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The clinical features of acute kidney injury in patients with acute paraquat intoxication

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Abstract

Background. Paraquat (PQ) is a non-selective herbicide that generates reactive oxygen species *in vivo*. We hypothesized that acute kidney injury (AKI) in patients with acute PQ poisoning would provide a model for the clinical features of ROS-induced AKI.

Methods. From January 2007 to December 2007, 278 patients with acute PQ intoxication were included in the study. AKI was defined based on the RIFLE classification. The serial changes of creatinine (Cr), the incidence of AKI and the mortality according to the RIFLE classification were analysed.

Results. An initial serum Cr >1.2 mg/dL was a significant predictor of mortality [odds ratio 9.00, 95% C.I. (4.747, 17.061), $P < 0.01$]. The incidence of AKI was 51.4% among the 173 patients who had an initial serum Cr ≤ 1.2 mg/dL. Among them, 34.7% were the failure group and oliguric AKI was observed in 10 patients. The average peak serum Cr level, among the 13 survivors in the failure group, was 4.38 mg/dL at the fifth day, after ingestion, and their Cr level normalized within 3 weeks. None of the 13 survivors had permanent loss of renal function. The estimated amount of PQ ingestion was a predictor of the incidence of AKI. The mortality risk was significantly higher in the failure group than in the group without failure.

Conclusion. The clinical feature was characterized by fully developed AKI at the fifth day after PQ ingestion and normalized within 3 weeks without exception.

Keywords: Acute renal failure; paraquat; reactive oxygen species

Introduction

Acute kidney injury (AKI) is a complex disorder that occurs in a variety of settings with clinical manifestations ranging

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from a minimal elevation in the serum creatinine (Cr) to anuric renal failure [1]. Among all patients admitted to the hospital, the incidence of AKI is known to be ∼1% at the time of admission and 2–5% during the hospitalization [2]. It is well known that ∼40% of all cases of AKI are intrinsic AKI directly involving the renal parenchyma; these cases are usually caused by ischaemic or toxic acute tubular necrosis (ATN). Most cases of AKI in the intensive care unit are caused by sepsis [3]. The reactive oxygen species (ROS) have been implicated as important effectors of tubule cell injury in both ischaemic and toxic acute tubular necrosis [4]. The ROS have numerous deleterious effects on cells, including lipid peroxidation, oxidation of cell proteins and damage to the DNA [5]. However, it is difficult to identify the single most important effect of ROS on the renal tubules *in vivo*, because multiple factors play a role in the development of AKI.

Paraquat (PQ) (1,1′-dimethyl-4,4′-bipyridinium dichloride) is used as a non-selective herbicide. Accidental or intentional ingestion of PQ is frequently fatal within a few days due to multiple organ failure mediated by ROS [6,7]. PQ is considered one of the most dangerous and controversial herbicides in the world. The EU Court of First Instance prohibited the use of PQ in the EU in July 2007. Elsewhere, PQ is currently the most common herbicide in other countries. Acute PQ intoxication is unique in causing a clinical condition due to the ROS. A high concentration of PQ in cells results in abnormal redox cycling and generates the toxic ROS [8]. Both lung and kidney injuries have been well established as the major causes of death after PQ poisoning. With this, we hypothesize that the AKI caused by acute PQ poisoning might provide a clinical model for ROS-induced AKI. In this study, we analysed the clinical features of 278 patients with acute PQ intoxication, focusing on renal function deterioration.

Materials and methods

Study population

This study was approved by Soonchunhyang Cheonan Hospital's Investigational Review Board. From January 2007 to December 2007, 296 patients (169 males and 127 females) with acute PQ intoxication were admitted to the Institute of Pesticide Poisoning, at the Soonchunhyang Hospital (SCH) in Cheonan, Korea. These patients either presented to our hospital or were transferred from another hospital. Among them, 278 cases (158 males and 120 females) were enrolled in this study. Eighteen patients, who were excluded, had unstable vital signs or were in a very poor physical condition within 1 day of ingestion. A urine dithionite test and/or plasma PQ level test by HPLC were performed in all patients.

Data collection and study variables

Trained physicians treated the patients and recorded all information on a standardized data-collection form. All data were reviewed by two pesticide specialists. On admission, a standardized questionnaire including demographic characteristics and specific questions about the PQ poisoning (amount of PQ ingestion, time interval between ingestion and SCH arrival) was completed. The amount of PQ ingestion was defined as one mouthful to 20 mL. Standardized medical emergency procedures were performed and are summarized in Table 1. The demographics of the 278 patients with acute PQ poisoning are summarized in Table 2.

Table 1. Summary of treatment guidelines for acute paraquat intoxication

1. Gastric lavage
2. Dithionite urine test
3. Fuller's earth, 100 gm in 200 mL mannitol
4. A. Antioxidant (intravenous administration)
N-Acetylcysteine
L-Glutathione
Vitamin C
Vitamin E
Thioctic acid
B. For renal preservation
Furosemide
15% mannitol
C. Others
Deferoxamine mesylate
Dexamethasone
5. Emergency haemoperfusion
6. Key laboratory parameters
Blood chemistry*: blood urea nitrogen, creatinine, amylase, lipase
Electrolyte: Na, K, Cl
Artery blood gas analysis*
Total antioxidant status
Malondialdehyde

*These are initial prognostic parameters [10,18].

Table 2. General characteristics and initial parameters of the 278 patients with paraquat poisoning

Age (years)	46.68 ± 14.04 [13, 82]
Sex (*n*)	
Males	158 (56.8%)
Females	120 (43.2%)
Time interval between paraquat ingestion and the arrival time at the hospital (h)	15.93 ± 26.03 [0.5, 193]
Plasma paraquat level (μg/mL)	24.47 ± 54.92 [0.001, 487]
Estimated amount of paraquat ingestion (mL)	64.29 ± 77.77 [1, 500]
AST (IU/L)	53.14 ± 84.78
ALT (IU/L)	38.81 ± 58.04
Total bilirubin (mg/dL)	0.87 ± 0.84
Amylase (IU/L)	337.95 ± 541.69
Lipase (IU/L)	110.51 ± 328.01
Blood urea nitrogen (mg/dL)	15.29 ± 9.91
Creatinine (mg/dL)	1.41 ± 1.43
Uric acid (mg/dL)	5.36 ± 2.18
pH	7.40 ± 0.09
$PaCO_2$ (mmHg)	29.90 ± 8.48
PaO_2 (mmHg)	95.34 ± 20.48
HCO_3^- (mEq/L)	18.51 ± 5.98
Survival (*n*)	122 (41.21%)

[Minimum values, maximum values], AST: aspartate aminotransferase, ALT: alanine aminotransferase.

Definition of AKI and assessment of clinical features of PQ-induced AKI

All of the patients had their blood Cr levels, arterial blood gas analysis and urine output checked daily during the hospitalization. The definition of AKI was based on the RIFLE (risk, injury, failure, loss and end stage) criteria and the changes in the levels of serum Cr, as proposed by the ADQI group [9]: 150–200% of basal level (risk category), 200–300% of basal level (injury category) and >300% and/or >4 mg/dL (failure category).

The initial parameters of the 278 patients at the time of arrival at SCH were compared between patients in the initial serum Cr ≤1.2 mg/dL group and those in the initial serum Cr >1.2 mg/dL group. The patients in the initial Cr ≤1.2 mg/dL group were divided according to the RIFLE criteria into failure group (failure) and non-failure group (normal, risk, injury). The clinical features and mortality of the failure group were compared to those of the non-failure group and the results were analysed. Oliguric AKI was defined as a 24-h urine collection of <400 mL. Serial changes in the serum Cr were evaluated to follow the clinical features associated with PQ-induced AKI. We investigated the frequency, initiation and duration of haemodialysis (HD), and analysed the mortality among patients with AKI who underwent HD. The nephrologist decided to perform HD (Gambro, Polyflux 6L, surface area 1.4 m^2, session time 4 h, blood flow 250 mL/min, dialysate flow 500 mL/min) based on the general indications.

Next to be tested was the association of PQ-induced AKI with other multiorgan dysfunction (lung, liver and pancreas).

Similar to a previous report from our centre [10], hepatic dysfunction was defined as an increase of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of more than two times upper normal limits. Pancreatic dysfunction was diagnosed when the serum amylase level and the serum lipase level were more than twice the upper normal limit. Respiratory failure was considered to be present when the arterial partial pressure of oxygen was <60 mmHg.

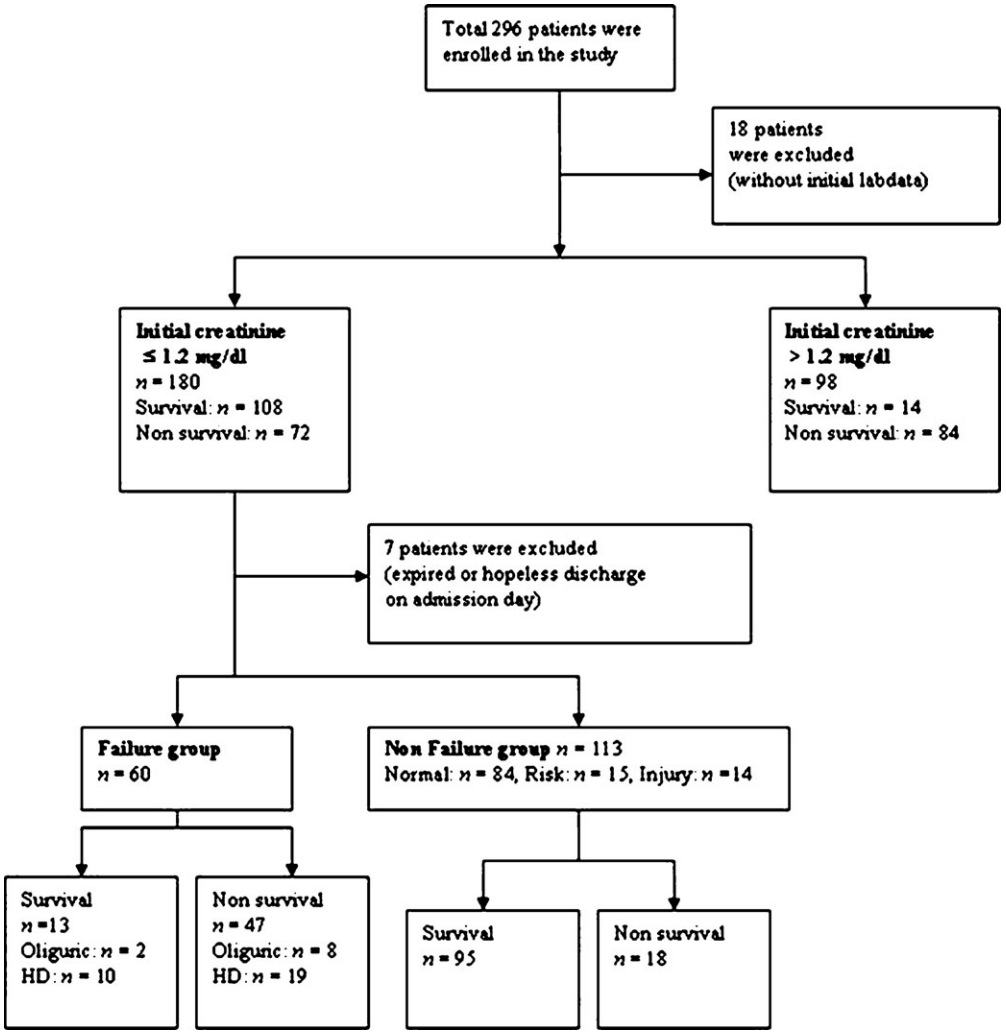

Fig. 1. Patient outcome and RIFLE classification.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and frequency (in percent) for categorical variables. A probability value of $P < 0.05$ was considered statically significant. The statistical analysis was performed using SPSS for Windows (version 12.0, Chicago, IL, USA). The differences between groups were compared with Student's *t*-test for continuous variables and the chi-square test for categorical variables. A multiple logistic regression analysis was used to determine the factors affecting AKI after PQ poisoning. The strength of the association between the RIFLE classification and the outcome after PQ poisoning was expressed as an odds ratio.

Results

Relation between initial Cr levels and other parameters (Figure 1)

Age, time interval between PQ ingestion and the arrival time at the hospital, plasma PQ level, estimated amount of PQ ingestion, AST, blood urea nitrogen, serum Cr and uric acid were significantly lower in the patients in the initial Cr ≤1.2 mg/dL group compared to those in the initial Cr >1.2 mg/dL group. In contrast, the pH, $PaCO_2$ and HCO_3^- were significantly higher in the patients in the initial Cr ≤1.2 mg/dL group than in those in the initial Cr >1.2 mg/dL group (Table 3). The survival rate was higher for patients in the initial Cr ≤1.2 mg/dL group (108/180, 60%) compared to the patients in the initial Cr >1.2 mg/dL group (14/98, 14.28%) (Figure 2). The results demonstrate that the initial serum Cr level was a very important prognostic factor for mortality [odds ratio 9.00, 95% C.I. (4.747, 17.061), *P*-value < 0.01].

Table 3. Comparisons of initial parameters between patients in the initial creatinine ≤1.2 mg/dL group and those in the initial creatinine >1.2 mg/dL group

	Initial creatinine ≤1.2 mg/dL group ($n = 180$)	Initial creatinine >1.2 mg/dL group ($n = 98$)	*P*-value
Age (years)	45.02 ± 13.31 [13, 82]	49.72 ± 14.90 [18, 77]	0.007
Sex (*n*)			0.473
Males	91 (50.55%)	67 (68.37%)	
Females	89 (49.45%)	31 (31.63%)	
Time interval between paraquat ingestion and the arrival time at the hospital (h)	13.08 ± 20.60 [1, 146]	21.12 ± 33.28 [0.5, 192]	0.031
Plasma paraquat level (μg/mL)	6.23 ± 19.61 [0, 218]	58.47 ± 78.64 [0, 487]	<0.001
Estimated amount of paraquat ingestion (mL)	45.84 ± 61.22 [1, 500]	98.16 ± 92.55 [10, 500]	<0.001
Albumin (g/dL)	4.46 ± 0.47	4.48 ± 0.67	0.853
AST (IU/L)	35.56 ± 52.38	85.43 ± 117.64	<0.001
ALT (IU/L)	33.31 ± 58.13	48.91 ± 56.79	0.032
Total bilirubin (mg/dL)	0.75 ± 0.47	1.08 ± 1.24	0.011
Blood urea nitrogen (mg/dL)	11.91 ± 4.65	21.50 ± 13.43	<0.001
Creatinine (mg/dL)	0.72 ± 0.21	2.68 ± 1.80	<0.001
Amylase (IU/L)	244.82 ± 404.62	509.01 ± 700.11	0.001
Lipase (IU/L)	48.65 ± 136.29	224.11 ± 502.83	0.001
Uric acid (mg/dL)	4.73 ± 1.62	6.54 ± 2.57	<0.001
pH	7.41 ± 0.07	7.38 ± 0.11	0.022
$PaCO_2$ (mmHg)	32.20 ± 6.63	25.68 ± 8.58	<0.001
PaO_2 (mmHg)	95.59 ± 18.24	94.89 ± 24.16	0.804
HCO_3^- (mEq/L)	20.04 ± 4.84	15.69 ± 6.82	<0.001
Survival (*n*)	108 (60.00%)	14 (14.28%)	

[Minimum values, maximum values], AST: aspartate aminotransferase, ALT: alanine aminotransferase.

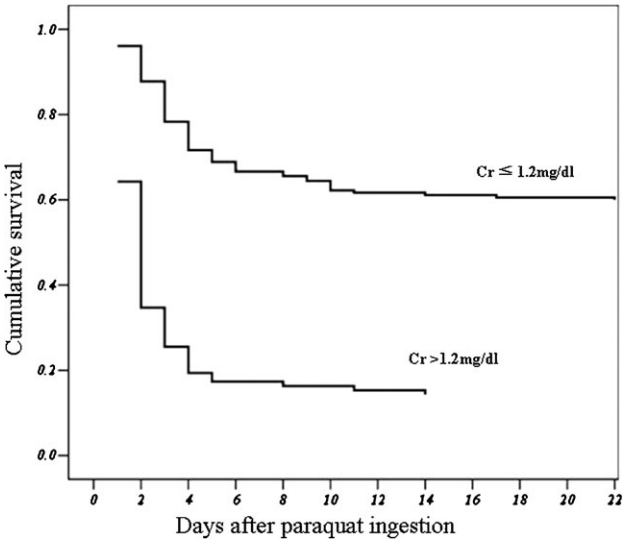

Fig. 2. Comparison of survival rates between initial serum Cr ≤1.2 mg/dL and initial serum Cr >1.2 mg/dL.

Clinical features of AKI in patients with initial Cr ≤1.2 mg/dL

The incidence of AKI in patients in the initial Cr ≤1.2 mg/dL group was 51.4% (89/173). Of these, Cr-measured failure occurred in 34.7% (60/173) (Figure 1). The average peak serum Cr level among the 13 survivors in the failure group was 4.38 mg/dL by the fifth day after PQ intoxication; their Cr levels normalized within 3 weeks of ingestion (Figure 3). None of the patients had permanent loss of renal function.

Oliguric AKI was observed in 10 patients. The development of oliguric AKI was noted on the third and fourth days after PQ ingestion, in two patients who survived among the 10 patients with oliguric AKI. After the fourth day, the urine output increased. All of the other patients expired. The number of patients who developed oliguric AKI was 1 on the second day, 2 on the third day, 3 on the fourth day and 2 on the fifth day.

The time interval between PQ ingestion and the arrival time at the hospital, the estimated amount of PQ ingestion, Cr levels, uric acid and PaO_2 were significantly higher in the failure group compared to the non-failure group among the patients who presented with initial Cr ≤1.2 mg/dL. In contrast, the $PaCO_2$ and HCO_3^- were significantly lower in the failure group than in the non-failure group (Table 4). The survival rate was 13% (13/60) among the patients with failure and 84.07% among those without failure.

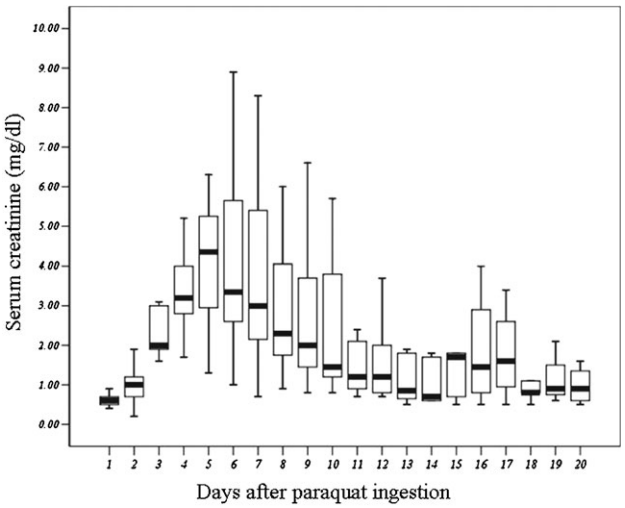

Fig. 3. Serial serum Cr levels of 13 survival patients in the failure group.

The estimated amount of PQ ingestion and the time interval between PQ ingestion and the arrival time at the hospital were factors predictive of the incidence of AKI by the multiple logistic analysis (Table 5). HD was performed in 29 patients with AKI during their clinical course. The mortality rate was 65.52% (19/29) among patients who underwent HD and 90.32% (28/31) among those who did not undergo HD. HD was performed, on average, 3.8 days after admission and was performed for 2.93 days. The odds ratio of mortality with HD was 0.024 [95% C.I. (0.049, 0.839), *P*-value = 0.05].

Mortality according to RIFLE classification

The risk for mortality was significantly higher in the patients with failure than in those without failure. According to the RIFLE classification, patients with renal injury and failure had a higher mortality risk than did patients without AKI (Table 6).

The association of renal failure with other organ functions

The incidence of multiorgan dysfunction accompanying AKI was 36.67% (22/60) with pancreatic dysfunction, 51.67% (31/60) with hepatic dysfunction and 75% (45/60) with respiratory failure. The odds ratio for patients with AKI developing other organ failure was 15.776 for pancreatic dysfunction [95.0% C.I. (5.109, 48.717), *P*-value < 0.01], 5.642 for hepatic failure [95.0% C.I. (2.762, 11.525, *P*-value < 0.01] and 19.600 for respiratory failure [95.0% C.I. (8.825, 43.532), *P*-value < 0.01].

RIFLE classification in patients with initial Cr ≤1.2 mg/dL

Because 48 patients died within two days of presentation, 50 patients were analysed. Among these patients, failure was present in 25 (18 died), injury in 10 (7 died), risk in two (2 died), and non-AKI in 13 (9 died). There was no significant difference in mortality between patients with AKI and those without AKI [odds ratio 1, 95.0% C.I. (0.291, 3.437), *P*-value = 1]. In addition, there was no significant difference in mortality between patients with injury and those

Table 4. Comparisons of initial parameters between failure group and non-failure group among the patients who presented with initial Cr ≤1.2 mg/dL

	Failure group ($n = 60$)	Non-failure group ($n = 113$)	*P*-value
Age (years)	43.38 ± 14.23 [15, 82]	45.63 ± 12.77 [13, 77]	0.292
Sex (*n*)			
Males	33 (37.5%)	55 (62.5%)	
Females	27 (29.41%)	58 (68.24%)	
Time interval between paraquat ingestion and the arrival time at the hospital (h)	7.85 ± 6.07 [2, 29]	16.38 ± 25.00 [1, 146]	<0.001
Plasma paraquat level (μg/mL)	5.40 ± 8.29 [0.11, 33]	4.84 ± 22.57 [0, 218]	0.854
Estimated amount of paraquat ingestion (mL)	61.25 ± 52.15 [5, 300]	31.04 ± 44.07 [1, 250]	<0.001
Albumin (g/dL)	4.52 ± 0.44	4.41 ± 0.45	0.152
AST (IU/L)	30.93 ± 24.41	32.82 ± 25.76	0.641
ALT (IU/L)	25.83 ± 23.61	31.79 ± 34.37	0.232
Total bilirubin (mg/dL)	0.74 ± 0.39	0.75 ± 0.45	0.940
Blood urea nitrogen (mg/dL)	12.01 ± 4.81	11.59 ± 4.52	0.576
Creatinine (mg/dL)	0.75 ± 0.22	0.68 ± 0.18	0.033
Amylase (IU/L)	300.70 ± 543.53	190.42 ± 258.16	0.142
Lipase (IU/L)	38.51 ± 52.97	48.34 ± 155.82	0.636
Uric acid (mg/dL)	5.13 ± 1.66	4.42 ± 1.47	0.005
pH	7.41 ± 0.08	7.41 ± 0.05	0.621
$PaCO_2$ (mmHg)	30.76 ± 6.80	33.48 ± 6.04	0.008
PaO_2 (mmHg)	100.19 ± 19.09	92.63 ± 16.12	0.007
HCO_3^- (mEq/L)	19.04 ± 4.56	21.13 ± 4.33	0.003
Survival (*n*)	13 (21.66%)	95 (84.07%)	

[Minimum values, maximum values], AST: aspartate aminotransferase, ALT: alanine aminotransferase.

Table 5. Multiple logistic regression analysis of the initial parameters of acute kidney injury after acute paraquat intoxication

	Adjusted O.R.	95.0% C.I.	*P*-value
Age (years)	0.975	[0.949, 1.003]	0.081
Sex (males:females)	1.114	[0.551, 2.212]	0.781
Time interval between paraquat ingestion and the arrival time at the hospital (h)	0.968	[0.938, 0.999]	0.046
Plasma paraquat level (μg/mL)	0.964	[0.923, 1.006]	0.096
Estimated amount of paraquat ingestion (mL)	1.025	[1.011, 1.039]	<0.001

O.R.: odds ratio; C.I.: confidence interval.

Table 6. The mortality risk according to the RIFLE classification

Compared AKI levels	OR	95% CI	*P*-value
Failure versus non-failure	19.081	[8.622, 42.229]	0.000
Failure versus non-AKI	2.991	[2.214, 4.04]	0.000
Injury versus non-AKI	2.356	[1.263, 4.396]	0.007
Risk versus non-AKI	1.138	[0.223, 5.802]	0.876

OR: odds ratio; CI: confidence interval.

with non-AKI [odds ratio 1.018, 95.0% C.I. (0.415, 2.497), *P*-value = 0.968] or between patients with failure and those with non-AKI [odds ratio 1.040, 95.0% C.I. (0.641, 1.704), *P*-value = 0.858]. However, in all patients who survived, the renal function fully recovered.

Discussion

To properly understand the pathophysiology of a disease, an experimental model of the disease is often needed. There have been many experimental models developed to study AKI including ischaemia, isolated perfusion kidney, radiocontrast, combined insults and drugs or endotoxin infusion [12–14]; however, these models are based on animal investigations. PQ ingestion can be used to study the effects of ROS. Patients with PQ intoxication have a high mortality rate due to the effects of the ROS [15]. Therefore, the acute renal failure (ARF) associated with acute PQ poisoning might provide a good model for the clinical features of ROS-induced AKI.

Renal insufficiency may exist in patients with initial Cr >1.2 mg/dL. We also analysed patients with initial Cr ≤1.2 mg/dL. Of the patients in the initial Cr ≤1.2 mg/dL group, 84 had normal renal function throughout the study, 15 were at risk, 14 were having renal injury and 60 patients were considered to have failure. The incidence of PQ-induced AKI was 51.4%, and the incidence of failure was 34.68%. PQ is toxic to renal proximal tubule cells through the generation of ROS, which cause lipid peroxidation of the cell membrane, leading to loss of membrane integrity and cell death [16]. Although PQ can induce ATN, there is limited information about this in the medical literature [16,17].

Our data showed that the average peak serum Cr level was achieved on the fifth day after ingestion, and the Cr level normalized within 3 weeks. There were no significant differences in the initial laboratory parameters, age, gender, amount of ingestion, time lapse after ingestion and plasma PQ levels between the 10 patients who developed oliguric AKI and the 50 with non-oliguric AKI. It is necessary to investigate the factors involved in oliguric AKI.

As we previously reported [11,18], the data showed that the initial renal function was a very important factor for survival. Taken together with our previous reports, a very large portion of the PQ is excreted via renal filtration and secretion. Therefore, early renal preservation is very important.

Many clinical studies have shown that the RIFLE classification is a valid tool for predicting outcome [19,20]. In addition, the presence of renal injury and failure, based on the RIFLE classification, predicts mortality in patients with PQ-induced AKI (Table 4). However, risk was not a predictor of outcome in patients in the initial Cr ≤1.2 mg/dL group. The patients at risk might have had subtle injuries that did not influence patient mortality after PQ-induced AKI. Further investigation is necessary to study the validity of the RIFLE classification for drug-induced nephropathies. Of the patients with initially abnormal Cr levels, many died early and the baseline Cr of the patients was not known. Therefore, the RIFLE classification cannot be used for patients in the initial Cr >1.2 mg/dL group.

The factors most related to the development of failure were the estimated amount of PQ ingestion and the time interval between ingestion and the arrival time at the hospital. The increased incidence of AKI in patients arriving to the hospital in the shortest time might be due to the fact that patients who ingest more PQ tend to go to the hospital faster. Contrary to our expectation, the PQ level in serum showed no significant association with developing of AKI. We believe this was due to the various time intervals between PQ ingestion and blood sampling time for PQ measurement.

In cases with a potential for ROS formation in clinical setting, acute PQ intoxication is the strongest and most urgent cause of tissue injury mediated by ROS. In outpatients, some had drunk unbelievable amount (several hundred millilitres) of PQ. We believed that a lot of ROS formation was produced. However, all of the AKI reversed by 3 weeks. A single exposure of ROS to the kidney is clinically benign regardless of the amount, but results of repeated exposure is needed to be studied.

The limitations of this study include the following. To more completely describe the clinical features of the patients with AKI, a control group of patients with ischaemia- or toxin-induced AKI would be needed. But since it is, for all practical purposes, impossible to study such human subjects, our study was carried out without a control group. Another question is about the ROS formation in our patients. We have previously published that in *in vitro* examinations the amount of ROS that is formed is decided by a reaction between both PQ concentrations and the duration of PQ exposure. However, in the current study the interpretation of the clinical outcome of AKI was carried out on the assumption that ROS generation would be consistent with the amount of PQ ingestion and/or serum PQ level at admission, without measurement of ROS and/or ROS by-product.

In conclusion, the incidence of AKI with PQ intoxication was 51.4% and the incidence of failure was 34.7%. The amount of PQ ingested is the most important factor influencing the development of AKI after PQ intoxication. The clinical feature was characterized by fully developed AKI at the fifth day after PQ ingestion and normalized within 3 weeks without exception.

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Conflict of interest Statement. None declared.

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Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD

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Abstract

Background. Metabolic acidosis, usually manifested by low serum bicarbonate level, is common in chronic kidney disease (CKD) and appears to be associated with higher mortality in dialysis patients. It is not known whether a similar association is present in patients with non-dialysis-dependent CKD (NDD-CKD).

Methods. We used multivariable-adjusted Cox models to examine the association between baseline and time-variable serum bicarbonate (measured as total CO_2) with the outcomes of all-cause mortality and the composite of predialysis mortality or end-stage renal disease in 1240 male patients with moderate and advanced NDD-CKD.

Results. Serum bicarbonate showed a significant U-shaped association with all-cause mortality, with the highest mortality rate observed in patients with baseline serum bicarbonate levels <22 mmol/L [multivariable-adjusted hazard ratio (95% confidence interval) for patients with serum bicarbonate <22 mmol/L versus ≥22 mmol/L: 1.33 (1.05–1.69), $P = 0.02$] and the lowest mortality observed in patients with baseline serum bicarbonate of 26–29 mmol/L. The associations between lower serum bicarbonate level and mortality were more accentuated in subgroups of patients with better nutritional status and lower inflammation.

Conclusions. Both lower and higher serum bicarbonates are associated with increased all-cause mortality in patients with moderate and advanced NDD-CKD. Clinical trials are needed to determine if therapeutic interventions aimed at optimizing serum bicarbonate can result in improved outcomes in this population.

Keywords: bicarbonate; chronic kidney disease; mortality

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