Original Article

Urine Sodium Dithionite Test for Determining Prognosis and Outcome of Paraquat Poisoning

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Objective: To determine the association between urine sodium dithionite test result, testing time from paraquat (PQ) exposure, and mortality or systemic effect in patients with PQ poisoning.

Materials and Methods: A retrospective study at the poison center identified cases with PQ exposure that receive urine sodium dithionite test results between 2015 and 2016. Urine sodium dithionite test results were reported in four groups, 1) no change in urine color, 2) green or light blue color, 3) dark blue color, and 4) purple or black color.

Results: One hundred ten PQ exposures with urine sodium dithionite test results are included in the present analysis. Multivariate analysis showed that age, initial urine sodium dithionite test color, and testing time were independently associated with mortality. There were 26 deaths (23.6%). The mortality rate was different between groups classified by urine sodium dithionite test results and testing time from PQ exposure ($p<0.01$). In groups with the dithionite test performed within 12 hours of exposure, the mortality rates were 0 in the green or light blue group, 33.3% in the dark blue group, and 63.2% in the purple or black group. In groups with the dithionite test performed more than 12 hours after exposure, the mortality rates were 27.3% in the green or light blue group, 60.0% in the dark blue group, and 100% in the purple or black group. There were forty-eight patients with no change in urine color, all survived. In patients who survived, there were different systemic effect rates between groups classified by urine sodium dithionite test results and testing time.

Conclusion: The initial urine sodium dithionite test result and testing time may be used as a tool to guide therapy and predict mortality and systemic involvement in patients with PQ poisoning.

Keywords: Urine sodium dithionite test, Prognostic factor, Mortality rate, Systemic effect

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Paraquat (PQ) is one of the most widely used herbicides because of its efficacy and environmental safety[1,2]. In most developing countries, PQ is the pesticide that is most often used to self-harm poisoning, and it has a high fatality rate worldwide[3]. Epidemiological data from the Ramathibodi Poison Center between 2010 and 2014 indicates that PQ was the major cause of pesticide-related fatalities in Thailand, from either accidental or intentional exposure[4].

Many studies attempted to provide predictive factors to determine survival and clinical outcomes of PQ exposure patients[5-10]. Many studies reported that the plasma PQ concentration is a reliable prognosis tool[1,5,11,12]. Unfortunately, plasma PQ concentration is not widely available in many developing countries including Thailand. The urine sodium dithionite test is a bedside semi-quantitative test that detects PQ. Additionally, it is easy to perform and interpret within minutes. Ingale et al reported that the urine sodium dithionite test is a useful tool to confirm PQ exposure in a patient who has an uncertain history of PQ poisoning[13]. Some studies have shown that urine dithionite is related to clinical outcome[12,14,15]. A study by Koo et al reported that 45 of 102 patients (44%) with positive urine dithionite but equivocal or negative plasma dithionite test died, while all 40 patients with a negative urine sodium dithionite test

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survived[12]. Liu et al also reported the association between urine sodium dithionite test results and the clinical outcome of PQ poisoning[15]. However, there was no report of the time from PQ exposure to administering the urine sodium dithionite test in either study. Seok et al reported that a testing time to the first negative result of urine dithionite can predict the systemic effect from PQ ingestion[14].

The current practice in Thailand is to perform a urine sodium dithionite test in all patients exposed to this herbicide either with a doubtful or a confirmed history of PQ exposure at initial presentation. As PQ is distributed quickly from the plasma to other organs, it is excreted rapidly in urine, with 80% to 90% excreted within the first six hours after exposure and almost 100% of PQ excreted within 24 hours[16]. If the urine sodium dithionite test result is positive, the treatment regimen with intravenous cyclophosphamide, dexamethasone, vitamin C, and oral vitamin E is recommended for at least seven days. Monitoring oxygen saturation, renal and liver function, and serial chest X-rays are also recommended. If the initial urine sodium dithionite test result is negative, a repeat urine sodium dithionite test is recommended again in the next six hours after the first test. For a patient who had a history of PQ exposure, if the first urine sodium dithionite test was performed more than 12 hours after exposure and the result was negative, or if there was no urine sodium dithionite test available, the treatment regimen is also recommended.

The primary objective of the present study was to determine the association between urine sodium dithionite test results, time from PQ exposure to the urine sodium dithionite test, and mortality. The secondary objective was to determine the association between urine sodium dithionite test results, time from PQ exposure to the urine sodium dithionite test, and systemic effects from PQ exposure in survivors.

Materials and Methods

Study design

The present study was a retrospective study of PQ exposure in humans who had urine sodium dithionite test results reported to the Ramathibodi Poison Center between January 2015 and December 2016. Cases without urine sodium dithionite test results or without a record of the time from PQ exposure to the urine sodium dithionite test were excluded. The study was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The Ramathibodi Poison Center serves the entire Thai population of 69 million people and receives approximately 20,000 calls per year. Calls are received by specialists in poison information (SPIs), who are nurses or pharmacists with additional training, which includes 30 hours of didactics and 20 sessions of supervised practical instruction. Patients were followed until recovery or definite outcome was reported. For complicated cases, consultations occurred with medical toxicologists. All records were reviewed and verified during daily staff meetings. After a complete follow-up and verification, cases were closed and entered into the electronic database.

Data collection

Case records were electronically abstracted by a senior SPI, who was trained in poison center database management. Case records were identified using the active ingredient name, coded as "paraquat". All records were reviewed and verified by discussion between medical toxicologists and SPIs.

Demographic characteristics such as age, gender, route, and reason for exposure, initial symptoms, initial laboratory test results such as white blood cell count, creatinine, blood urea nitrogen, aspartate aminotransferase, and alanine aminotransferase, urine sodium dithionite test results, time from PQ exposure to the dithionite test, treatments, and outcomes were collected. The primary outcome was mortality at hospital discharge, or survival status at two months, which was confirmed from the patient's identity card number, after discharge if the patients were discharged before they fully recovered. Outcomes of exposures in the present study were deaths and systemic effects such as renal, liver, and pulmonary toxicity.

Urine sodium dithionite test

Urine sodium dithionite test kits in the present study were supplied by Syngenta® (Basel, Switzerland). The kit's lower limit of PQ detection in urine was 0.2 mg/L[17]. Urine from individual patients was separated into a 10-mL test sample and a 10-mL control sample. For the test sample, 2 g of sodium bicarbonate was added to the urine followed by 1 g of sodium dithionite. After mixing well, the color of the test sample was compared with the control using the naked eye. Two SPIs and one medical toxicologist independently interpreted the color results. Urine sodium dithionite test results were graded into the following four groups, 1) no change in urine color, 2) green or light blue color, 3) dark blue color, and 4) purple or black color (Figure 1). In cases with discordant interpretation between the three

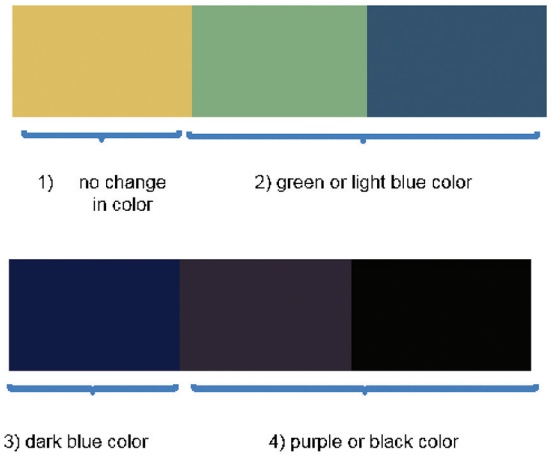

Figure 1. The color of urine sodium dithionite test in PQ poisoning patients.

observers, the urine color was determined following a discussion that included three medical toxicologists and five SPIs.

Time from PQ exposure to the urine sodium dithionite test was collected as continuous data and these data were later divided into two groups, test performed within 12 hours and test performed after more than 12 hours.

Definitions

Systemic effects were defined as the presence of at least one toxicity, either renal, liver, or pulmonary toxicity. The definition of renal toxicity was based on the RIFLE classification system for acute kidney injury and the change in the level of serum creatinine, as reported by the Acute Dialysis Quality Initiative group[18]. Liver toxicity was defined as an increase in aspartate aminotransferase or alanine aminotransferase levels that was greater than twice the upper limit of normal. Pulmonary toxicity was defined as hypoxia or new pulmonary infiltration[14].

Statistical analysis

Categorical data were presented as the number and percentage. For continuous data, the normal distribution was determined using the Kolmogorov-Smirnov test. Continuous data were presented as the median and interquartile range (IQR) or the mean and standard deviation (SD) for non-normally and normally distributed data, respectively. Univariate analyses to determine the differences between the survival and mortality groups were performed using the Wilcoxon rank-sum test for continuous variables, and the chi-squared or Fisher's exact test for categorical variables. Mortality rates were also revealed by grading the urine sodium dithionite test results and time from exposure to the dithionite test. Multicollinearity was determined among suspected predictors of death or systemic effects. Among the variables with a variance of inflation factor (VIF) that was greater than 10, only one was selected for multivariate analysis.

Forward stepwise multiple logistic regression analysis was applied to determine predictors of death and systemic effects. Subgroup analysis among the surviving patients was explored to reveal the prevalence of systemic effects using the urine sodium dithionite test results and time from exposure to the dithionite test. A p-value of less than 0.05 was defined as statistically significant.

Statistical analyses were performed using Stata Statistical Software, version 15.1 (StataCorp LLC, College Station, TX, USA).

Results

During the study period, there were 1,832 cases of PQ exposure reported to the Ramathibodi Poison Center. Among the exposures, urine sodium dithionite tests were performed in 117 patients. Seven patients were excluded because there was no record of the urine sodium dithionite test result color in six cases and no record of the testing time in one case. Therefore, 110 patients (61 men, 49 women) were included in the analysis (Table 1). Eighty of the 110 patients (72.7%) that had urine color test photographs. The median age was 34 (IQR 20 to 47) years. One hundred one patients were exposed to PQ by ingestion. Seventy-eight exposures (70.9%) were suicidal or self-harm intent. The median time from exposure to attending a healthcare facility was one (IQR 0.5 to 3.8) hour. There were 26 (23.6%) deaths. In the univariate analysis, demographic factors associated with death were age and suicidal or self-harm intent.

Commonly presenting symptoms included nausea or vomiting (59.1%), oral mucosal burn (15.5%), and blue or green color staining of the skin or mucosa (14.6%, Table 2).

Twenty-five patients (22.7%), including two who died, presented without any symptoms. The symptom associated with death was nausea or vomiting. Being asymptomatic at presentation was associated with a higher survival rate. Initial laboratory tests, an increase in the white blood cell count, creatinine, alanine aminotransferase, and aspartate aminotransferase were significantly associated with death (Table 3).

Common treatments were gastric lavage (67.3%),

Table 1. Demographic data of paraquat exposure cases reported to Ramathibodi Poison Center from January 2015 to December 2016

Demographic data	Numbers of cases; n (%)			p-value
	Total (110 cases)	Survive (84 cases)	Death (26 cases)	
Sex: male	61 (55.5)	44 (52.4)	17 (65.4)	0.24+
Pregnant	5 (4.5)	4 (4.8)	1 (3.8)	0.57*
Age (year); median (IQR)	34 (20 to 47)	29 (15 to 44)	44 (39 to 48)	<0.01**
Reason of exposure				<0.01*
Suicidal	78 (70.9)	54 (67.5)	24 (92.3)	
Accidental	32 (29.1)	30 (37.5)	2 (7.7)	
Route of exposure				0.70*
Oral	101 (91.8)	75 (89.2)	26 (100)	
Dermal	5 (4.5)	5 (6.0)	0	
Oral and dermal	2 (1.8)	2 (2.4)	0	
Placental	2 (1.8)	2 (2.4)	0	
Time from exposure to healthcare facility; median (IQR)	1 (0.5 to 3.8)	1 (0.5 to 3.5)	1.8 (0.5 to 5.4)	0.44**

IQR=interquartile range

* p-value by Fisher's exact test, ** p-value by Wilcoxon rank-sum test, + p-value by chi-square test

Table 2. Initial symptoms of paraquat exposure cases reported to Ramathibodi Poison Center from January 2015 to December 2016

Initial symptoms	Numbers of cases; n (%)			p-value*
	Total (110 cases)	Survive (84 cases)	Death (26 cases)	
Nausea or vomiting	65 (59.1)	41 (48.8)	24 (92.3)	<0.01
Oral mucosa burns	17 (15.5)	15 (17.9)	2 (7.7)	0.21
Abdominal pain	12 (10.9)	8 (9.5)	4 (15.3)	0.40
Blue or green color staining on skin or mucosa	16 (14.5)	10 (11.9)	6 (23.1)	0.16+
Skin burn	1 (0.9)	1 (1.2)	0	1.00
Dyspnea	1 (0.9)	1 (1.2)	0	1.00
Asymptomatic	25 (22.7)	23 (27.4)	2 (7.7)	0.06

* p-value by Fisher's exact test, + p-value by chi-square test

Table 3. Initial investigation results of paraquat exposure cases reported to Ramathibodi Poison Center from January 2015 to December 2016

Initial investigations	Number of tests	Median (IQR)			p-value*
		Total	Survive	Death	
White blood cell (cell/mcL)	97	9,820 (6,960 to 13,600)	9,020 (6,600 to 13,000)	13,300 (10,400 to 20,000)	<0.01
Creatinine (mg/dL)	105	0.75 (0.60 to 1.01)	0.70 (0.52 to 0.90)	1.14 (0.87 to 2.19)	<0.01
Blood urea nitrogen (mg/dL)	103	11.0 (8.0 to 14.6)	10.8 (7.7 to 14.0)	11.0 (10.0 to 16.5)	0.17
Alanine aminotransferase (IU/L)	101	18.0 (14.0 to 36.0)	16.0 (12.0 to 26.5)	41.0 (32.0 to 53.0)	<0.01
Aspartate aminotransferase (IU/L)	100	28.0 (19.0 to 44.5)	25.0 (17.0 to 36.0)	43.0 (29.0 to 61.0)	<0.01

IQR=interquartile range

* p-value by Wilcoxon rank-sum test

activated charcoal (60.9%), dexamethasone (65.5%), cyclophosphamide (61.8%), vitamin C (62.7%), and vitamin E (60.9%) (Table 4).

In univariate analysis, administration of dexamethasone, cyclophosphamide, vitamin C, and vitamin E were associated with mortality. All

Table 4. Treatments of paraquat exposure cases reported to Ramathibodi Poison Center from January 2015 to December 2016

Treatments	Numbers of cases; n (%)			p-value*
	Total (110 cases)	Survive (84 cases)	Death (26 cases)	
Gastric lavage	74 (67.3)	53 (63.1)	21 (80.7)	0.15
Activated charcoal	67 (60.9)	49 (58.3)	18 (69.2)	0.32+
Cyclophosphamide	68 (61.8)	46 (54.8)	22 (84.6)	0.01
Dexamethasone	72 (65.5)	49 (58.3)	23 (88.5)	0.01
Vitamin C	69 (62.7)	46 (54.8)	23 (88.5)	<0.01
Vitamin E	67 (60.9)	45 (53.6)	22 (84.6)	<0.01
Antibiotic	8 (7.3)	7 (8.3)	1 (3.9)	0.68
Oxygen	7 (6.4)	0 (0.0)	7 (26.9)	<0.01
Intubation	6 (5.5)	0 (0.0)	6 (23.1)	<0.01
Non-invasive mechanical ventilation	1 (0.91)	0 (0.0)	1 (3.9)	0.24
Hemodialysis	3 (2.7)	2 (2.4)	1 (3.9)	0.56

* p-value by Fisher's exact test, + p-value by chi-square test

Table 5. Initial urine sodium dithionite test results of paraquat exposure cases reported to Ramathibodi Poison Center from January 2015 to December 2016

Initial urine sodium dithionite test results	Numbers of cases; n (%)			p-value
	Total (110 cases)	Survive (84 cases)	Death (26 cases)	
Initial urine sodium dithionite test results				<0.01*
No change in color	48 (43.6)	48 (57.1)	0 (0.0)	
Green or light blue color	22 (20.0)	19 (22.6)	3 (11.5)	
Dark blue color	19 (17.3)	10 (11.9)	9 (34.6)	
Purple or black color	21 (19.1)	7 (8.3)	14 (53.9)	
Time from exposure to initial urine sodium dithionite test (hours); median (IQR)	6.1 (4.0 to 15.0)	5.9 (4.0 to 15.5)	10.3 (3.5 to 15.0)	0.15**
Urine sodium dithionite test performed later than 12 hours	34 (30.9)	23 (27.4)	11 (42.3)	0.06+

IQR=interquartile range

* p-value by Wilcoxon rank-sum test, ** p-value by Fisher's exact test, + p-value by chi-square test

patients with endotracheal intubation and mechanical ventilation (six patients), oxygen supplement (seven patients), or non-invasive mechanical ventilation (one patient) died.

The median time from exposure to performing the urine sodium dithionite test was 6.1 (IQR 4.0 to 15.0) hours. Thirty-four patients (30.9%) had urine dithionite performed more than 12 hours after exposure. There were differences in the result of urine sodium dithionite test color between survivors and patients who died (Table 5).

All 48 patients with no change in their urine color in the dithionite test survived. There were differences in the mortality rate between patient groups classified by urine sodium dithionite test results and time from PQ exposure to the dithionite test. A dose-response relationship was found between death rate and color of the test results in both the initial urine sodium dithionite test performed within and after 12 hours (Table 6).

For multivariate analysis, oxygen supplementation and intubation with mechanical ventilation were excluded because they predicted the outcome 100% of the time. Vitamin C and cyclophosphamide administration were excluded because of multicollinearity (VIF 19.3 for vitamin C, and 11.4 for cyclophosphamide). A forward stepwise multiple logistic regression analysis was performed to determine the association between mortality outcome and predictors including age, suicide or self-harm intent, nausea or vomiting at presentation, initial white blood cell count, initial creatinine, initial alanine aminotransferase, initial aspartate aminotransferase, dexamethasone, vitamin E, urine sodium dithionite

Table 6. Mortality rates in paraquat exposure cases reported to Ramathibodi Poison Center from January 2015 to December 2016 categorized by results and time of the initial urine sodium dithionite test

Initial urine sodium dithionite test results	Numbers of deaths/number of cases; n (%)			
	No change in color	Green or light blue color	Dark blue color	Purple or black color
Initial urine sodium dithionite test performed within 12 hours	0/38 (0.0)	0/11 (0.0)	3/9 (33.3)	12/19 (63.2)
Initial urine sodium dithionite test performed later than 12 hours	0/10 (0.0)	3/11 (27.3)	6/10 (60.0)	2/2 (100)
p-value <0.01				

Table 7. Multivariate analysis of factors associated with mortality in paraquat exposure cases reported to Ramathibodi Poison Center from January 2015 to December 2016

Factors	Odd ratio	95% confidence interval	p-value
Age (every 1 year)	1.07	1.02 to 1.12	0.01
Dark blue, purple, or black color results of initial urine sodium dithionite test	37.70	7.47 to 190.07	<0.01
Initial urine sodium dithionite test performed later than 12 hours	7.31	1.54 to 34.63	0.01

Table 8. Rates of systemic effect from paraquat in survival cases reported to Ramathibodi Poison Center from January 2015 to December 2016 categorized by results and time of the initial urine sodium dithionite test

Factors	Number of survival cases with systemic effect/number of survival cases; n (%)			
	No change in color	Green or light blue color	Dark blue color	Purple or black color
Initial urine sodium dithionite test performed within 12 hours	3/38 (7.9)	1/11 (9.1)	1/6 (16.7)	6/7 (85.7)
Initial urine sodium dithionite test performed later than 12 hours	1/10 (10.0)	2/8 (25.0)	4/4 (100)	No survival case in this category
p-value <0.01				

test results, and time from PQ exposure to the urine sodium dithionite test. A multivariate analysis indicated that age (OR 1.07, 95% CI 1.02 to 1.12), dark blue, purple, or black urine color on the initial urine sodium dithionite test (OR 37.70, 95% CI 7.47 to 190.07), and a time from PQ exposure to the urine sodium dithionite test of more than 12 hours after exposure (OR 7.31, 95% CI 1.54 to 34.63) were significantly associated with death (Table 7).

Among the 84 survivors, 18 (21.4%) were reported to have at least one systemic effect including renal toxicity (13 patients, 15.5%), liver toxicity (eight patients, 9.5%), and pulmonary toxicity (six patients, 7.1%). There were differences in the rates of the systemic effects between patient groups classified by urine sodium dithionite test results and time from PQ exposure to the dithionite test (Table 8).

Discussion

The present study analyzed the association between urine sodium dithionite test results, time from exposure to the urine sodium dithionite test, and mortality in patients exposed to PQ. Both urine sodium dithionite test results and the time from exposure to the urine sodium dithionite test were associated with mortality. PQ has a dose-linear toxicokinetic property in human. A mean distribution and elimination half live were seven hours and more than 12 hours[19,20]. A large amount of ingestion can contribute cardiovascular collapse within a few days after ingestion. For the patients who can survive from the early phase, they developed lung fibrosis in a late phase of toxicity[19]. In the present report, the authors believed that a urine dithionite test performed within 12 hours with a strongly positive color result was associated with the increased risk of mortality whereas a strongly positive color result performed later than 12 hours was related with a higher incidence of lung fibrosis. The present study findings were consistent with previous studies[1,3,12,15,21,22]. Liu et al revealed a significant association between a positive color on the urine sodium dithionite test and severity of clinical outcome ($p<0.01$)[15].

Similar to Koo et al's study, the authors found no death in the patients with negative urine test result[12]. In a subgroup analysis of survivors, there

were differences in rates of the systemic effects between patient groups classified by urine sodium dithionite test results and time from PQ exposure to the dithionite test (Table 8). Only 8.3% of the patients with a negative test result developed systemic effect. Many of them developed acute kidney injury and some developed hepatitis. No patient developed lung injury. For the patients who had an initial urine sodium dithionite negative result, the measurement of renal function or hepatic function on the first and third day of exposure should be considered.

Similar to previous studies, age[22], oxygen supplement, and intubation[1] were significantly associated with death.

Although the plasma PQ concentration within the first 24 hours after ingestion is an excellent predictor of clinical outcome for the patients, this method required a specific laboratory technic and it not be readily available in most hospitals. The urine sodium dithionite test is a bedside test that is easy to use and interpret. The authors showed that the urine sodium dithionite test results and time from exposure to the urine sodium dithionite test can be used as prognostic factors in PQ exposure cases.

Although the univariate analysis showed that suicide or self-harm intent, initial white blood cell, creatinine, aspartate aminotransferase, and alanine aminotransferase were associated with mortality, they were not significant in the multivariate analysis. Previous studies also reported that self-harm intention[1,3,21,22] and initial abnormal laboratory test results[1,12,23] were associated with death. Self-harm intention and initial abnormal laboratory results were surrogate markers of the PQ exposure dose and initial PQ effects, which were reported to be associated with death.

Besides oxygen supplementation and intubation, none of the treatments affected the outcome of patients exposed to PQ in the present study. Many studies have attempted to provide treatment tools that can reverse lung function and predicts the prognosis of PQ exposure patients[1]. There is no consensus on whether a single treatment could prevent lung function deterioration[1,24]. The present study was not designed to evaluate the effect of specific treatments in patients exposed to PQ. Further research on the effects of treatments for patients with PQ poisoning should be performed.

Limitation

The urine sodium dithionite test results in the present study were color groups graded by the naked eye. There may be a wide range of PQ concentration in urine for each group. In a setting with limited resources, serum and urine PQ concentration cannot be universally accessed. The grading urine color results using the naked eye is a feasible practice in this setting. Urine color results were confirmed by photographs in 80 cases (72.7%). In the present study, subgroup analysis was done in both the patient group with and without photographs. The primary outcome was shown in parallel result between two groups. Further study to determine the reliability of color grading, and correlation between color grading and PQ concentration in plasma or urine is required. The present center is a single poison center study in Thailand. The standard care and treatment regimen may be different in other countries. Rates of mortality and systemic effects are not generalizable to other settings or study designs. Because this was voluntarily reported data, the number of exposures may be underreported.

Conclusion

Among PQ exposure cases that were reported to the Ramathibodi Poison Center, urine sodium dithionite test results and time from exposure to the urine sodium dithionite test were prognostic factors of mortality and systemic effects from PQ. Age, oxygen supplement, and intubation were significantly associated with mortality.

What is already known on this topic?

Urine sodium dithionite test is a useful tool to predict clinical outcome of PQ patient. Some studies report the association between the color test results and clinical outcome. However, there was no report about the time from PQ exposure to urine sodium dithionite test result.

What this study adds?

The present study is a first study that clearly classify the urine sodium dithionite test result and initial time from PQ exposure. Urine sodium dithionite test results and time from exposure to the urine sodium dithionite test were prognostic factors of mortality and systemic effects from PQ poisoning.

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Conflicts of interest

The authors declare no conflicts of interest in this work.

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