Thinking Induced by Acute Kidney Injury of Diquat Poisoning: Cases Report

Yu-qi Tao, Jia-yi Zheng, Zi-chen Xie and Ke-yu Sun

Emergency Department, Minhang Hospital, Fudan University, Shanghai, China.

Clinical Medicine Insights: Case Reports
Volume 17: 1–5

DOI: 10.1177/11795476241288840

Sage

ABSTRACT: Diquat poisoning is a fatal condition that is becoming increasingly common. The mortality risk of patients taking lethal doses of diquat is extremely high. It typically leads to rapid dysfunction of multiple organs, including the kidneys, heart, lungs, and brain. Acute kidney injury is usually the first manifestation of this poisoning. However, the optimal treatment strategy for diquat poisoning remains uncertain. Additionally, the mechanism of multiple organ dysfunction syndrome caused by diquat poisoning may resemble the progression of sepsis. In this report, we present 3 cases of diquat poisoning, all of which resulted in death. We emphasize that acute kidney injury is the primary cause of death, and suggest that some strategies used in the treatment of sepsis could be beneficial in managing diquat poisoning-induced acute kidney injury.

KEYWORDS: Diquat poisoning, acute kidney injury, inflammation

RECEIVED: February 12, 2024. **ACCEPTED:** September 12, 2024.

TYPE: Case Report

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was sponsored by Natural Science Foundation of Shanghai (21ZR1456400) and Natural Science Foundation of Shanghai (22ZR1455000).

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHORS: Zi-chen Xie, Emergency Department, Minhang Hospital, Fudan University, 39 Xinling Road, Minhang District, Shanghai, 201100, China. Email: x_zc@fudan.edu.cn

Ke-yu Sun, Emergency Department, Minhang Hospital, Fudan University, 39 Xinling Road, Minhang District, Shanghai, 201100, China. Email: sunkeyu@fudan.edu.cn

Introduction

Diquat (DQ) is a highly lethal water-soluble herbicide known for its strong polarity. Exposure to a high dose of this herbicide can rapidly cause damage to multiple organs, such as the kidneys, gastrointestinal system, and neurologic system.[1]Previous studies have extensively investigated the mechanisms of organ damage induced by DQ.[2,3] Limited attention has been given to the kidney, despite one of the primary target organs affected by DQ poisoning.[4] This report presents 3 cases of DQ poisoning from the emergency department of Minhang Hospital, Fudan University, Shanghai, China. Despite receiving active treatment, all the patients eventually succumbed to the multiple organ dysfunction syndrome (MODS) caused by poisoning. We have obtained consent from the families of the patients to publish these cases.

Case Description

Case 1: A previously healthy 23-year-old female presented to the emergency department 4 hours after consuming approximately 100 mL of DQ (20 g/100 mL) by accident. She experienced gastrointestinal symptoms and received gastric lavage and hemoperfusion immediately upon arrival, other treatments include diuretics(furosemide injection), acid suppression, and gastric protection (PPI), antioxidant measures (acetylcysteine and high-dose vitamin C) have been implemented. In addition to abdominal tenderness, rebound pain, and oliguria (urine output of 150 mL/24 hours), she did not show any other symptoms or signs. Initial blood tests yielded almost normal results, and the *Poisoning Severity Score* (PSS) showed moderate toxication (PSS = 2) (Table 1). Toxicological analysis (result from Xuhui District Central Hospital, Shanghai) of the blood confirmed the presence of DQ, although the exact concentration was not measured. Considering the oliguria, it was suspected that the patient had already experienced acute kidney injury (AKI) before her arrival. Consequently, the patient was admitted to the emergency intensive care unit (EICU) and received treatment with hemoperfusion (HP) in conjunction with continuous veno-venous hemofdiailtration (CVVHDF). Regrettably, the patient's renal function did not show any signs of improvement. Around 30 hours later, she experienced difficulty in breathing and started foaming at the mouth. Point-of-care testing of arterial blood showed metabolic acidosis and an oxygenation index (PO_2/FiO_2 ratio) of 195 mmHg (Table 2), which indicated the presence of acute lung injury (ALI). Consequently, her condition fulfilled the diagnostic criteria for disseminated Intravascular Coagulation (DIC) and MODS. Bedside ECG monitoring showed sinus tachycardia with a rhythm of 130 bpm. Endotracheal intubation was performed to assist with invasive ventilator-assisted ventilation, while renal replacement therapy was maintained. Despite these interventions, there was progressive deterioration in the function of various organs, such as the liver, and a gradual decline in consciousness (PSS = 3) (Table 1). Approximately 48 hours after consuming DQ, the patient fell into a coma and went into shock, resulting in her eventual demise (PSS = 4).

Case 2: A 35-year-old male patient arrived at a local hospital 1.5 hours after ingesting approximately 100 mL of DQ (20 g/100 mL) accidently. Upon arrival, the medical staff performed gastric lavage and administered appropriate treatment (Other treatments mentioned in Case 1 have also been implemented). Subsequently, the patient was transferred to our

Table 1. Results of blood tests.

	CASE 1		CASE 2		CASE 3	
TIME AFTER POISONING (HOURS)	24	31	4	23	3	24
Scr (umol/L)	80	382	83	400	55	273
BUN (mmol/L)	2.95	11.24	5.85	15.6	3.31	8.99
eGFR-EPI	90.05	15.24	112.64	13.57	98.45	13.57
UA (umol/L)	406	341	563	471	374	471
Lac (mmol/L)	2.6	15	3.7	11.7	1.0	11.7
NTpro-BNP (pg/mL)	34	>35000	34	>35000	46	>35000
TnT (ngmL)	0.003	0.195	0.003	0.241	0.003	0.241
AST (U/L)	27	311	21	60	39	532
Mb (ng/mL)	37.43	>3000.0	<21.0	>3000.0	52.55	2254.2
CK (U/L)	56	1411	60	3693	340	9420
LDH (U/L)	468	4370	513	2651	251	1615
PT (s)	11.3	22.4	10.3	13.2	11.5	22.4
APTT (s)	28.4	—	23.9	46.3	29.3	70.7
FIB (g/L)	2.13	4.63	2.10	4.45	2.30	3.90
D-D (mg/L)	0.22	0.70	0.43	5.50	0.19	1.06
PLT ($\times 10^9$/L)	273	48	265	100	367	31

APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; D-D, D-dimer; eGFR-EPI, glomerular filtration rate-epithelium; FIB, fibrinogen; Lac, lactic acid; LDH, lactate dehydrogenase; Mb, myoglobin; NTpro-BNP, N-terminal pro-B-type natriuretic peptide; PLT, platelet count; PT, prothrombin time; Scr, serum creatinine; TnT, troponin T; UA, uric acid.

Table 2. Results of point-of-care testing of arterial blood.

	CASE 1		CASE 2			CASE 3		
TIME AFTER POISONING (HOURS)	4	30	6	11	34	3	24	65
PH	7.34	7.263	7.321	7.268	7.4	7.371	7.161	7.225
pO_2 (mmHg)	118	195	67.7	66.9	111	86.6	78.4	45.1
pCO_2 (mmHg)	21.5	28.9	48.3	34.3	34	33.2	32	36.9
FiO_2 (%)	21	100	21	61	100	21	61	100
pO_2/FiO_2	561.9	195	322.5	109.7	111	412.4	128.5	45.1

FiO_2, fraction of inspiration O_2; PH, potential of hydrogen; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen.

emergency department, 4 hours after the ingestion. He presented with symptoms of vomiting, chest pain, fatigue, limb numbness, and oliguria (urine output less than 100 mL in 4 hours), indicating a suspected case of AKI (PSS = 2). Upon admission to the EICU, the patient underwent treatment with HP and CVVHDF. Approximately 6 hours later, the individual experienced tachypnea, along with a low-grade fever, elevated heart rate and breathing rate. The physical examination revealed abdominal stiffness, pharyngeal hyperemia, and anuria. Point-of-care testing of arterial blood indicated a combination of metabolic alkalosis and respiratory alkalosis, with an oxygenation index of 322.5 mmHg (Table 2). Other blood test results were within almost normal limits (Table 1), and the concentration of DQ in the blood was not measured; 11 hours later, the patient experienced dyspnea and agitation despite receiving oxygen through a mask. Bedside ECG monitoring revealed sinus tachycardia with a 120-bpm rhythm and 95% SpO_2. Point-of-care testing revealed metabolic acidosis and a PO_2/FiO_2 ratio of 109.7 mmHg (Table 2), confirming the diagnosis of ALI and MODS. The patient underwent

endotracheal intubation and continued to receive renal replacement therapy. However, subsequent laboratory tests indicated ongoing damage to the kidneys, lungs, liver, and heart (PSS = 3) (Table 1). Supraventricular tachycardia could be seen in the bedside monitoring. After 34 hours, the patient developed irreversible shock and ultimately succumbed to the complications 41 hours after ingesting DQ (PSS = 4).

Case 3: A 16-year-old female patient who was suffer from mental illness was admitted to the emergency department 3 hours after consuming 100 mL of DQ (20 g/100 mL) for suicide. She mentioned inducing vomiting by drinking water before arriving at the hospital. Besides feeling tired, she did not display any additional symptoms or signs. Blood tests showed hypokalemia with 2.9 mmol/L, while all other parameters were within normal range (PSS = 1) (Table 1). Blood toxicological analysis confirmed the presence of characteristic fragments of DQ, although the specific concentration was not determined (result from Xuhui District Central Hospital, Shanghai). After 6 hours, the patient experienced anuria and AKI. To address this, HP was combined with CVVHDF and initiated (Other treatments mentioned above have also been implemented in this case). Subsequently, the patient was transferred to the EICU. Approximately 24 hours later, tests indicated the presence of ALI and abnormal coagulation function, while the AKI did not show signs of recovery. Bedside ECG monitoring revealed sinus tachycardia with a rhythm of 135 bpm. Consequently, the diagnosis of MODS was established. Despite this diagnosis, the patient remained asymptomatic, except for experiencing sensations of coldness and fatigue. After thirty-four hours, the patient developed delirium, and subsequent tests showed worsening damage to various organs, such as the liver, cardiac muscle, and nervous system. Supraventricular tachycardia also showed with 155 bpm rhythm. Arterial blood testing revealed the presence of metabolic acidosis (Table 2) (PSS = 3), even though haemodialysis was ongoing and re-hemoperfusion therapy (Table 1) had been initiated. Around 65 hours after ingestion, the patient fell into a coma and went into shock, ultimately resulting in her death (PSS = 4).

Discussion

The underlying processes observed in these cases exhibited remarkable similarities. The administration of DQ led to the development of AKI, and despite taking appropriate measures, MODS occurred. Early reports have emphasized similar cases that highlight the significant impact of refractory AKI on patient mortality.[5-7]

According to the consensus of Chinese experts,[8] diquat poisoning can be classified into 3 levels based on the oral dose of diquat. The ingestion of 1 g to 12 g of diquat cation is moderately to severely toxic, with acute renal failure being the most common. The main manifestation of DQ poisoning, at the same time, is that the higher the dose, the higher the mortality. When ingestion is greater than 12 g of diquat cation, it is defined as explosive poisoning and most patients die within 24 to 48 hours. The International Programme on Chemical Safety defines the lethal dose of diquat as 6 to 12 grams.[2] The 3 patients mentioned in this paper all ingested cationic doses of approximately 10 g diquat, which is very close to 12 g. The poor prognosis for patients is therefore to be expected. Second, the consensus still states that the optimal time for gastric lavage is 1 hour after exposure to the poison, and that adsorbates such as activated carbon, clay, etc. should be added at the same time. However, 3 patients arrived at the hospital longer than the optimal time for gastric lavage, and in one of these cases, gastric lavage was performed at other hospital without adsorbates. The consensus also states that blood purification therapy should be performed within 2 to 4 hours of exposure to the poison. However, the arrival times of the 3 patients at our hospital were close to or much longer than 4 hours. Also, in comparison to the successful treatment cases,[9] aside from the time-window of renal replacement therapy and gastrolavage, the model of the perfusion device utilized may have contributed to the differences in treatment efficacy. We employed the HA230 perfusion device, whereas the successful cases utilized the HA380 model. According to their specifications,[10] these devices possess distinct functions and capabilities concerning protein filtration. Research indicates that the HA380 device is more effective in removing inflammatory factors, while the HA230 is primarily designed for addressing drug poisoning, which corresponds with the underlying mechanisms of action. Furthermore, we implemented continuous venovenous hemodiafiltration (CVVHDF) but only utilized a single perfusion device at any given time. The extended use of a single perfusion device may have compromised the perfusion effect, ultimately increasing the likelihood of treatment failure. As a result, all 3 patients had problems beyond the optimal time window for treatment. These deficiencies in the treatment process may be associated with poor outcomes. However, there is currently no antidote for diquat poisoning. This lack may be related to the unclear mechanism of Diquat-induced MODS.

The mechanism by which DQ induces AKI remains uncertain and can be attributed to both direct and indirect injuries. Previous studies have shown that DQ is absorbed and metabolized in the kidneys, resulting in the direct destruction of renal cells and the rapid onset of severe damage.[11,12] This process is associated with the activation of reactive oxygen species (ROS).[13,14] DQ, a bivalent cationic compound with strong polarity,[15] has a chemical structure that exhibits high oxidation-reduction (REDOX) potential. This leads to the rapid production of abundant ROS when it is poisoned.[16] DQ is reduced to an unstable free radical form ($DQ2^{+}$),[17] which is primarily involved in REDOX processes.[16] Upon entering cells and localizing within mitochondria, DQ consumes significant amounts of nicotinamide adenine dinucleotide phosphate (NADPH), leading to the generation of ROS and reactive nitrogen species.[3]

This ultimately results in the death of renal cells. It has been reported that the absorption and excretion of DQ occur relatively quickly,[18] which may explain the inability to detect DQ in case two. Therefore, it is recommended to initiate renal replacement therapy for high-dose DQ poisoning within 2 to 4 hours of ingestion.[8] However, considering the time it takes for patients to take drugs to the hospital, it becomes challenging to prevent the occurrence and progression of AKI.

Following mitochondrial damage, the recruitment of inflammatory cells occurs, along with the subsequent release of inflammatory mediators such as interleukin-6 (IL-6) and interleukin-17 (IL-17).[3] These inflammatory factors stimulate an oxidative stress response, leading to the activation of nuclear factor kappa B (NF-κB) and the upregulation of apoptotic gene expression, ultimately resulting in renal injury. This mechanism helps explain why AKI continues to develop despite renal replacement therapy. The release of large amounts of inflammatory factors can lead to vascular endothelial injury, subsequently altering kidney permeability and potentially affecting the entire body, resulting in third-space fluid leakage. Furthermore, when irreversible damage to kidney cells occurs, it can disrupt the body's water-electrolyte balance, manifesting as hyperosmolarity and hypokalemia. However, based on the 3 cases we have described, the patients' conditions deteriorated rapidly in the later stages. The exudation of third-space fluids (such as pleural and pericardial effusions), in addition to subcutaneous edema, could not be monitored in a timely manner, making it challenging to maintain a balanced water-electrolyte equilibrium. This ultimately leads to insufficient blood volume in the patients, further exacerbating damage to multiple organs, including the kidneys. For this since, it is interesting to note that the mechanism of DQ-induced AKI shares similarities with the early stages of sepsis, which is characterized by an inflammatory storm or cytokine storm. Therefore, treatment strategies for sepsis-related acute kidney injury (S-AKI) may be applicable to DQ-induced AKI.

Recent studies have highlighted the significance of ferroptosis, a type of cell death associated with ROS, in S-AKI.[19] It is plausible to consider that ferroptosis could also occur in cases of DQ poisoning, indicating that drugs targeting pathways related to ferroptosis could be beneficial in treating DQ-induced AKI. Moreover, post-translational modification (PTM) treatments, commonly employed in cancer therapy, have shown promise in sepsis treatment,[20] suggesting their potential effectiveness in cases of DQ poisoning as well. Additionally, regulating cell death (RCD) is also considered a promising approach for sepsis treatment and may have similar implications in cases of DQ poisoning.[21]

In conclusion, addressing the development of AKI is crucial in reducing mortality rates associated with DQ poisoning. However, it is important to note that solely implementing renal replacement therapy may not be sufficient, similar to sepsis. The sepsis-like inflammatory responses observed in DQ poisoning warrant further investigation as a potential focal point, aiming to improve outcomes in cases of acute DQ poisoning.

Acknowledgements

The authors thanks Dr Ke-yu Sun, Fudan University, China, for his technical assistance for this report.

Author contributions

Ke-yu Sun has involved in conceptualization. Jia-yi Zheng has involved in data curation. Ke-yu Sun and Zi-chen Xie have involved in funding acquisition and writing-review and editing. Yu-qi Tao has involved in investigation, methodology, validation, visualization, and writing-original draft. Zi-chen Xie has involved in software.

ORCID iDs

Jia-yi Zheng https://orcid.org/0009-0009-2236-6074
Ke-yu Sun https://orcid.org/0000-0001-7878-3226

REFERENCES

1. Okonek S, Hofmann A. On the question of extracorporeal hemodialysis in diquat intoxication. *Arch Toxicol* 1975;33:251-257.
2. Wang J, Li ZX, Yang DD, et al. Diquat determines a deregulation of lncRNA and mRNA expression in the liver of postweaned piglets. *Oxid Med Cell Longev* 2019;2019:9148535.
3. Choi SE, Park YS, Koh HC. NF-kappaB/p53-activated inflammatory response involves in diquat-induced mitochondrial dysfunction and apoptosis. *Environ Toxicol* 2018;33:1005-1018.
4. Xing J, Chu Z, Han D, et al. Lethal diquat poisoning manifesting as central pontine myelinolysis and acute kidney injury: a case report and literature review. *J Int Med Res* 2020;48:300060520943824.
5. Aloise DM, Memon A, Zaldivar A. Diquat herbicide organophosphate poisoning and multi-organ failure: a case report. *Cureus* 2022;14: e27241.
6. Guck D, Hernandez R, Moore S, et al. Rapid glomerulotubular nephritis as an initial presentation of a lethal diquat ingestion. *Case Rep Nephrol* 2021;2021:4723092.
7. Vanholder R, Colardyn F, De Reuck J, et al. Diquat intoxication: report of two cases and review of the literature. *Am J Med* 1981;70:1267-1271.
8. Zhang J, Hao F, Tian Y, et al. Expert consensus on the diagnosis and treatment of acute diquat poisoning. *Chin J Emerg Med* 2020;29:10.
9. Chen Y, Ou Z, Zhang R, et al. Case report: successful outcome of a young patient with rhabdomyolysis and shock caused by diquat poisoning. *Front Med* 2023;10:1116912.
10. Yang J, Ji D, Zhu Y Q, et al. Hemoperfusion with HA380 in acute type A aortic dissection patients undergoing aortic arch operation (HPAO): a randomized, controlled, double-blind clinical trial. *Trials* 2020;21:954.
11. Tomita M. Comparison of one-electron reduction activity against the bipyridylium herbicides, paraquat and diquat, in microsomal and mitochondrial fractions of liver, lung and kidney (in vitro). *Biochem Pharmacol* 1991;42:303-309.
12. Lock EA. The effect of paraquat and diquat on renal function in the rat. *Toxicol Appl Pharmacol* 1979;48:327-336.
13. Zhang H, Liu Y, Fang X, et al. Vitamin D(3) protects mice from diquat-induced oxidative stress through the NF-kappaB/Nrf2/HO-1 signaling pathway. *Oxid Med Cell Longev* 2021;2021:6776956.
14. Rogers LK, Bates CM, Welty SE, et al. Diquat induces renal proximal tubule injury in glutathione reductase-deficient mice. *Toxicol Appl Pharmacol* 2006;217:289-298.
15. Lewinsohn E, Gressel J. Benzyl viologen-mediated counteraction of diquat and paraquat phytotoxicities. *Plant Physiol* 1984;76:125-130.
16. Fussell KC, Udasin RG, Gray JP, et al. Redox cycling and increased oxygen utilization contribute to diquat-induced oxidative stress and cytotoxicity in Chinese hamster ovary cells overexpressing NADPH-cytochrome P450 reductase. *Free Radic Biol Med* 2011;50:874-882.
17. Magalhaes N, Carvalho F, Dinis-Oliveira RJ. Human and experimental toxicology of diquat poisoning: toxicokinetics, mechanisms of toxicity, clinical features, and treatment. *Hum Exp Toxicol* 2018;37:1131-1160.

18. Wu Y, Cui S, Wang W, et al. Kidney and lung injury in rats following acute diquat exposure. *Exp Ther Med* 2022;23:275.
19. Wu Z, Deng J, Zhou H, et al. Programmed cell death in sepsis associated acute kidney injury. *Front Med* 2022;9:883028.
20. Chang P, Li Y. Editorial: targeting protein post-translational modifications (PTMs) for diagnosis and treatment of sepsis. *Front Immunol* 2022;13:856146.
21. Qu M, Wang Y, Qiu Z, et al. Necroptosis, pyroptosis, ferroptosis in sepsis and treatment. *Shock* 2022;57(6):161-171.