into diquat, another type of herbicide. When we treat poisoning caused by diquat, we should also pay attention to whether there is poisoning caused by PQ.

Preventing absorption and burn wound management

When people are inadvertently exposed to PQ, any contaminants should be removed immediately and washed with soapy water. Non-damaged skin or mucosa can also be covered by clay or bleached soil to reduce the absorption of toxicants. For large skin exposure areas, silver sulfadiazine cream should be applied externally to prevent wound infection and promote wound healing in the early stages of the disease. Wait for tissue to dissolve, manage the exposure with mupirocin ointment and rhEGF twice a day, along with a damp dressing of chlorhexidine gauze.

Promoting excretion

When a large number of toxicants are absorbed through the skin, a rapid reduction of plasma PQ concentration and a reduction in the accumulation of toxicants in tissues and organs becomes the key to successful treatment. Researchers analyzed the cases of 164 patients with PQ poisoning showed that HP combined with CRRT can better improve patients' prognosis and protect the metabolic function of important organs. The early use of HP can rapidly reduce the concentration of blood poisons, and then combined with CRRT can continuously remove poisons and keep the concentration of blood poisons at a low level, It also can remove inflammatory mediators, replace important organ functions, and maintain internal environment stability [12].

Drug application

The mechanisms of poisoning are many, and there is no specific antidote, but the mechanism of systemic inflammation caused by PQ poisoning includes an oxidative stress reaction and subsequent inflammatory reactions in organs and tissues such as the lungs, mainly.

Pulse immunosuppressive therapy with glucocorticoid and cyclophosphamide

After 2 hours of PQ absorption, the plasma concentration reaches its peak, and the lung tissue concentration reaches its peak after 5-7 hours [13]. The early use of cyclophosphamide combined with high-doses of glucocorticoid in the treatment of PQ poisoning can effectively improve clinical efficacy and reduce lung, kid-

ney, and liver damage in patients with PQ skin absorption poisoning because large amounts of glucocorticoid can effectively prevent the accumulation of PQ in lung tissue. However, the therapy does not decrease the incidence of acute respiratory failure (ARF) or hypoxia [14].

Antioxidants

PQ entering tissues results in a large amount of ROS release, leading to mitochondrial damage. How to reduce the production of ROS and accelerate ROS clearance has become a research hot spot in the treatment of PQ poisoning. The most commonly used treatments are vitamin C and reduced glutathione. In recently basic medical research, many antioxidants have been explored, such as naringin, silymarin, lipoic acid, and daravone, leading to an increase in the concentration of antioxidant enzymes including catalase (CAT), superoxide dismutase (SOD), glutathione-S-transferase (GST), glutathione peroxidase (GPx), and heme-oxygenase-1 (HO-1), which can effectively reduce lung, liver and kidney damage in a PQ poisoning model. Although the clinical effect is not obvious at present, it provides new insights into antioxidant strategies against PQ toxicity [15].

Atorvastatin and propranolol

Propranolol and atorvastatin may be potential drugs for the treatment of pulmonary fibrosis. Recent studies reported that atorvastatin prevented PQ-induced cytotoxicity and pulmonary fibrosis by decreasing the HIF-1 α and β -catenin levels, which leads to regulating the epithelial-mesenchymal transition (EMT) in which PQ-induced macrophages act as a trigger for the chronic inflammatory response, and the anti-inflammatory and antioxidant effects aim for macrophages of atorvastatin which can alleviate the symptoms of PQ poisoning in patients. Propranolol is a competitive antagonistic agent of PQ, which can compete for receptors with PQ binding in the lung, reducing the absorption of PQ in the body and releasing it, where it can finally be cleared by the kidneys [16].

Pirfenidone

Our recent research proved that pirfenidone improves PQ-induced lung injury and fibrosis in mice by inhibiting inflammation and oxidative

stress and down-regulating fibrogenic cytokines produced by ROS. Another study showed that pirfenidone reduced lung fibrosis, edema, and inflammatory cell infiltration by reducing the expressions of bFGF, TGF- β 1, CTGF, and TIMP-1, concentrations in a dose-dependent manner [17]. In a rat model, the anti-pulmonary fibrosis effect of pirfenidone can be expanded by regulating hydroxyproline that provides more evidence for clinical medication.

Chinese medicine

Clinical practice proved that Chinese medicine has been used to treat PQ poisoning. It has unique therapeutic effects, and a xuebijing injection can effectively reduce injury to lung tissue by inhibiting the expressions of TNF- α , NF- κ B, and Caspase-3 and alleviating the apoptosis caused by PQ poisoning. The rational use of traditional Chinese medicine in patients with acute PQ poisoning may contribute to the recovery of patients, but its efficacy is still in the research stage [18].

Prevention and treatment of complications

Acute respiratory distress syndrome (ARDS) caused by pulmonary fibrosis after acute lung injury is the main cause of death in patients with PQ poisoning, so active anti-pulmonary fibrosis can effectively improve the prognosis of patients. Paraquat burns the skin of patients, so the barrier function of the skin is destroyed, and it's easy to cause infection through the burned skin, so successful treatment should involve the use of antibiotics. Some side effects of glucocorticoid usage in large doses are known, such as hyperglycemia, alopecia, and necrosis of the femoral head. The doses and duration of corticosteroids used in the treatment of PQ poisoning patients are controversial. An early study recommended dexamethasone administration of 24 mg per day for the first two weeks, 1.5 mg per day for the second two weeks, and a meta-analysis confirmed that 1 g of methylprednisolone daily for 3 days was safe and tolerable. In general, the control of glucocorticoid usage must be according to the patient's actual condition [19].

Oxygen therapy

Oxygen therapy is still controversial because the mechanism of PQ poisoning is currently

believed to be caused by the damage of alveolar cells resulting from a large number of oxygen free radicals. Oxygen therapy may aggravate the toxicity of PQ, so it is thought that patients should prohibit oxygen therapy. Others hold the view that oxygen therapy should be judged according to the actual situation of the patient. Patients with early and low dose poisoning accompanied by non-persistent hypoxemia should resolutely avoid oxygen inhalation. When patients are subject to lethal PQ poisoning, oxygen supply and demand balance should be considered [20]. When hypoxemia accompanied by persistent or progressive aggravation, patients should be given palliative treatment. High concentration oxygen therapy should be avoided in low concentration oxygen therapy. Previous researchers have suggested that $\text{PaO}_2 < 40$ mmHg be used as the standard of oxygen therapy, but others recommend that oxygen therapy be used when the SO_2 is below 80% or when there is obvious dyspnea. The main purpose of treating patients with late poisoning and lethal doses is to alleviate the clinical symptoms and patients' pain and prolong survival time. Oxygen therapy can not improve the prognosis of PQ lung patients, so the focus of PQ poisoning treatment should still be on how to prevent and control the occurrence and development of PQ pulmonary fibrosis.

Lung transplantation

Lung transplantation can fundamentally reverse the pulmonary fibrosis caused by PQ poisoning. However, there are few reports on the treatment of PQ poisoning by lung transplantation. Moreover the donor lacks sufficient funding, and the high cost is difficult to popularize successfully. The success rate of early lung transplantation is very low, and PQ retained in the body will continue to cause lung damage and progress to fibrosis, so it is recommended to conduct lung transplantation after PQ is exhausted from the body [21].

Conclusions

PQ is commonly but not easily absorbed into the body through intact skin, but the corrosive effects of PQ may cause burns to the skin, leading to the absorption of PQ through tiny wounds. Removing paraquat from the skin plays central roles in preventing the absorption of the poison. Once PQ poisoning, especially that leading

to lung injury, occurs, treatment will be difficult. The basic treatment methods include general treatment and symptomatic support. These include HP combined with CRRT, pulse immunosuppressive therapy with glucocorticoids, cyclophosphamide, pirfenidone, care for burns and the like to control the development of illness. Although PQ poisoning has been extensively studied in many countries, there are still some gaps in the field. Therefore, it is essential to continuously discuss and further deepen the understanding of PQ's toxicological mechanism on the basis of integrating its endogenous antioxidant pathogenesis, so as to find new effective therapeutic drugs and thus save more patients' lives.

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Disclosure of conflict of interest

None.

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