Original Article

Therapeutic effects of smecta or smectite powder on rats with paraquat toxication

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BACKGROUND: The plasma concentration of paraquat is closely related to the prognosis of patients with paraquat toxication, and the most common cause of death from paraquat poisoning is multiple organ failure (MOF). This study aimed to evaluate therapeutic effect of smecta on the plasma concentrations of paraquat and multi-organ injury induced by paraquat intoxication in rats.

METHODS: A total of 76 healthy adult SD rats were randomly divided into group A (control group, *n*=6), group B (poisoned group, *n*=30) and group C (smecta-treated group, *n*=30). Rats in groups B and C were treated intragastrically with PQ at 50 mg/kg, and rats in group A was treated intragastrically with saline (1 mL). Rats in group C were given intragastrically smecta at 400 mg/kg 10 minutes after administration of PQ, while rats in other two groups were treated intragastrically with 1 mL saline at the same time. Live rats in groups B and C were sacrificed at 2, 6, 24, 48, 72 hours after administration of PQ for the determination of paraquat plasma concentrations and for HE staining of the lung, stomach and jejunum. The rats were executed at the end of trial by the same way in group A.

RESULTS: The plasma concentration of paraquat (ng/mL) ranged from 440.314±49.776 to 4320.6150±413.947. Distinctive pathological changes were seen in the lung, stomach and jejunum in group B. Lung injuries deteriorated gradually, edema, leukocyte infiltration, pneumorrhagia, incrassated septa and lung consolidation were observed. Abruption of mucosa, hyperemic gastric mucosa and leukocyte infiltration were obvious in the stomach. The hemorrhage of jejunum mucosa, the abruption of villus, the gland damage with the addition of inflammatory cell infiltration were found. Compared to group B, the plasma concentration of paraquat reduced (P<0.01) and the pathological changes mentioned above were obviously alleviated in group C (P<0.05, P<0.01).

CONCLUSION: Smecta reduced the plasma concentration of paraquat and alleviated pathologic injury of rats with PQ poisoning.

KEY WORDS: Smecta; Paraquat; Pathological change; Therapeutic injury

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INTRODUCTION

Paraquat (PQ) is a nonselective contact herbicide, and has been widely used in the world, especially in developing countries since the 1960s. However, PQ poisoning remains a major cause of death among patients with acute poisoning in Asia[1] and its mortality is as high as 80%.[2] PQ is absorbed mainly through the intestinal tract, its plasma level peaked within 4 hours after oral administration. PQ extensively accumulates in the whole body, but is mainly stored in the lung and stomach where it is retained even the blood concentration decreases, finally is excreted by the kidney.[3]

A lot of animal experiments and clinical trials have proved that the toxicity of PQ usually lead to multiorgan injury.[4–6] Because of the polyamine uptake system, the pulmonary concentration of PQ is 6–10 times higher than that in the plasma, so the lung is the target organ of PQ poisoning. The acute phase, in which lung injury

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is characterized by pulmonary alveolitis, is followed by the proliferative phase defined by the occurrence of progressive fibrosis.[7] Kim et al[8] reported that the distinct change of pulmonary fibrosis in the high resolution computerized tomography (HRCT) was characterized by ground glass opacities (GGOs), and this suggested that the area of GGOs be a useful predictor of survival in acute PQ intoxication, especially in patients with a low plasma PQ level. With regard to poisoning symptoms, the digestive tract appeared at the soonest, such as stomachache, vomitus, and alimentary tract hemorrhage. Gastrointestinal dysfunction can speed up the absorption of poison or delay the excretion of poison, so it is necessary for physicians to take effective measures to reduce gastrointestinal damage resulting from PQ. Nevertheless, there are few studies on the protection of gastrointestinal structure.

So far, the treatment of PQ intoxication is still in the exploratory stage. A number of therapeutic methods for the treatment of PQ intoxication have shown poor efficacy,[9, 10] and only a few treatments revealed effectiveness.[11–13] Studies[14–16] focus mostly on gastric lavage, blood purification, glucocorticoid and cyclophosphamide, but there are different opinions on these methods. It was reported that to prevent the absorption of PQ by the gastrointestinal tract, patients were administered with activated charcoal in 250 mL magnesium citrate via a nasogastric tube,[14] suggesting that superactive adsorbent is beneficial to reduce blood concentration.

Smecta or smectite powder, a kind of natural aluminosilicate consisting of a double aluminium and magnesium silicate, is mainly made up of the octagonal montmorillonite particles which show the layer structure and heterogeneity charge distribution. One of the most remarkable pharmacological characteristics of smecta is its strong adsorption activity.[17] It not only adsorbs eight times its own weight of water, but also adsorbs toxins, bacteria, and rotavirus, keeping virulence factors from adhering to intestinal membranes.[18–20] In addition, with the ability to cover the mucosa and to combine with mucous glycoprotein, smecta strengthens the mucosal barrier.[21] Furthermore, smecta will not pass into the blood circulation after combination with morbid substances and barely decreases intestinal dynamics,[22] causing few side effects. As adsorbent, smecta has been widely used to treat various diseases,[23–25] including diarrhea, gastrointestinal bleeding, and peptic ulcer. A recent study[22] revealed that smecta at 6 g tid was well tolerated and reduced the time to recovery from acute watery diarrhoea episode. Even though the efficacy of Smecta in the treatment of digestive system diseases has been confirmed, the study on the use of smecta in PQ poisoning is rare.

Thus, this study aimed to testify whether smecta can reduce the plasma concentration determined by high-performance liquid chromatography (HPLC)[26,27] and improve pathological damage of the rats with PQ intoxication.

METHODS

Chemicals and instruments

Paraquat dichloride (HPLC) 99.9 area%, 0.1 g, was purchased from Sigma-Aldrich, USA. Acetonitrile (chromatographic pure), methyl alcohol (chromatographic pure), triethylamine (analytical pure), and thophosphoric acid (analytical pure) were purchased from Tianjin Guangfu Reagent Co., Ltd, China. Sodium 1-heptanesulfonate (analytical pure purity ≥98%, 20 g) was produced by BBI, Canada. Smecta was produced by Beauour Ipsen (Tianjin) Pharmaceutical Co., Ltd. Eclipse plus Chromatographic Column (4.6×250 mm, 5 μm) was purchased from Agilent, USA. LC-20A High Performance Liquid Chromatograph, LC-20AT Pump, CBM-20A Controller, SPD-M20A Detector, SIL-20A Autosampler, CTO-10AS VP Column oven were all purchased from Shimadzu, Japan.

Animals

This study was performed using adult male SD rats (200±20 g) obtained from the Xinjiang Disease Prevention and Control Center. The rats were kept under standard laboratory conditions (12/12 h light/darkness, 22±2 ºC room temperature, 50%–60% humidity) for at least 1 week before the start of the experiment. The rats were allowed free access to tap water and rat chow ad libitum during the experiment.

Experimental protocol

A total of 66 healthy adult SD rats were randomly divided into group A (control group, n=6), group B (poisoned group, n=30), and group C (smecta treated group, n=30). Rats in groups B and C were treated intragastrically with a single dose of PQ (PQ, 50 mg/kg), and those in group A were treated intragastrically with 1 mL of saline. Rats in group C were given intragastrically smecta at 400 mg/kg 10 minutes after the administration of PQ, whereas rats in the other two groups were treated intragastrically with 1 mL of saline at the same time. Rats in groups B and C were sacrificed 2, 6, 24, 48, 72 hours after the administration of PQ, respectively. The rats were sacrificed, and their blood samples were taken. The serum

of the rats was separated immediately and stored at –72 ºC for the determination of PQ plasma concentrations. The tissues of the lung, stomach and jejunum were taken for HE staining and pathological examination.[28–30] The rats in group A were executed similarly.

Determination of plasma PQ concentration

PQ concentration was determined with the reported methods[26,27] with minor modifications. Plasma samples were sent to Shihezi University College of Pharmacy for quantitative analysis using HPLC. Briefly, 35% perchloric acid (100 μL) was added to a test tube containing plasma supernatant (0.5 mL), and the mixed liquor of perchloric acid and plasma supernatant was centrifuged and the supernatant of the mixed liquor was analyzed with HPLC. Six blank control plasma samples (concentrations of samples was 20, 50, 100, 500, 1 000, 5 000 ng/mL, respectively) were prepared, then the peak area of these samples was detected. The regression equation of PQ plasma samples, which was used to calculate concentration of PQ, can be obtained according to peak area (Y) and concentration (X).

Statistical analysis

Statistical analysis was made using SPSS 13.0. All data were expressed as means±standard deviation. The survival rates of rats were compared using Fisher's exact test for unordered categorical variables, pathological scores were compared with independent samples t test, and PQ concentrations were compared using analysis of variance (ANOVA) followed by LSD multiple comparison test. A P value less than 0.05 was considered statistically significant.

RESULTS

Behavioral changes of rats

Two hours after PQ poisoning, symptoms including rapid shallow respiration, dyspnea, loss of appetite, piloerection, and hemorrhage in the nostril and angulus oris, were observed in rats of group B as compared with normal rats. After the thoracic cavity and abdominal cavity of rats in group B were open, pulmonary edema, pulmonary congestion, gastric distention, intestinal tympanites, and intestinal obstruction were seen. These

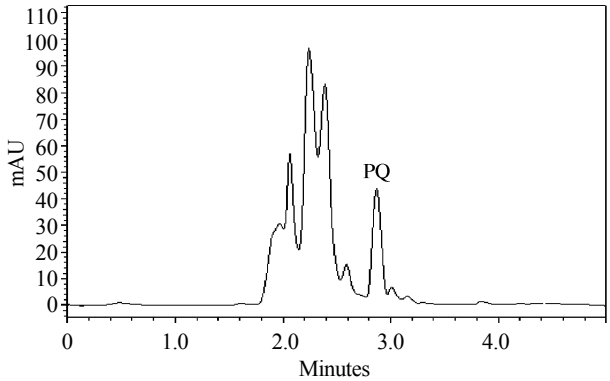

Figure 1. HPLC chromatogram of blank control plasma sample in the control group (PQ concentration, 1000 ng/mL).

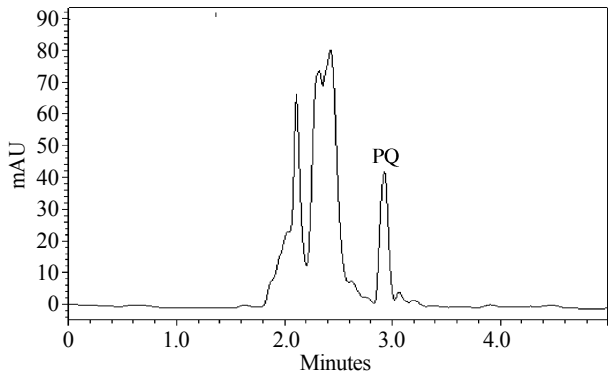

Figure 2. HPLC chromatogram of plasma sample in group B (2 hours after PQ administration).

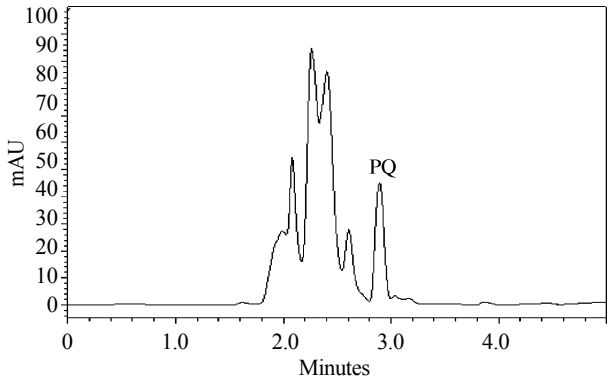

Figure 3. HPLC chromatogram of plasma sample in group C (2 hours after PQ administration).

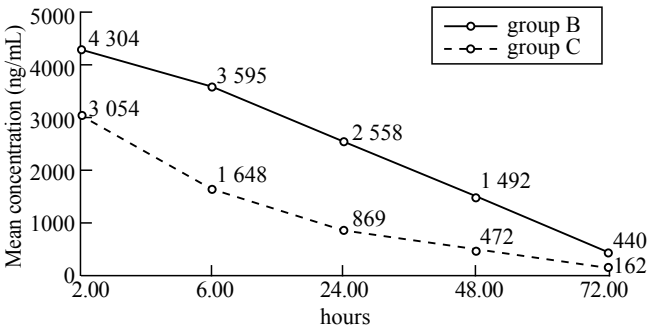

Figure 4. Comparison of PQ concentrations between groups B and C. P value at 2, 6, 24, 48, 72 hours after PQ administration was 0.000, 0.001, 0.017, 0.001, and 0.000, respectively.

symptoms were less marked in group C. Seventy-two hours after treatment, the survival rate of rats in the control group was 100%, whereas it was 90% in group B and 97% in group C, respectively. There were no changes in group A.

Linear correlation and concentration of paraquat

The regression equation of plasma PQ: Y=98.8210 X +5707.5407. The PQ concentration varied from 20 ng/mL to 5000 ng/mL, and the minimum detection limit was 20 ng/mL. Partial HPLC chromatograms are shown in Figures 1–3.

In groups B and C, the plasma concentration of PQ lowered with the time, peaked at 2 hours after PQ administration, and kept at a higher level within 6 hours after intoxication. After that, the plasma concentration of PQ started to decrease, and reached the minimum level 72 hours after PQ administration (Figure 4). Compared to group B, the plasma concentration of PQ in group C reduced rapidly, but there was no significant difference between the two groups (P<0.05 or P<0.01).

Pathological injury

There were marked pathological changes in the lung, stomach and jejunum in group B. Lung injuries deteriorated with time. Congestion, edema, and slight leukocyte infiltration were the early pathologic changes of the lung. Twenty-four hours after PQ poisoning, pneumorrhagia, incrassated septa, and consolidation of the lung were observed (Figure 5).

Marked pathologic changes were observed in

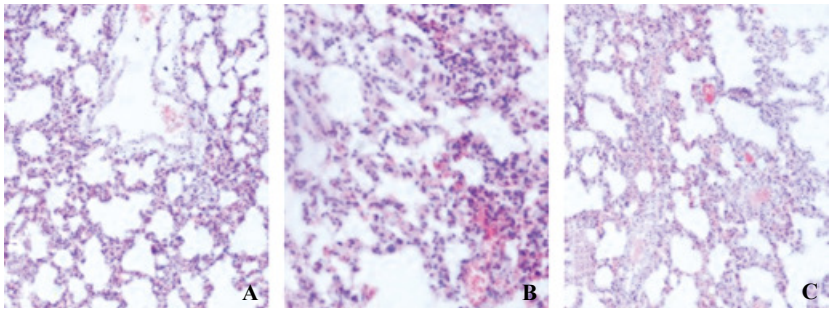

Figure 5. Comparison of lung injury among the three groups 72 hours after PQ poisoning (HE, original magnification×100).

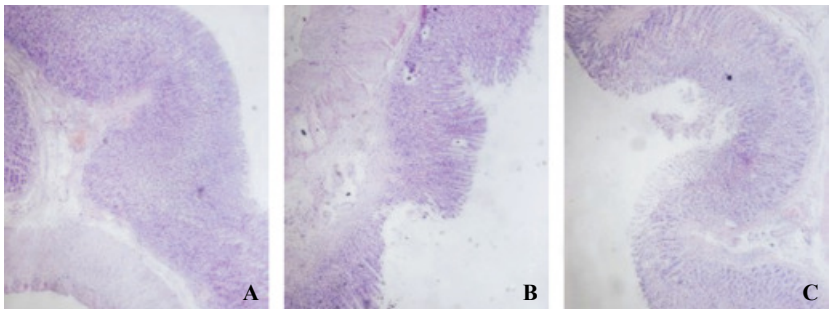

Figure 6. Comparison of stomach injury among the three groups 2 hours after PQ poisoning (HE, original magnification×100).

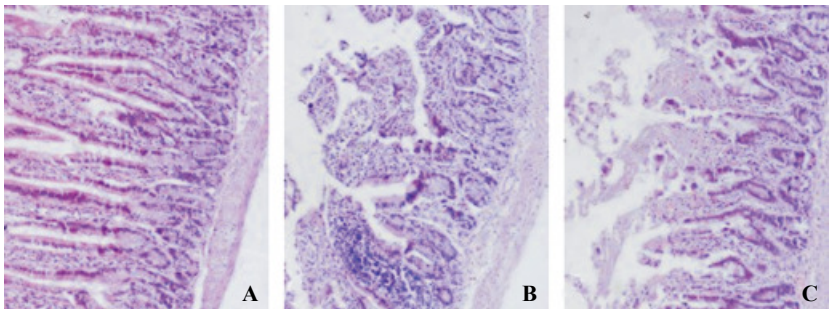

Figure 7. Comparison of jejunum injury among the three groups 2 hours after PQ poisoning (HE, original magnification×100).

Table 1. Pathological scores of rats (mean±SD)

Groups	Lung	Stomach	Jejunum
A	0.500±0.632	0.333±0.516	0.555±0.403
B			
2 h	2.000±0.447**	4.000±1.788**	2.444±0.455**
6 h	2.916±0.801**	7.000±0.894**	1.944±0.389**
24 h	4.500±0.707**	6.000±0.894**	2.445±0.455**
48 h	5.250±0.861**	4.000±0.894**	2.444±0.455**
72 h	7.833±1.032**	3.833±0.752**	1.778±0.621**
C			
2 h	1.500±0.447**	2.000±0.894*#	1.777±0.621**
6 h	1.917±0.585**#	3.000±0.895**##	1.333±0.298**##
24 h	3.500±0447**#	4.333±1.862**	1.389±0.389**##
48 h	4.083±0.917**#	3.6670±1.633**#	1.333±0.471*##
72 h	5.583±0.585**##	2.833±1.169**	1.000±0.298##

Compared with group A, $^{*}P<0.05$, $^{**}P<0.01$; compared with group B, $^{\#}P<0.05$, $^{\#\#}P<0.01$.

stomach tissue such as abruption of mucosa, hyperemic gastric mucosa and gastrorrhagia within 24 hours after PQ poisoning. Leukocyte infiltration and impairment of gastric glands were also found. Thus the repair of stomach tissue was followed (Figure 6).

The jejunum injuries of rats were characterized by hemorrhage of mucosa, abruption of villus, gland damage, and inflammatory cell infiltration within 24 hours after PQ poisoning. Then, the hemorrhage of mucosa was alleviated and gland damage aggravated (Figure 7). These pathological changes were markedly alleviated in group C compared with group B ($P<0.05$, $P<0.01$) (Figures 5–7, Table 1). In group B, no marked pathological changes were seen in the lung, stomach and jejunum (Figures 5–7).

DISCUSSION

The first case of paraquat mortality was published in 1966,[31] followed by a large number reports. PQ poisoning as a medical problem has become a social burden and attracted much attention. Ingestion of over 20 mL of PQ is likely to cause death due to multi-organ failure, and 10–20 mL may result in irreversible lung fibrosis leading to death within several weeks.[32] Suntres[33] made a large sample analysis showing that the oral lethal dose of PQ for adults was 30–40 mg/kg. There was a close relationship between PQ plasma concentration and mortality.[34] Current treatment of PQ poisoning focuses on reducing the absorption of PQ from the gastrointestinal tract and increasing its elimination.[32] Even though activated charcoal was used to treat PQ toxication,[14] evidence was not enough to confirm that charcoal can improve the prognosis of patients. Since the therapeutic effect of smecta on rats with PQ toxication has rarely been studied, we tried to explore whether smecta can reduce the PQ plasma concentration and improve the pathological changes of rats after PQ poisoning.

The pharmacokinetics of PQ is different in people and animals. The peak plasma concentration of patients occurs within 2–4 hours after ingestion of PQ and then decreases.[35] The initial decrease, which is called the distribution phase, is faster and has a half life of about 5 hours, while the volume of distribution is about 1.2–1.6 L/kg. The half life in the subsequent elimination phase is about 84 hours. On the other hand, the peak plasma concentration occurs in dogs about 60–90 minutes after ingestion of PQ and disruption of the gastric mucosal barrier.[36,37] PQ distribution can be described as a three-compartment model: 1) plasma compartment; 2) compartment with rapid uptake and removal such as the kidney; 3) slow uptake compartment such as the lung, reaching a maximum concentration 4–5 hours after ingestion of PQ regardless of the plasma PQ level. This model explains the unique changes in plasma PQ level. However, the dynamics of PQ in rats has been rarely investigated. Studies[38,39] revealed that plasma paraquat concentration of rats maintained high within 24 hours after PQ poisoning and vanished within 72 hours, which can be detected in the lungs, stomach and intestine 10 days after administration of PQ.

In our study, the dead rats were eliminated. The plasma concentrations of PQ in rats with intoxication decreased with time, and the peak concentration occurred at 2 hours after PQ administration and it was kept at a higher level within 6 hours after intoxication. After that, the plasma concentration of PQ started to decrease and reached the minimum level 72 hours after administration of PQ (Figure 4). At the same time, the plasma concentration of PQ was lower in the smecta-treated group than in the poisoned group ($P<0.05$ or $P<0.01$). This finding indicates that smecta is useful to reduce the plasma concentration of PQ in rats. The conspicuous effect of smecta on the plasma concentration of PQ is ascribed to its ability to adsorb toxicant, and combination of PQ and smeta completely excreted through the intestinal tract. Tiwary et al[40] observed the adsorption capacity of different adsorbents including Kaolin, smecta (montmorillonite powder) and activated charcoal, and found that smecta is effective to reduce the PQ concentration in patient's urine.

The acute toxic effects of PQ on human and rats included a series of symptoms, multiple organ dysfunction

associated with pathological injury provoked by superoxide anion together with inflammatory activation. Because of a polyamine uptake system, the lung is a primary target organ of PQ toxicity. In the current study, the lung injury of rats in the poisoned group was concordant with the results of a previous study.[41] Pulmonary alveolitis, pneumorrhagia, and lung consolidation were serious and supported by such symptoms as rapid shallow respiration, cyanosis, hemorrhage in the nostril. The damage induced by PQ to the stomach and jejunum was also found. This damage was characterized by hemorrhage of mucosa, abruption of mucosa, gland damage and inflammatory cell infiltration. It is reasonable to determine that apparent symptoms consisting of poor appetite, loss of weight and gastrointestinal dysfunction are associated with above changes. The toxic symptoms were ameliorated and pathologic damages were improved in the smecta-treated group compared with the poisoned group, indicating the protective effects of smecta against PQ induced toxicity. Even though there was no significant mortality, all rats were alive after smecta treatment. The protective mechanism of smecta against PQ toxicity may be bound up with the ability to reduce the plasma concentration of PQ and to repair gastrointestinal tract injury.[20]

The results of the present study proved that smecta can protect rats with toxication from PQ by antagonizing pathologic damage and reducing the plasma concentration. This study also suggests that the administration of smecta after PQ toxication is an effective treatment for PQ poisoning.

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Ethical approval: The present study was approved the Animal Care and Use Committee of Affiliated Hospital of Shihezi University, Shihezi, China.

Conflicts of interest: The authors have no competing interests relevant to the present study.

Contributors: Jiang YS proposed and wrote the paper. All authors contributed to editing the final manuscript for content and style.

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