Serum uric acid level as a marker for mortality and 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 (ROS) in vivo. Uric acid emerged as a marker of oxidative stress and may enhance ROS-mediated injury in acute PQ intoxication. Therefore, we investigated the association between uric acid levels and mortality and acute kidney injury (AKI) in the present study.

Methods. From January 2007 to December 2008, patients who arrived at our hospital with acute PQ intoxication (n = 513) were included in the study. Patients were divided into two groups (hyperuricaemia vs non-hyperuricaemia) based on uric acid levels. Mortality and AKI were analysed in reference to uric acid level.

Results. Patient mortality was higher in the hyperuricaemia group than the non-hyperuricaemia group (68.4% vs 38.3%, P < 0.05). The incidence of AKI and kidney failure was 64% and 43.3%, respectively. Hyperuricaemia increased the risk of mortality and kidney failure to 3.7-fold and 3.3-fold after adjustments for age, sex and the estimated amounts of PQ ingestion. Mean serum uric acid level was higher in death group than survival group and higher in kidney failure group than non-AKI group and non-failure group.

Conclusions. Baseline serum uric acid level might be a good clinical marker for patients at risk of mortality and AKI after acute PQ intoxication.

Keywords: acute renal failure; paraquat; uric acid

Introduction

Uric acid is an important antioxidant in human biological fluids and a powerful scavenger of reactive oxygen species (ROS); it can function as an electron donor to protect against oxidative damage [1,2]. Conversely, uric acid may also function as a pro-oxidant, and may mediate ROS production and stimulate the synthesis of pro-inflammatory molecules [3,4]. Several studies have demonstrated that uric acid is a marker of oxidative stress; it has been associated with hypertension, cardiovascular disease, metabolic syndrome, atherosclerosis and the progression of chronic kidney disease [5–9].
Uric acid: mortality and AKI in parquat ingestion

Paraquat (PQ) (1,1-dimethyl-4,4-bipyridinium dichloride) is a non-selective herbicide. Intentional or accidental ingestion of PQ in humans is often fatal [10]. PQ is a powerful ROS-generating chemical and, once ingested, accumulates in the cells. This frequently results in redox cycling, generation of ROS, lipid peroxidation, cell protein oxidation and DNA damage, ultimately leading to cell death and multi-organ failure [11].

We previously reported that patient age, ingestion route, initial arterial blood gas analysis, white blood cell count, and renal and pancreatic function tests were reliable predictors of prognosis in patients with PQ intoxication [12,13]. However, the relationship between initial uric acid levels and mortality has not yet been investigated, despite the fact that tests to assess the uric acid levels are easily performed and relatively inexpensive. We examined the association of the initial serum uric acid levels, mortality and acute kidney injury (AKI) in the present study to determine whether uric acid enhances ROS-mediated injury in patients with acute PQ intoxication and whether initial uric acid levels could be used for prediction of mortality and AKI.

Materials and methods

Study design and setting
Patients with acute PQ intoxication (n = 513) were admitted to the Institute of Pesticide Poisoning at the Soonchunhyang Hospital (SCH) in Cheonan, Republic of Korea, from January 2007 to December 2008. This study was approved by the Soonchunhyang Cheonan Hospital’s Investigational Review Board, and all participants provided written informed consent.

Selection of participants
Patients were either initially admitted to SCH or transferred from another hospital. Individuals with >5 mL of the estimated amount of PQ ingestion and the presence of oral mucosal ulceration were observed for 24 h during admission and were included in the study. Patients who had PQ exposures by routes other than ingestion, who arrived at SCH >24 h after PQ ingestion, who had an initial serum creatinine >1.2 mg/dL, who died on the day of admission, who left the hospital against medical advice or who were transferred to another hospital were excluded; 266 patients were excluded from further study (Figure 1).

Data collection and processing
A standardized questionnaire, including questions about demographic characteristics and PQ poisoning details (amount of PQ ingestion, time interval between ingestion and SCH arrival), was completed on admission; the amount of PQ ingestion was defined as from one mouthful to 20 mL. Information was recorded on a standardized data collection form, and all the data were reviewed by two pesticide specialists.

Methods of measurement
Blood samples for the initial clinical parameters, including haemoglobin, white blood cell count, pH, arterial O2 concentration (PaO2), blood urea nitrogen, creatinine, uric acid, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, amylase, lipase and plasma PQ levels (tested by HPLC), were obtained immediately upon admission to the emergency room.

Outcome measures
Hyperuricaemia was defined according to our population-based control group. From January 2002 to May 2007, persons (n = 7354) examined during a medical check-up at the SCH health promotion centre were enrolled as a control group to define the reference standards for hyperuricaemia; those with haematuria or proteinuria and those with hypertension and diabetes were excluded from the control group (n = 1109). The mean uric acid level was 5.24 ± 1.43 mg/dL among the controls (n = 6245); it was 6.02 ± 1.27 mg/dL in men and 4.32 ± 0.97 mg/dL in women. Hyperuricaemia defined as a level of serum uric acid ≥7.3 mg/dL in men or ≥5.3 mg/dL in women was the upper level of one standard deviation in the present study.

Mortality, AKI and other organ injuries were the assessed outcomes. The definition of AKI was based on the Risk, Injury, Failure, Loss and End-Stage Kidney Disease (RIFLE) criteria and the changes in the levels of serum creatinine, as reported by the Acute Dialysis Quality Initiative group [14]: (i) risk was defined as a 1.5-fold increase in serum creatinine or a >25% decrease in glomerular filtration rate (GFR); (ii) injury was defined as a 2-fold increase in serum creatinine or a >50% decrease in GFR; and (iii) failure was defined as a 3-fold increase in serum creatinine, a >75% decrease in GFR or serum creatinine levels of ≥4 mg/dL in patients with initial creatinine levels of ≤1.2 mg/dL. The Modification of Diet in Renal Disease (MDRD) formula was used to estimate GFR [15].

As within a previous report from our centre [13], liver injury was defined as an increase in the AST or ALT greater than twice the upper limit of normal. Pancreatic injury was diagnosed when the serum amylase and lipase levels were greater than twice the upper limit of normal. Respiratory failure was defined by an arterial partial oxygen pressures <60 mmHg (in room air). Survivors were defined as individuals who survived >90 days after PQ ingestion.

Statistical methods
Data are presented as the mean ± SD values for continuous variables and as the frequency (percentage) for categorical variables. Statistical significance was defined as P-values <0.05. All analyses were performed with the SPSS program for Windows (version 14.0, Chicago, IL, USA). Differences in the uric acid group were tested by the Student’s t-test for continuous variables and by the chi-square test for categorical variables. Survival curves were generated using the Kaplan–Meier technique and tested with the log-rank test. Multiple logistic regression analysis was performed to predict outcomes after acute PQ intoxication, after controlling for possible confounders. The strength of the association between the uric acid groups and the outcomes after PQ poisoning was expressed as odds ratios.

Results

Baseline characteristics
A total of 247 patients were included in the study. The mean age of the study participants was 46.1 ± 13.7 years; 52% of all patients were men. The mean estimated amount of PQ ingestion was 47 ± 53 mL, the mean serum uric acid level was 5.6 ± 1.6 mg/dL in men and 4.1 ± 1.3 mg/dL in women, and the mean serum creatinine level was 0.7 ± 0.2 mg/dL.

Uric acid as a marker for mortality
The crude mortality rates were 68.4% (26/38) in the hyperuricaemia group and 38.3% (80/209) in the non-hyperuricaemia group (Table 1), and 43% of the study patients died. The hyperuricaemia group had a lower cumulative survival rate than the group without hyperuricaemia (Figure 2A). The majority of the deaths occurred within 2 weeks of hospital admission. The majority of individuals who survived for >3 weeks survived until study completion (Figure 2A). The mean uric acid level was significantly higher in the patients who died than in the patients who survived (Figure 2B). Hyperuricaemia increased the risk of
mortality 3.5-fold by unadjusted analyses (Table 2). Hyperuricaemia still significantly increased the risk of mortality after adjustments for age, gender and the estimated amount of PQ ingestion. The adjusted odds ratio (OR) for mortality was 3.67 [95% confidence interval (CI), 1.35–9.98] with hyperuricaemia (Table 2).

Uric acid as a marker for AKI

The frequency of non-AKI, risk, injury and failure were 36%, 6.9%, 13.8% and 43.3%, respectively, and the frequency of AKI was higher in the hyperuricaemia group (Table 3). Mortality in the non-AKI, risk, injury and failure

### Table 1. Baseline characteristics of hyperuricaemia and non-hyperuricaemia group

<table>
<thead>
<tr>
<th></th>
<th>Hyperuricaemia (n = 38)</th>
<th>Non-hyperuricaemia (n = 209)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.63 ± 14.81</td>
<td>45.45 ± 13.37</td>
<td>0.083</td>
</tr>
<tr>
<td>Sex, men, n (%)</td>
<td>17 (45%)</td>
<td>111 (53%)</td>
<td>0.344</td>
</tr>
<tr>
<td>Plasma PQ level (μg/mL)</td>
<td>6.04 ± 8.11</td>
<td>4.57 ± 17.49</td>
<td>0.613</td>
</tr>
<tr>
<td>Estimated amount of PQ ingestion (mL)</td>
<td>58.29 ± 55.65</td>
<td>44.97 ± 52.07</td>
<td>0.152</td>
</tr>
<tr>
<td>Time intervala (hour)</td>
<td>6.11 ± 4.39</td>
<td>7.16 ± 5.19</td>
<td>0.239</td>
</tr>
<tr>
<td>WBC (×10³)</td>
<td>6453 ± 8317</td>
<td>7750 ± 7350</td>
<td>0.328</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.51 ± 0.48</td>
<td>4.41 ± 0.49</td>
<td>0.242</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.71 ± 0.34</td>
<td>0.84 ± 0.90</td>
<td>0.371</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>55.34 ± 143.58</td>
<td>38.73 ± 56.74</td>
<td>0.219</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>31.82 ± 26.42</td>
<td>32.79 ± 51.82</td>
<td>0.910</td>
</tr>
<tr>
<td>Lipase (IU/L)</td>
<td>241.63 ± 331.06</td>
<td>228.44 ± 332.11</td>
<td>0.822</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>13.59 ± 5.15</td>
<td>11.82 ± 4.33</td>
<td>0.025</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.79 ± 0.19</td>
<td>0.690 ± 0.21</td>
<td>0.007</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.98 ± 1.26</td>
<td>4.46 ± 1.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.09</td>
<td>7.41 ± 0.06</td>
<td>0.093</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>90.99 ± 23.28</td>
<td>93.89 ± 16.80</td>
<td>0.360</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>26 (68%)</td>
<td>80 (38%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or number (percent). To convert albumin to g/L, multiply by 10; total bilirubin to μmol/L, multiply by 17.104; ALT to μkat/L, multiply by 0.0167; AST to μkat/L, multiply by 0.01667; lipase to μkat/L, multiply by 0.01667; blood urea nitrogen to mmol/L, multiply by 0.357; creatinine to μmol/L, multiply by 88.4; uric acid to μmol/L, multiply by 59.48; PaO₂ to kPa, multiply by 0.133.

PQ, paraquat; WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

*aTime interval between PQ ingestion and the arrival time at the hospital (hour).*
groups were 12.4% (11/89), 5.9% (1/17), 38.2% (13/34) and 75.7% (81/107), respectively. The mortality in the group without kidney failure was 17.9% (25/140), while the mortality in the kidney failure group was 75.7% (81/107). The mean uric acid level of the AKI group was higher than in the non-AKI group; however, this difference was not statistically significant (Figure 3A). The failure group was significantly higher when compared with the non-AKI and non-failure groups (Figure 3B and C). The unadjusted analysis of hyperuricaemia was associated with an increased risk of AKI (odds ratio, 2.37; 95% CI, 1.04–5.43). After adjustments for age, gender and the estimated amount of PQ ingestion, hyperuricaemia was still significantly associated with an increased risk of kidney failure (OR, 3.30; 95% CI, 1.33–8.20) (Table 4).

Hyperuricaemia and other organ injury

There was an increased prevalence of respiratory failure associated with hyperuricaemia. The incidence of liver injury and pancreatic injury was higher in patients with hyperuricaemia.

Table 2. Hyperuricaemia a increased the risk of mortality

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR for death</td>
<td>3.49 (1.67–7.31)</td>
<td>3.34 (1.59–7.03)</td>
<td>3.67 (1.35–9.98)</td>
</tr>
</tbody>
</table>

Values are expressed as odds ratio (95% confidence interval). OR, odds ratio; Model 1, unadjusted; Model 2, adjusted for age and gender; Model 3, adjusted for age, gender and the estimated amount of PQ ingestion.

aSerum uric acid ≥7.3 mg/dL in men or ≥5.3 mg/dL in women.
peruricaemia; however, this was not statistically significant (Table 3). The mean number of injured organs was 1.53 ± 1.34, and the overall frequency of organ injury was increased in the hyperuricaemia group (Figure 4A). The mean uric acid level increased in association with an increase in the number of organ injuries (Figure 4B).

Discussion

The reported mortality from acute paraquat intoxication has ranged from 33% to 78% [16,17]. Several methods for modifying the toxicity of paraquat have been examined: prevention of absorption by the gastrointestinal tract, removal from the bloodstream, prevention of accumulation in the lungs, scavenging oxygen-free radicals and prevention of lung fibrosis. Recently, immunosuppressive therapy and anti-proliferative agents such as rapamycin treatment have emerged. Rapamycin treatment in patients with a large amount of paraquat ingestion seemed to increase survival period but failed to halt the progression of pulmonary fibrosis [18,19].

Approximately 300 patients with PQ poisoning are admitted to our centre annually and treated according to standard uniform treatment protocols. However, there are differences in the survival of patients with similar ingested quantities of PQ. This may be partially attributable to individual differences in antioxidation; however, a previous study from our laboratory examining the antioxidant status demonstrated no associations [20]. In this study, we investigated whether increased uric acid levels were associated with increased vulnerability to ROS-mediated injury or with the outcomes of ROS-mediated injury.

ROS are continuously present in cells under physiological conditions; the cellular redox state is tightly regulated. Toxic ROS effects become apparent when their generation rate exceeds the defence capacity of the cell antioxidant system. Large amounts of ROS are generated in PQ intoxication, and this results in multi-organ failure and pulmonary fibrosis.

We hypothesized that uric acid could enhance ROS-mediated injury, and individuals with hyperuricaemia would have higher mortality rates. Hyperuricaemia increased the risk of mortality 3.5-fold in the unadjusted analysis (Table 2). Patients in the hyperuricaemia group were 3.7-fold more likely to die than those in without hyperuricaemia, after adjustments for age, gender and the estimated amounts of PQ ingestion. Hyperuricaemia was associated with a greater odds ratio of mortality, and the hyperuricaemia group appeared to have ingested a greater amount of PQ (Table 1). The greater quantities of ingested PQ appeared to be associated with increased uric acid levels. The increased rates of mortality in the hyperuricae-
Uric acid: mortality and AKI in paraquat ingestion

ROS-mediated injury is not entirely clear. Whether increased uric acid levels indicate increased vulnerability to ROS-mediated injury or the outcomes of ROS-mediated injury. However, the difference was not statistically significant. The mean uric acid levels increased in parallel with the number of organ injuries (Figure 4A) and may reflect the systemic injuries as a result of PQ toxicity, which might explain the higher mortality in patients with hyperuricaemia.

In cisplatin-induced acute renal failure (ARF) in rat, mild hyperuricaemia increases renal tubular injury and inflammation, and the mechanism appeared to be the stimulation of monocyte chemokines with an enhanced infiltration of infiltrating leucocytes [21]. Hence, serum uric acid has been suggested to contribute pathogenetically to renal vasocstriction as well as to endothelial dysfunction, the inflammatory response, oxidative stress, and the disturbances in autoregulation that occur with ARF [22]. ARF in acute paraquat intoxication may occur as a result of direct tubular toxicity caused by PQ as well as the haemodynamic changes that occur as a result of PQ ingestion [23,24].

The amount of ingested PQ was the most important factor influencing the development of AKI after PQ intoxication [25]. Patients with an initial serum creatinine >1.2 mg/dL were excluded from our study because they had no basal creatinine values. De novo AKI was more prevalent in patients in the hyperuricaemia group, suggesting that ROS-mediated kidney injury may be associated with uric acid levels. In addition to the direct effects of PQ toxicity, uric acid may also be associated with the development of AKI via other indirect and direct mechanisms.

The frequency of respiratory failure was significantly higher in the hyperuricaemia group than in the non-hyperuricaemia group (P < 0.05). (B) The mean uric acid level was higher in groups that had accompanying more than two organ injuries than accompanying no organ injury group (P < 0.05). To convert uric acid levels to µmol/L, multiply by 59.48. Results represent means ± SE.

The limitations of this study include the following: first, there were no data collected on the uric acid levels before PQ intoxication; therefore, it was not confirmed that the increased uric levels were due to PQ ingestion. Several factors, such as volume depletion, alcohol intake and high-purine diet, may be causes of hyperuricaemia [7,26]. Furthermore, decreased glomerular filtration rate may result in decreased uric acid urinary excretion, which may lead to hyperuricaemia if not compensated by gastrointestinal excretion [27,28]. In our treatment protocol, 5 L of normal saline was infused during the first 24 h of admission for forced diuresis of absorbed paraquat which makes volume depletion unlikely. Acute kidney injury induced by paraquat may have influenced basal serum uric acid levels during the time interval between PQ ingestion and admission to the emergency room. Therefore, we excluded patients who showed initial serum creatinine levels >1.2 mg/dL and obtained blood samples for uric acid levels immediately upon arrival to the emergency room to limit such possibilities. Nevertheless, there is a possibility that patients with serum creatinine levels <1.2 mg/dL had a reduced GFR.

Second, the current results do not prove that increased uric acid levels lead to increased vulnerability to ROS-mediated injury or the outcomes of ROS-mediated injury because of the observational study design. Uric acid is an

Table 4. Hyperuricaemia increased the risk of AKI and kidney failure

<table>
<thead>
<tr>
<th>Model</th>
<th>OR for AKI (95% CI)</th>
<th>OR for failure (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>2.37 (1.04–5.43)</td>
<td>3.09 (1.32–7.25)</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.46 (1.07–5.67)</td>
<td>3.39 (1.42–8.06)</td>
</tr>
<tr>
<td>Model 3</td>
<td>2.20 (0.93–5.22)</td>
<td>3.30 (1.33–8.20)</td>
</tr>
</tbody>
</table>

Values are expressed as odds ratio (95% confidence interval). OR, odds ratio; Model 1, unadjusted; Model 2, adjusted for age and gender; Model 3, adjusted for age, gender and the estimated amount of PQ ingestion.
important antioxidant in human. Hyperuricaemia could be a compensatory mechanism to protect the body from pro-oxidants. And several studies have demonstrated that uric acid is a marker of oxidative stress [5–9]. In atherosclerosis, an antioxidant–pro-oxidant urate redox shuttle theory has been suggested according to which, in a pro-oxidative environmental milieu, the original antioxidative properties of uric acid paradoxically become pro-oxidative [29]. In adipocytes, the redox-dependent effects of uric acid are not mediated by the redox chemistry of urate but by the activation of intracellular production of oxidants by NADPH oxidase [3]. Hence, in patients with acute PQ intoxication, elevated serum uric acid may be a marker of increased oxidative stress. Individuals with hyperuricaemia have a higher mortality rate, and higher uric acid levels may reflect the degree of systemic injury in patients with acute PQ intoxication.

In conclusion, baseline serum uric acid level might be a good clinical marker for patients at risk of mortality and AKI after acute PQ intoxication.

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Conflict of interest statement. None declared.

References

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