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Experimental study of sucralfate intervention for paraquat poisoning in rats

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ABSTRACT

Objective: This study explored the effects of sucralfate intervention as a novel treatment for paraquat (PQ) poisoning in Sprague-Dawley (SD) rats.

Methods: After PQ poisoning, the SD rats were randomly divided into the PQ control group (treated with normal saline), the sodium bicarbonate (SB) treatment group, and the sucralfate (LTL) treatment group. Then, the rats were administered normal saline, sodium bicarbonate solution, or sucralfate suspension as an intervention by gastric lavage. At 1, 3, 6, and 10 days after poisoning, the left lungs of some rats were removed to determine the lung wet/dry (W/D) weight ratio. Additionally, the serum cytokine levels were measured, and the lung and kidney tissues were pathologically examined.

Results: After treatment, the signs and symptoms of the rats were improved, the mortality rate was reduced, the W/D weight ratio of the lung was lower, the cytokine levels [transforming growth factor (TGF)-β1, interleukin (IL)-10, and tumor necrosis factor (TNF)-α] were decreased, and the pathological injuries of the lungs and kidneys were improved. Moreover, sucralfate was significantly more effective than the control (normal saline) group and the SB treatment group.

Conclusion: The results showed that early gastrointestinal lavage with sucralfate effectively reduced the inflammatory response and lung and kidney injuries and improved the survival of the SD rats.

Paraquat or N,Ń-dimethyl-4,4′-bipyridinium dichloride (systematic name) is the organic compound with the chemical formula $[(C_6H_7N)_2]Cl_2$. This salt is one of the most widely used herbicides. It is quick-acting and non-selective, killing green plant tissue on contact. According to the Centers for Disease Control, ingesting paraquat causes symptoms such as liver, lung, heart, and kidney failure within several days to several weeks that can lead to death up to 30 days after ingestion. Those who suffer large exposures are unlikely to survive. Chronic exposure can lead to lung damage, kidney failure, heart failure, and oesophageal strictures (Centers for Disease Control, 2006). Accidental deaths and suicides from paraquat ingestion are relatively common (Stevens, 2008). Long-term exposures to paraquat would most likely cause lung and eye damage, but reproductive/fertility damage was not found by the United States Environmental Protection Agency (EPA) in their review.

A large majority (93%) of fatalities from paraquat poisoning are suicides, which occur mostly in developing countries (Dinham, 1996). For instance, in Samoa from 1979 to 2001, 70% of suicides were by paraquat poisoning. Trinidad and Tobago is particularly well known for its incidence of suicides involving the use of Gramoxone (commercial name of paraquat). In southern Trinidad, particularly in Penal, Debe from 1996 to 1997, 76% of suicides were by paraquat, 96% of which involved the over-consumption of alcohol such as rum. Paraquat is widely used as a suicide agent in third-world countries because it is widely available at low cost. Further, the toxic dose is low (10 ml or 2 teaspoons is enough to kill).

Pure paraquat, when ingested, is highly toxic to mammals, including humans, potentially leading to acute respiratory distress syndrome (ARDS). Although there are no specific antidotes, fuller's earth or activated charcoal is an effective treatment if taken in time. There have been some successful cases of using cyclophosphamide (Endoxan) to treat paraquat poisoning (Newstead, 1996). Death may occur up to 30 days after ingestion. The alveolar epithelial cells of the lung selectively concentrates paraquat (Kliegman, 2017). Even a single swig, immediately spat out, can cause death from fibrous tissue developing in the lungs, leading to asphyxiation (Buzik et al., 1997).

Sucralfate is basic aluminum sucrose sulfate, Sucrose octasulfate aluminum complex, its chemical formula is C12H30Al8O51S8.8

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; HE, hematoxylin eosin; IL-10, interleukin-10; LTL, sucralfate suspension; OFR, oxygen free radicals; PQ, paraquat; SB, sodium bicarbonate; SIRS, systemic inflammatory response syndrome; TNF-α, tumor necrosis factor α; TGF-β1, transforming growth factor β1; W/D, lung wet/dry weight ratio

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(H3AlO3),and dry sucralfate, containing 18%–22% (Al), sulfur (S) from 8.5% to 12.5%, is white powder, odorless and tasteless, with moisture. In water, ethanol or almost insoluble in chloroform; dilute hydrochloric acid or dilute sulfuric acid soluble in dilute nitric acid, slightly soluble in the acidic environment, it can dissociate into the negatively charged sulfate eight sucrose and insoluble polymeric colloid, positively charged protein binding band with exudative inflammation or ulceration of the formation of a layer of thin film in the ulcer or inflammation, ulcer or inflammation of mucosa protection against the invasion of gastric acid, and neutralize stomach acid, 1 g of sucralfate could neutralize 2.5 mmol/L hydrochloride.

A sucralfate suspension is an oral preparation consisting of sucralfate, agar, glycerol, ethyl paraben ethanol and water. The sucralfate suspension is stable, does not form layers after long-term storage, and is commonly used in clinical practice as an anti-peptic ulcer agent with potent anti-acid and gastric mucosal protective effects (Bauer and Hanstein, 1986). The sucralfate suspension adheres to and increases the contact surface with the gastric mucosa and consequently its bioavailability. During clinical treatment of drug poisoning-induced gastric mucosal injury, a sucralfate suspension is used as an anti-acid agent to inhibit gastric acid secretion; it forms a gel-like substance on the gastric mucosa surface, thereby blocking direct erosion of the ulcer surface by gastric acid and pepsin (Cohen et al., 1989). Sucralfate induces mucosal cells to synthesize prostaglandin E (PGE) (Wallace et al., 1988), promotes gastrointestinal secretion of mucus and bicarbonate, strengthens the gastrointestinal barrier, inhibits Helicobacter pylori (HP) proliferation and mucosal destruction, maintains mucosal integrity, and facilitates lesion repair (Louw et al., 2015).

The purpose of this study was to investigate the effect of early sucralfate intervention after paraquat (PQ) poisoning. This study took advantage of sucralfate's ability to form a protective layer through its potent adherence to the gastric mucosa, thereby quickly blocking gastric absorption of the toxin, effectively neutralizing and isolating the poison in the early stage of poison absorption, and eliminating the gastrointestinal toxin. On the other hand, in the early stage of poison into the digestive tract, the neutralization reaction of alkaline sucralfate and acidic paraquat, to some degree, can consume and remove acidic toxins on the alimentary tract. We conducted this experiment in rats; we observed their survival and assessed the lung wet/dry (W/D) weight ratio, cytokine levels, and lung and kidney injuries. The data show that sucralfate intervention effectively reduces the toxic effects of PQ poisoning in Sprague-Dawley (SD) rats. The experimental data show that sucralfate inhibited paraquat poisoning rats cytokine of TGF beta 1, IL - 10, TNF - alpha levels, reduce inflammation, and improve the survival rate after poisoning. Such experiments have not been reported in the medical literature at home and abroad, and the sucralfate treatment method of blocking and neutralizing poison into the digestive tract can be applied to a variety of harmful poisoning, the effect and mechanism of treatment of toxic reaction with sucralfate is worthy of in-depth study.

1. Methods

1.1. Materials

A total of 72 healthy male SD rats aged from 10 to 12 weeks and weighing 200–250 g (experimental animal license: SYXK (Dian) 2011-0004, licensing agency: Yunnan Provincial Science and Technology Agency) were used in this study. The rats were subjected to adaptive feeding and were provided by the Experimental Animal Center, Kunming Medical University. The rats were divided into the PQ control group, the sodium bicarbonate (SB) treatment group, and the sucralfate (LTL) suspension treatment group, with 24 rats per group.

PQ was manufactured by Red Sun Biochemical Co., Ltd in Nanjing, China (pesticide registration No.: PD20131912, state standard certificate No.: GB 19307-2003, effective date: 2013-09-25, expiration date: 2018-09-25).

The sucralfate (LTL) suspension containing sucralfate 100 g, agar 5.5 g, glycerol 20 g, ethyl paraben ethanol solution 10 ml (50 g/L), three kinds of Analytical reagents and Ultrapure water reagent, 1L, stir them for 30 min with high speed. It was manufactured by Kunming Jida Pharmaceutical Co., Ltd. (CFDA Approval No.: H20080322, implementation standard: YBH05462008).

Sodium bicarbonate chemical formula: NaHCO3, melting point: 270°, 18°, the solubility of 7.8 g/100 ml, Analytical reagent kit, it was provided by Shandong Haitian Bio-Chemical Co., Ltd. (production license No.: SC20113102300069, state standard certificate No.: GB 1887).

1.2. Dose selection and justification

PQ was administered to rats via gastric lavage at a 25 mg/kg dose in this study. We referenced Zhi et al's PQ dose-finding study for PQ-induced typical lung injury in rats (Zhi et al., 2008). A higher dose of PQ solution may be given to rats to initiate PC-induced acute lung injury, such as 20 mg/kg or 25 mg/kg. We used 25 mg/kg in this study because we were investigating the effect of early intervention for PQ poisoning.

The sodium bicarbonate dose was selected according to the usage standard of Food Additive Sodium Bicarbonate (Standard B O I, 2016). Due to acute poisoning and for enhancing its effect the recommended concentration was 5%, and 10% (2 times the human dose) was used in this study to assess early gastric lavage intervention (Ren et al., 2015).

The sucralfate dose was selected with reference to the Chinese Pharmacopoeia (2010, Vol II), in which the maximum daily dose for human use was 8 g/70 kg. No carcinogenicity or reproduction injury in rats was observed in the 24-month oral toxicity study at a dose of 1 g/kg (7.5 times the human dose) (Zhang et al., 2005). In this early intervention study, 1 g/kg was used as the gastric lavage dose in the rats.

1.3. Group assignment and treatment

To prepare the rat poisoning model, 2.5 ml of PQ solution (200 g/L; 500 mg PQ) was diluted in sterile saline to 100 ml to obtain a 5 mg/ml uniform PQ mixture. The mixture was prepared immediately before each use. The gastric lavage volume was calculated at 0.5 ml of solution per 100 g of rat weight after each rat was weighed; each rat received a single oral gavage dose of 25 mg/kg of PQ for PQ poisoning.

After being poisoned, the SD rats were randomly divided into three groups (n = 24).

(1) The PQ control group was treated by gastric lavage with sterile normal saline (5 ml/kg/d) within 2 h of poisoning.
(2) The SB treatment group was treated by gastric lavage with sodium bicarbonate (100 mg/ml; 5 ml/kg/d) within 2 h of poisoning.
(3) The sucralfate (LTL) suspension treatment group was treated by gastric lavage with sucralfate suspension (200 mg/ml; 5 ml/kg/d) within 2 h of poisoning.

The administration method in each group is shown in Table 1.

Table 1
Dosage setting of each group.

Group	dose(g/L)	Intragastric administration medicine	Multiple clinical dose
PQ control group	9	Normal saline	1
SB treatment group	100	SB	2
LTL treatment group	200	LTL	7.5