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CASE REPORT

Urea Fertilizer Poisoning-induced Multiorgan Failure: A Case Report

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Abstract

Background: Urea agricultural products normally have low toxicity. However, most of the severe poisoning occurs after urea ingestion, which causes gastrointestinal symptoms. There is no robust evidence about inhalation or topical exposure; however, in animals, it has been documented dyspnea, methemoglobinemia, carboxyhemoglobin, hemorrhages, and brain degenerative changes.
Case report: A 31-year-old male without medical history had a fainting episode prior to the use of urea fertilizer. Laboratory tests showed a progressive increase in renal function, from 1.47 mg/dl up to 10 mg/dl requiring renal replacement therapy, and remarkably high aminotransferase levels. Also an aspartate aminotransferase and alanine aminotransferase at 10150 U/L and 2150 U/L, were reported respectively. The clinical manifestations progressed to respiratory failure, requiring invasive mechanical ventilation for 10 days with successful extubation and a return to normal saturation without supplemental oxygen.
Discussion: Urea poisoning due to agricultural product use is a rare condition. In this exceptional case, our patient presented with a life-threatening condition. Even though it is not well-established as a standard treatment, management with intravenous methylene blue can improve the symptoms associated with methemoglobinemia, provide breathing support, and prevent renal damage or the use of renal replacement therapy in cases of acute renal failure.
Conclusion: Reports of urea herbicide poisoning are extremely rare, and little is known about how to effectively manage urea poisoning as it normally presents mild symptoms. Correct identification of the agricultural product causing the poisoning is crucial to direct therapeutic efforts.

Key words: Fertilizers; Urea; Poisoning; Toxicity; Methylene Blue.

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INTRODUCTION

Fertilizer has been used for many years to supply plant nutrients. There are three main macronutrients, phosphorus (P), potassium (K), and nitrogen (N) [1]. Organic nitrogen-based fertilizer includes ammonium (NH_3), ammonium nitrate (NH_4NO_3), and urea ($CO(NH_2)_2$) [1]. Swallowing, inhaling, or touching fertilizer can lead to poisoning and trigger a lot of symptoms, such as gray or blue-colored fingernails, burning skin, throat, nose, or eyes, dizziness, fainting, shock, seizures, shortness of breath, stomach pain, nausea, vomiting, or cramps [2].

Urea also possesses herbicidal properties because excessive application may be detrimental to plants [3]. In addition, it can be harmful for humans, too. The alanine derivatives from urea metabolism are potent hemoglobin oxidants, so methemoglobinemia as well as hemolysis have been documented. In this scenario, methylthioninium chloride (methylene blue) should be used intravenously in patients with methemoglobin concentrations >30% or acute symptoms compatible with methemoglobinemia [4]. Urea herbicides normally have low toxicity; most of the severe poisoning occurs after urea ingestion, causing nausea, vomiting, diarrhea, and abdominal pain. There is no robust evidence or reports about inhalation or topical exposure [5]. Some acute effects of urea poisoning documented in animals included dyspnea, methemoglobinemia, and carboxyhemoglobin in the intratracheal route and brain degenerative changes, hemorrhages, and dyspnea in the oral route [6].

There is a lack of scientific evidence about urea poisoning in humans. There is only one case report about urea herbicide poisoning in Sri Lanka in a 15-year-old girl [7]. In addition, a few other reports have been made regarding intoxication by a urea derivative product, bromvalerylurea, which is included in over-the-counter analgesics and is often a product of choice for overdoses in suicidal attempts and in which numerous life-threatening adverse events have been described [8-10].

We presented a case of poisoning by organic fertilizer based on ureic nitrogen, phosphate, and potassium.

CASE REPORT

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A 31-year-old male without medical history had a fainting episode prior to the use of 18-18-18 fertilizer (18.58% total nitrogen (15.5% ureic nitrogen, 0.84% nitric nitrogen, 2.24% ammoniacal nitrogen), 18.7% water soluble phosphate, and 18.6% water soluble potassium oxide) during labor activities in a rice field. Initial vital signs showed a blood pressure of 110/85 mmHg, a heart rate of 134 beats per minute, a breath rate of 26 breaths per minute, a temperature of 36 °C, and an oxygen saturation of 90%. The patient was in poor general condition, presenting cyanosis, skin paleness, dehydration, diaphoresis, drowsiness, miotic pupils, hyperemic conjunctiva, dyspnea, breaths with the use of accessory muscles, bilateral cracklings, and a bladder catheter showing hematuria.

Initial laboratories (Table 1) showed elevated leukocytes, neutrophilia, significant transaminitis, acute kidney injury, electrolyte disorder with hyperkalemia, electrocardiogram with sinus tachycardia and left bundle branch block, arterial blood gas with acute metabolic acidosis, hyperlactatemia, and severe oxygenation disorder, and a urine panel drug test positive for THC.

The patient's clinical manifestations were not compatible with any pure toxidrome. However, the emergency medicine team considered an anticholinergic syndrome. The patient was treated in a resuscitation room with oxygen supplemented with a non-rebreather mask at 10 liters per minute. Nevertheless, the patient progressed to respiratory failure and required orotracheal intubation. Due to the multiple medical requirements, a central venous catheter was placed, and the patient was transferred to an intensive care unit (ICU).

After orotracheal intubation, the patient presented a decrease in blood pressure up to 86/69 mmHg, so he was treated with Norepinephrine 0.2 mcg/kg/min and subsequently with dobutamine 2.5 mg/kg/min to improve renal perfusion, achieving an increase in blood pressure up to 101/77 mmHg. Also, he was treated with methylene blue (1 mg/kg) considering pallor, cyanosis, weakness, metabolic acidosis, and central nervous system depression, to avoid or treat methemoglobinemia due to the non-availability of co-oximetry to confirm diagnosis.

Thorax radiography reported bilateral interstitial opacities suspicious for lung edema, which were associated with acid

Table 1. Record of Blood Investigation of the Patient

	Units	Day of poisoning	Two days after poisoning	Five days after poisoning	Six days after poisoning	Ten days after poisoning	15 days after poisoning	18 days after poisoning	Discharged day
Leukocytes	10^3/mm^3	46.01	28.81	16.65	15.95	14.02	18.50	37.430	36.28
Neutrophiles	%	96	96	88	92	86.5	84	96.4	89.4
Hemoglobin	g/dl	15.4	14.2	12.4	11.8	11.1	10	10.5	8.3
Plaquettes	10^3/mm^3	328	218	165	155	162	304	282	219
Serum electrolytes									
	Units	Day of poisoning	Two days after poisoning	Five days after poisoning	Six days after poisoning	Ten days after poisoning	15 days after poisoning	18 days after poisoning	
Potassium	mmol/L	6.11	6.84	4.5	4.5	4.0	3.6	4.6	
Sodium	mmol/L	139.8	138.8	144	145	146	140	138	
Liver function test									
	Units	Day of poisoning	Two days after poisoning	Six days after poisoning	13 days after poisoning				
AST	U/L	10150	7059	3051	492				
ALT	U/L	2150	1930	2303	284				
Renal function test									
	Units	Day of poisoning	Two days after poisoning	Five days after poisoning	Six days after poisoning	Ten days after poisoning	15 days after poisoning	18 days after poisoning	
Creatinine	mg/dl	1.47	3.06	4.2	4.7	6.0	10	6.2	
BUN	mg/dl	31.5	35.1	39	46	82	95	52	
Arterial Blood Gas									
	Units	Day of poisoning	Two days after poisoning		Five days after poisoning	Six days after poisoning	Ten days after poisoning	13 days after poisoning	
Lactate	mmol/L	7.6	4.4	1.4	1.6	2	1.32	0.9	
pH		7.10	7.15	7.20	7.38	7.39	7.44	7.47	
pO2	mmHg	65	85	52	88	59	117.6	82.4	
pCO2	mmHg	35	55	58	49	36	38.2	33	
HCO3	mmol/L	11.2	19.1	22.5	23	22	26.3	24.2	
BE	mmol/L	-17.9	-10.5	-6.5	-1.9	2.7	-26.3	0.4	

base and electrolyte disturbances and anuria. The patient fulfilled the dialytic criteria, so it was decided to start renal replacement therapy every other day with a femoral catheter. Additional laboratory tests evidenced significant elevated lactate dehydrogenase (15430 U/L), human immunodeficiency virus and treponemal test non-reactive, and hepatitis B surface antigen negative.

On day three, the medical group tried to reduce analgesics and wean the patient, but the patient presented a new episode of dyspnea and oxygen desaturation. A computed tomography of the chest showed chemical pneumonitis and a bilateral pleural effusion (Figure 1).

Urine cultures were positive for *Enterococcus Faecalis*, and the patient was treated with ampicillin sulbactam (250 mg IV every 8 hours) for three days, followed by piperacillin tazobactam (2.5 gr IV every 8 hours) for five days. He started pulse-steroid therapy because he was suspicious of a lupus flare.

On day ten, the patient was satisfactorily extubated, and the antimicrobial treatment was changed to vancomycin and meropenem. The patient continued medical treatment in the ICU. Subsequently, on day 17, the patient had a fever and a raised level of leukocytosis, suggesting a nosocomial infection due to the change in antimicrobial to cefepime (2 g IV each 8 hours), the removal of invasive devices, and polycultures. During hospitalization, hemoglobin levels dropped from 15.4 g/dl to 8.3 g/dl. In addition to an extremely important level of lactate dehydrogenase and a high ALT, which may suggest hemolytic anemia, no reticulocyte count or Coombs' test was requested, and the patient did not require a blood transfusion. The patient continued hospitalization for three more days with the same medical management. Unfortunately, the patient and his wife requested voluntary discharge from the hospital. For weeks, we checked the registry to verify new admissions for the patient and tried to contact him by telephone, but it was not possible.

DISCUSSION

Urea poisoning due to fertilizer or herbicide use is a rare condition [3]. Normally, urea produces low toxicity after swallowing, inhaling, or touching [2], but in this exceptional case, our patient presented a life-threatening condition after using an organic fertilizer.

Only a case report about urea herbicide poisoning has been described in scientific literature, reporting a 15-year-old girl, who had self-ingestion of a substituted urea herbicide (Diuron), presenting dizziness, faintness, vomiting, and oxygen desaturation, and subsequently developed methemoglobinemia (methemoglobin level

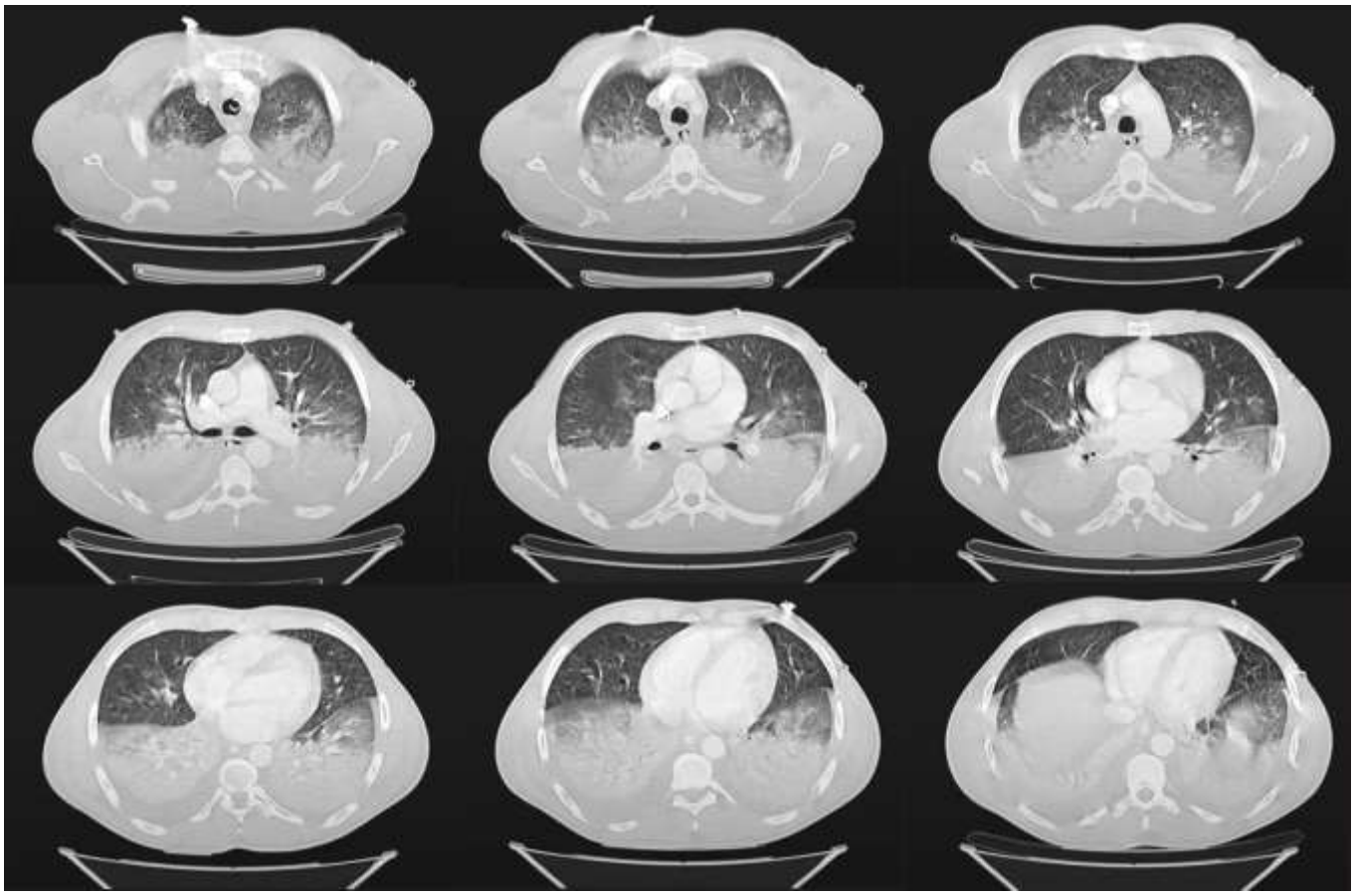

Figure 1. Axial Computed Tomographic Slices in the Pulmonary Window Show Ground Glass Opacities with a Tendency toward Bronchial Alveolar Consolidation, a Predominance in the Bases, and the Presence of Fluid Compatible with Bilateral Pleural Effusion.

40%), requiring the use of intravenous methylene blue to obtain a drop in methemoglobin level to 15%. She presented a decrease in hemoglobin levels from 12.6 g/dl to 6.7 g/dl confirming induced hemolytic anemia and requiring three units of packed red cell transfusion [7]. Our case presented some similarities, first, the initial clinical poor condition and desaturation, but, in our case, early orotracheal intubation was required to secure the airway. Second, both patients required intravenous methylene blue, but in our case, this management was preventive to prevent methemoglobinemia. Third, both patients develop anemia; in our case, the patient presented a decrease in hemoglobin levels of 15.4 g/dl to 8.3 g/dl during hospitalization, and due to the lack of laboratories, it is not possible to confirm it, but the presence of concomitant hemolytic anemia is probable. It is important to highlight that this case report presented a poisoning after the use of organic fertilizer, assuming contact and inhalation routes for poisoning.

There are other types of herbicidal agents that can cause different symptoms, some of which are extremely dangerous and have fatal outcomes. The most serious of all herbicide poisonings is paraquat, a lethal agent that produces symptoms after skin contact, inhalation, or ingestion, whether intentional or accidental [11]. Unfortunately, this herbicide does not have any antidotes, and after lethal dose ingestion, the worst outcome is expected [11]. Clinical symptoms may vary according to exposure and dose; smaller quantities usually lead to toxicity to the kidneys and lungs, can cause renal failure, and can cause lung cell damage, decrease gas exchange, and cause respiratory impairment, going first for acute alveolitis and later for secondary lung fibrosis. If the route of poisoning is swallowing, it can cause gastrointestinal mucosal lesions and perforations. High quantities cause hypoxia, shock, and metabolic acidosis, resulting in fulminant organ failure [12]. There is no specific treatment for paraquat poisoning; however, the use of N-acetylcysteine, vitamin C, salicylate, and dexamethasone is frequent, and different drug cocktails have failed to reduce mortality. Renal replacement therapy is frequent due to renal failure; the use of oxygen therapy and orotracheal intubation are palliative measures considered to treat respiratory failure because they worsen pulmonary injury [13]. Due to clinical manifestations, at some point during hospitalization in the ICU, the medical staff considered poisoning with a different agent and thought about paraquat as the cause of this condition. However, in the interrogation of the patient and family members, they reaffirmed the use of the 18-18-18 fertilizer exclusively. Notice that the patient had an early initiation of oxygen therapy and, subsequently, an orotracheal intubation, presenting an improvement in respiratory pattern and achieving extubation and withdrawal of oxygen supplementation without developing pulmonary fibrosis, an event that is not compatible with paraquat intoxication.

Normally, other types of agricultural agents like pesticides, mainly composed of organophosphates and carbamates, are more common and more dangerous, producing cholinergic syndrome after cutaneous exposure, inhalation, or ingestion [14]. In this case, the clinical symptoms were not consistent with a pure toxidrome after the fertilizer contact. However, it is correct to analyze a range of options in the context of an intoxicated farmer because of the number of products they use daily and the high toxic potential of each one.

CONCLUSION

Severe toxicity from urea fertilizer or herbicides is an extremely rare condition in humans. The primary urea exposure route is oral; however, other routes like inhalation and cutaneous can be considered, as well as the variability in symptoms. Correct identification of the agricultural product causing the poisoning is crucial to direct therapeutic efforts. Even though it is not well established as a standard treatment, management with intravenous methylene blue can improve the symptoms associated with methemoglobinemia.

Ethics: The patient provided informed written consent prior to study enrollment.

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REFERENCES

1. Stewart RC. Fertilizer [Internet]. 2023. Available from: https://www.britannica.com/topic/fertilizer. (Accessed 8 August 2023).
2. MedlinePlus. Plant fertilizer poisoning [Internet]. 2021. Available from: https://medlineplus.gov/ency/article/002841.htm. (Accessed 8 August 2023).
3. Gupta RC, Crissman JW. Agricultural Chemicals. Haschek and Rousseaux's Handbook of Toxicologic Pathology. 2013:1349–72.
4. Hancı V, Yurtlu S, Ayoğlu H, Erdoğan G, Dilek R, Deniz Y, Özkoçak I. Oral Intoxication By Fertiliser With Ammonium Nitrate And Ammonium Sulfate: Atypical İntake (Case Report). Haydarpasa Numune Med J. 2015;55(3): 208-211
5. Dickerson AS, Lee JS, Keshava C, Hotchkiss A, Persad AS. Assessment of Health Effects of Exogenous Urea: Summary and Key Findings. Curr Environ Health Rep. 2018;5:205–12.
6. National Center for Biotechnology Information. Urea [Internet]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/1176. (Accessed 8 August 2023).
7. Weerasinghe WS, Gawarammana IB, Colambage A. Substituted urea herbicide (Diuron) induced haemolytic anemia: A case of unknown complication in humans. Asia Pac J Med Toxicol. 2019;8(4):136-9.
8. Ishikura K, Katayama K, Hara A, Kotani H, Suzuki K, Kaneko T, et al. A case of acute bromvalerylurea intoxication that was successfully treated with direct hemoperfusion. CEN Case Reports. 2021;11:269–72.
9. Otani N, Hifumi T, Kitamoto T, Kobayashi K, Nakaya N, Tomioka J. Current state of drug analysis in Japanese emergency departments: a nationwide survey. Acute Med Surg. 2020;7:e566.

10. Taura M, Asai J, Yamazato S, Kanehisa F, Masuda K, Katoh N. Anaphylaxis due to bromovalerylurea. J Dermatol. 2015;43:707–8.
11. Centers for Disease Control and Prevention (CDC). Facts about Paraquat [Internet]. 2018. Available from: https://emergency.cdc.gov/agent/paraquat/basics/facts.asp. (Accessed 10 August 2023).
12. Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. Br J Clin Pharmacol. 2011;72:745–57.
13. Lin XH, Pan HY, Cheng FJ, Huang KC, Li CJ, Chen CC, et al. Association between liberal oxygen therapy and mortality in patients with paraquat poisoning: A multi-center retrospective cohort study. PLoS One. 2021;16:e0245363.
14. Bird S. Organophosphate and carbamate poisoning. [Internet]. 2023. Available from: https://www.uptodate.com/contents/organophosphate-and-carbamate-poisoning/print. (Accessed 11 August 2023)