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Alveolar–arterial partial pressure difference as an early predictor for patients with acute paraquat poisoning

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Abstract

Objective: Paraquat (PQ) is associated with high mortality rates in acute poisoning. This study aimed to determine the importance of the alveolar–arterial partial pressure difference ($A\text{-}aDo_2$) in the expected consequences of acute PQ poisoning.

Methods: Patients who were hospitalized for PQ poisoning in 2018 were enrolled in this retrospective study. $A\text{-}aDo_2$ data were collected. Multivariate analysis was performed using binary logistic regression to determine whether $A\text{-}aDo_2$ is an independent risk factor for mortality from PQ.

Results: A total of 352 cases were analyzed. The mean PQ dose was 36.84 ± 50.30 mL (0.3–500 mL). There were 185 survivors and 167 non-survivors. The mean $A\text{-}aDo_2$ was not significantly correlated between survivors and non-survivors on day 1. However, there were significant differences in $A\text{-}aDo_2$ between survivors and non-survivors on days 3, 7, 14, and 21. Increased $A\text{-}aDo_2$ values were correlated with an increased mortality rate. The mean $A\text{-}aDo_2$ on day 14 showed the most significant difference between survivors and non-survivors.

Conclusion: Our study suggests that $A\text{-}aDo_2$ plays an important role as a reference index, which could be a useful predictor in assessing acute PQ poisoning, especially on the 14th day after onset of poisoning.

Keywords

Alveolar–arterial partial pressure difference, paraquat, poisoning, arterial blood gas, mortality, pulmonary fibrosis

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Introduction

Paraquat (PQ) (1,1′-dimethyl-4,4′-bipyridinium chloride) is a widely used herbicide. PQ was discovered in 1955 and developed in the early 1960s by Imperial Chemical Industries (currently Syngenta).[1,2] This rapid and effective herbicide has become the second most commonly used herbicide worldwide, and China produces 70% of the global consumption. Although many countries have banned PQ use, the number of patients with acute PQ poisoning due to oral ingestion or accidental use has been increasing yearly. The use of PQ is prominent in developing countries,[3,4] such as China. In fact, bibliometric analyses have shown 4328 publications on PQ from 1962 to 2015, of which 1971 were related to PQ poisoning.[5] There have been 338 publications on PQ poisoning in the United States and 159 in China.[5] Acute PQ poisoning is concerning and its consequences are serious. PQ rapidly accumulates in the lungs, kidneys, liver, muscles, and other tissues after it enters the body. The typical cause of death from PQ poisoning is pulmonary fibrosis with multiple organ failure.[6] Most PQ victims, including those who have ingested only a small amount, also gradually die, and those who swallow large doses usually only live for 72 hours. PQ causes oxidative stress, leading to systemic inflammatory response syndrome, which may cause multiorgan failure and eventually death.[7] In the majority of PQ cases, the cause of death is pulmonary fibrosis due to its progression.[8]

The alveolar–arterial partial pressure difference ($A\text{-}aDo_2$) refers to the difference between the alveolar and arterial oxygen partial pressure, with a reference value of 15 to 20 mmHg in normal young people, With an increase in age, the partial pressure difference also increases, but generally the highest difference is 30 mmHg. $A\text{-}aDo_2$ is an important indicator for determining lung ventilation and oxygen diffusion capacity, and is also an indicator for determining the ability of blood to extract oxygen from the alveoli. $A\text{-}aDo_2$ might also be an early predictor for evaluating the prognosis of PQ. However, to the best of our knowledge, the association between $A\text{-}aDo_2$ and acute PQ poisoning has not been published in the English literature. Therefore, we attempted to assess the predictive value of $A\text{-}aDo_2$ as a risk of death from PQ poisoning.[9] We collected cases of PQ poisoning in patients who were hospitalized and treated in the past 10 years. We collected data on arterial blood gas analysis that was completed on days 1, 3, 7, 14, and 21 after the onset of PQ poisoning. This study aimed to evaluate the relationship between $A\text{-}aDo_2$ and the prognosis of acute PQ poisoning.

Methods

Ethics statement

This retrospective study was approved by the Medical Ethics Committee of Guangzhou Occupational Disease Prevention and Treatment Hospital (Guangzhou Twelfth People's Hospital). Patients' medical records were retrospectively reviewed, all names in the records were hidden, and all information was securely protected. Written informed consent for publication was obtained from all individual participants included in the study. Only investigators could view the recorded information.[10] The reporting of this study conforms to the STROBE guidelines.[11]

Data collection

Our unit is an occupational disease prevention and treatment hospital, and is also a chemical poisoning rescue center for the

region. We performed a 10-year, observational, retrospective analysis of all patients who were admitted to our hospital after drinking PQ pesticide and who had already been discharged from hospital or had died from 1 January 2009 to 31 December 2018.[12] All patients were admitted to the hospital in accordance with standard medical emergency procedures.[13]

We recorded information, such as age, sex, symptoms, the amount of PQ ingested, a dithionite urine test for PQ, the time of the first gastric lavage, and the treatment outcome. Arterial blood gas analysis was required to be performed in the morning on days 1, 3, 7, 14, and 21. Patients with PQ poisoning were divided into two groups (survivors and non-survivors) according to their final treatment outcome. Patients with acute PQ poisoning usually die within a few weeks after PQ ingestion.[12] Therefore, an effective treatment was described as patients who survived more than 3 months after PQ poisoning, had stable vital signs, and had no evidence of progressive organ failure (especially the kidneys and lungs).[13] We also determined survival using medical records or telephone follow-up.

Measurement of PQ and A-aDo$_2$

PQ was measured in urine by a semi-quantitative test. The reagents used for urine PQ testing were 20 mg of sodium dithionite powder and 0.5 mL of strong ammonia. We determined urine PQ concentrations by colorimetric comparison with a standard colorimetric plate. Urine PQ was positive once the mixture of these reagents to urine turned blue.[14] The detection sensitivity was 3 μg/mL. Positive results were classified into five levels according to the color depth. Level 0 indicated that the color did not change, with a urine PQ concentration <3 μg/mL ($-$group). Level 1 was grass green or green, with a urine PQ concentration of 3 to 9 μg/mL ($+$group). Level 2 was light blue or blue, with a urine PQ concentration of 10 to 29 μg/mL ($++$group). Level 3 was dark blue, with a urine PQ concentration of 30 to 100 μg/mL ($+++$group). Level 4 was purple-black or even black, with a urine PQ concentration of >100 μg/mL ($++++$group).

The A-aDo$_2$ was calculated for each arterial blood gas by the following formula: A-aDo$_2$ = inspired oxygen $\times$ (barometric pressure $-$ vapor pressure of water) $-$ (partial pressure of arterial carbon dioxide/0.8) $-$ partial pressure of arterial oxygen, with 0.8 representing the respiratory quotient.[9] Therefore, we excluded patients with all factors that could potentially affect the outcome, such as uncorrected congenital heart disease, chronic lung disease (including asthma), neuromuscular disease, and patients who were already treated with oxygen.

For patients who could not recall the amount of PQ ingested, we estimated the oral dose from experimental experience. A small mouthful of PQ ingested was estimated to be 20 mL for men and 10 to 15 mL for women. A moderate mouthful of PQ ingested was estimated to be 40 mL for men and 30 mL for women. A large mouthful of PQ ingested was estimated to be 60 mL for men and 40 mL for women.[6]

The time lag after PQ ingestion refers to the time taken for patients to be treated in the hospital after being exposed to PQ.

Treatment protocols. Gastric lavage was carried out within 2 hours of herbicide intake when individuals presented to the emergency room. However, 250 mL of 20% mannitol mix with 30 g of fuller's earth was administered to those who had been intoxicated for up to 12 hours before admission.[10] Hemoperfusion was started as soon as possible after receiving the patient's consent. The patients accepted one to two courses of 3 hours of active charcoal containing hemoperfusion therapy every day

until a urine sodium dithionite test turned negative. Hemofiltration was carried out when acute renal failure occurred. Other major treatments used were fluid infusion and diuresis (furosemide 40–120 mg/day), anti-fibrosis (cyclophosphamide 0.2 g/day for 5–7 days for patients with severe lung injury), an immunosuppressant (methylprednisolone 240–500 mg/day for 10–14 days), and glutathione 2.0 g/day.[12]

Statistical analysis. The data are shown as mean ± standard deviation. We compared the amount of ingested PQ, time of first gastric lavage, exposure dose, A-aDo_2 on days 1, 3, 7, 14, and 21, and outcome of acute PQ poisoning between survivors and non-survivors. The chi-square test and analysis of variance were used for analyzing the various variables as appropriate. The Spearman rank method was used as a nonparametric measure of correlation between two variables.[15] Multivariate logistic regression analysis and receiver operating characteristics (ROC) curve analysis were used to examine the association of A-aDo_2 and the prognosis of acute PQ poisoning. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were performed using IBM SPSS software Version 24.0 (IBM Corp., Armonk, NY, USA). P values <0.05 were regarded as statistically significant.

Results

Patients' characteristics

From 1 January 2009 to 31 December 2018, 352 patients were included in the study. A total of 185 (52.56%) patients survived (survivor group) and 167 (47.44%) died (non-survivor group) of acute PQ intoxication. There were 177 men and 175 women, with a mean age of 31.18 ± 1.38 years (12–88 years). The mean time of visiting the hospital after PQ ingestion was 39.35 ± 56.03 hours (1–432 hours). The mean PQ dose was 36.84 ± 50.30 mL (0.3–500 mL). The mean hospital stay was 10.88 ± 10.48 days (0.5–86 days). Some of the patients had been treated in another hospital for several days before admission to our hospital. The mean A-aDo_2 on days 1, 3, 7, 14, and 21 was 3.64 ± 4.09, 5.19 ± 1.12, 4.81 ± 5.23, 6.94 ± 7.94, and 8.88 ± 13.62 mmHg, respectively.

All patients underwent urine sodium dithionite testing and 255 (72.44%) tested positive. Most of them had varying degrees of nausea and vomiting, oral mucosal ulceration, cough, upper abdominal pain, difficulty swallowing, chest tightness, shortness of breath, jaundice, and other system damage. Most of the 167 patients who died had severe fibrosis in both lungs.

Associations between various parameters and outcome of PQ poisoning

There was no difference in age between the survivor and non-survivor groups. However, the time lag after PQ ingestion was significantly shorter ($P = 0.006$) and the estimated ingestion amount of PQ was larger ($P < 0.001$) in the survivor group than in the non-survivor group. The mean A-aDo_2 was not different between the two groups on day 1. However, the mean A-aDo_2 was significantly different between the two groups on days 3 ($P = 0.026$), 7 ($P = 0.002$), 14 ($P < 0.001$), and 21 ($P = 0.034$) (Table 1). Different levels of urine PQ concentrations in the survivor and non-survivor groups are shown in Table 2. Spearman rank correlation analysis showed a significant positive correlation between PQ concentrations and the outcome (Spearman correlation coefficient = 0.400 ($P < 0.001$).

Risk factor analysis for survival of patients with acute PQ poisoning

From the beginning of acute PQ poisoning to day 21 after the onset of poisoning,

Table 1. Comparison of parameters between survivors and non-survivors.

Variable	Survivors (n = 185)	Non-survivors (n = 167)	*P* value
Age (years)	32.65 ± 13.84	33.04 ± 15.39	0.054
Time lag after PQ ingestion (hours)	31.25 ± 33.57	47.48 ± 63.14	0.006
Ingestion amount (mL)	20.09 ± 17.84	17.32 ± 25.14	<0.001
A-aDo_2 (mmHg)			
Day 1	2.76 ± 1.68	3.22 ± 1.85	0.839
Day 3	3.21 ± 1.85	5.90 ± 3.72	0.026
Day 7	11.35 ± 13.73	9.05 ± 7.32	0.002
Day 14	16.23 ± 13.48	18.44 ± 10.57	<0.001
Day 21	2.56 ± 1.48	30.74 ± 16.47	0.034

Values are mean ± standard deviation. The time lag after PQ ingestion, ingestion amount, and A-aDo_2 at different times were compared with the Mann–Whitney test (range of data).
PQ, paraquat; A-aDo_2, alveolar–arterial partial pressure difference.

Table 2. Urine paraquat concentrations in survivors and non-survivors.

	Outcome	
Positive PQ urine semi-quantitative test	Survivors (n = 185)	Non-survivors (n = 167)
−	121 (65.41)	55 (32.93)
+	53 (28.65)	51 (30.54)
++	8 (4.32)	32 (19.16)
+++	2 (1.08)	23 (13.77)
++++	1 (0.54)	6 (3.60)

Values are n (%).
PQ, paraquat.
The Spearman correlation coefficient was 0.400, $P < 0.001$.

A-aDo_2 in the non-survivor group gradually increased, but it did not change in the survivor group (Figure 1). We performed multivariate logistic regression analysis of A-aDo_2 to identify significant factors and treatment outcomes (Table 3). We found that A-aDo_2 on day 14 (OR = 2.077; 95% CI, 1.246–3.461; $P = 0.005$) and on day 21 (OR = 1.811; 95% CI, 1.272–2.579; $P = 0.001$) were independent risk factors for the survival of patients with acute PQ poisoning. Furthermore, we evaluated A-aDo_2 at different times for predicting the prognosis of patients with acute PQ poisoning using the ROC curve. The areas under the ROC curve of A-aDo_2 on days 21 and 14 were 0.998 and 0.975, respectively (Figure 2).

Discussion

PQ remains a popular pesticide in China. Acute PQ poisoning has high morbidity and mortality rates. There is still no specific antidote for acute PQ poisoning.[3,16] Many prognostic indicators for PQ intoxication have been identified, such as arterial blood gas analysis (pH, partial pressure of arterial carbon dioxide), lactate, amylase,[17–19] and a blood cell count, including leukocytes, neutrophils, and lymphocytes.

Our study showed that A-aDo_2 was a reliable predictive index of acute PQ poisoning. A-aDo_2 is an indicator of arterial blood gas analysis. A change in A-aDo_2 is related to the degree of lung damage. To the best of our knowledge, there have been no studies on A-aDo_2 as a prognostic indicator of PQ poisoning. In the first few hours of PQ intoxication, PQ cation radicals with a high affinity for the alveoli directly damage the lungs, and then cause death from respiratory failure.[15,20] Death from PQ poisoning is mainly associated with acute lung injury.[21] Therapies for PQ poisoning usually include diuretic, anti-oxidation, anti-inflammatory, anti-fibrotic, and clearing

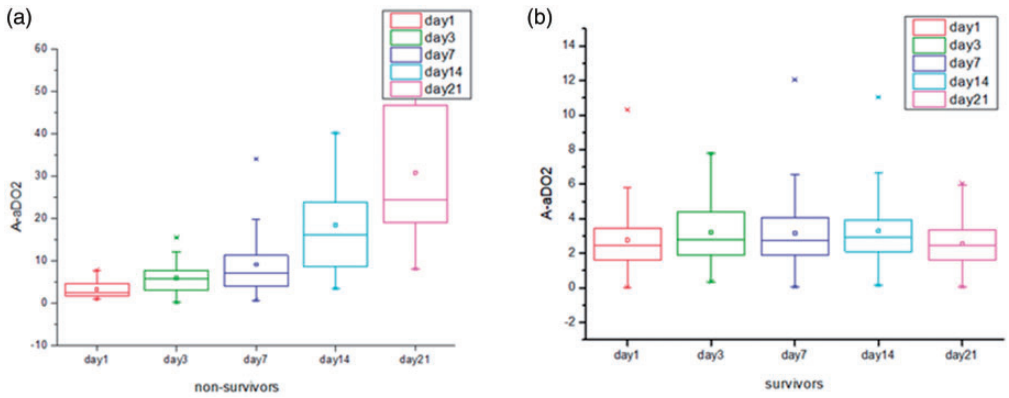

Figure 1. Changes in A-aDo$_2$ from days 1 to 21 after the onset of acute paraquat poisoning. Box plots show (a) that A-aDo$_2$ in the non-survivor group (a) gradually increase, but do not significantly change over time in the survivor group. The location of each outlier is indicated by an asterisk. A-aDo$_2$, alveolar–arterial partial pressure difference.

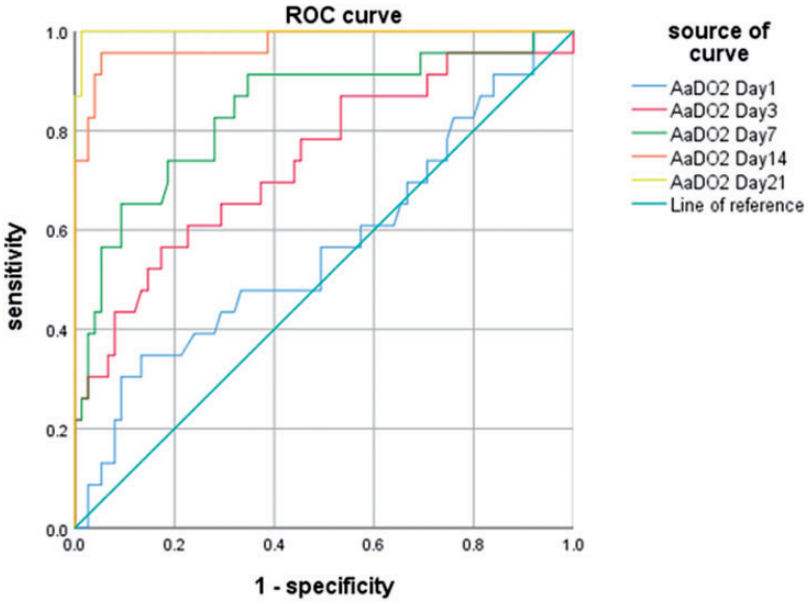

Figure 2. ROC curve showing A-aDo$_2$ at different times for prognostic prediction in patients with acute paraquat poisoning.
ROC, receiver operating characteristics; A-aDo$_2$, alveolar–arterial partial pressure difference.

plasma PQ measures, but there is still no effective method of treating patients with acute PQ poisoning.[10] As lung damage worsens, most patients with acute PQ poisoning patients cannot survive.

We previously analyzed the dynamic changes in A-aDo$_2$ in patients with PQ intoxication.[22] We found that A-aDo$_2$ was related to pulmonary injury and could be considered as an indicator for assessing

Table 3. Multivariate logistic regression analysis for identifying significant determinants of survival.

Variable		*P*	OR	95% CI	
Time lag after PQ ingestion (hours)		0.002	1.790	1.000	2.160
Ingestion amount (mL)		0.009	1.769	1.049	2.972
	Day 1	0.870	1.062	0.515	2.189
	Day 3	0.562	0.812	0.402	1.640
$A\text{-}aDo_2$	Day 7	0.733	0.921	0.576	1.474
	Day 14	0.005	2.077	1.246	3.461
	Day 21	0.001	1.811	1.272	2.579

PQ, paraquat; OR, odds ratio, CI, confidence interval; $A\text{-}aDo_2$, alveolar–arterial partial pressure difference.

the prognosis of PQ. Additionally, the peak time of organ damage in acute PQ poisoning was approximately on the 14th day. Therefore, we consider that $A\text{-}aDo_2$ has advantages over other indicators, such as pH, partial pressure of arterial carbon dioxide, lactate, amylase, the blood cell count, and corrected QT interval prolongation. Furthermore, we consider that the 14th day is important for determining whether treatment is successful. After the 14th day, $A\text{-}aDo_2$ values in the survivor group tended to be stable or showed a downward trend, but those in the non-survivor group continuously increased.

Our study showed that $A\text{-}aDo_2$ played an important role as a prognostic indicator for PQ poisoning. Therefore, $A\text{-}aDo_2$ could be a useful prognostic tool for assessing acute PQ poisoning. However, there are some limitations to this study. First, we did not describe the exact concentration of urine PQ, and plasma PQ concentrations were not determined because we do not have a validated test method of PQ in our institution. Therefore, only semi-quantitative results were obtained. Second, most of the successfully treated patients were exposed to low doses of PQ. Therefore, our success rate exceeded 50%. Finally, 352 patients with acute PQ were included for analysis in this study. However, only 255 (72.44%) patients were positive for the urine PQ colorimetric test because of the following reasons. First, some of the patients ingested a small amount of paraquat. Second, there was a long interval between the patients' onset of PQ poisoning and arrival to our hospital. We will continue to record our experience of PQ poisoning to improve its treatment.

In conclusion, our study shows that $A\text{-}aDo_2$ is a useful predictor for the survival of PQ poisoning in clinical practice, particularly on the 14th day after onset of poisoning.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Final review: Yu-Quan Chen and Yi-Min Liu
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Writing – review and editing: Yu-Quan Chen, Yu-Qiang Lin, Wen-Zhong Jiang, Yi-Min Liu, and Zhi-Qian Yang
Approval of the final manuscript: all authors

Availability of data and materials

We declare that the data described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching the participants' confidentiality.

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