ASIA PACIFIC JOURNAL of MEDICAL TOXICOLOGY
APJMT 13;3 http://apjmt.mums.ac.ir September 2024

CASE REPORT

Successful Management of Acute Kidney Injury in a case of Herbicide 2,4 Dichlorophenoxy Acetic acid Poisoning

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Abstract

Introduction: The compound 2,4 Dichlorophenoxyacetic acid (2,4-D) is present in most combinations of herbicides and is widely used by farmers in India, especially against weeds in cereal crops. Inadequate history regarding deliberate intoxication, indistinct clinical presentation, and unavailability of diagnostic facilities to detect and estimate the agent make it a significant concern in poisoning as it mimics one of the commonest poisoning which is organophosphorus poisoning. The therapy and management of this poisoning as well as prognosis of patients are not well described due to the paucity of cases in published literature.

Case report: We present a case of 2,4-D poisoning with a successful clinical outcome and highlight the challenges faced in management. Our patient (a 41-year-old farmer) had a stormy clinical course in the hospital with acute kidney injury developing after a few days; he received supportive therapy along with renal replacement therapy in the form of hemodialysis. He however recovered completely and was well at follow-up.

Discussion: The toxicity of 2,4 D poisoning mimics the common organophosphorus poisoning in terms of symptoms. Nephrotoxicity has been described mainly due to tubular toxicity though this may manifest later in the course of hospitalization. Early initiation of alkaline diuresis not only augments the elimination of toxins but also prevents nephrotoxicity. The worsening toxin-induced acute kidney injury/acute renal failure should be promptly managed by hemodialysis, as it also helps in the elimination of 2,4-D.

Conclusion: 2,4-D poisoning remains a significant clinical challenge due to its non-specific presentation. This article contributes to the limited available literature on this potentially fatal condition highlighting the successful management of a severe case through a multi-modal approach involving alkaline diuresis, hemodialysis, and potentially corticosteroids.

Key Words: Herbicide, 2,4 Dichlorophenoxyacetic acid, Acute kidney injury, Hemodialysis

How to cite this article: Nayak Rao Sh, KK A, N PK. Successful Management of Acute Kidney Injury in a case of Herbicide 2,4 Dichlorophenoxy Acetic acid Poisoning. *Asia Pac J Med Toxicol* 2024; 13(3): 121-124.

INTRODUCTION

Chlorinated phenoxy compounds are widely used as herbicides all over the world. 2,4 Dichlorophenoxyacetic acid (2,4-D) is present in most combinations of herbicides and is widely used by farmers, especially against weeds in cereal crops. Few cases of chronic cutaneous/inhalational occupational exposure and deliberate oral poisoning have been reported [1-15]. Fewer self-poisoning cases have been reported worldwide with a guarded prognosis [1-8]. Though the lethal dose is still not well defined, generally 6.5g is considered the lethal dose of ingestion according to a few reported cases, and plasma concentration is above 447 mg/liter [13]. Following oral ingestion, it is readily absorbed and distributed widely over the tissues. At toxic doses, it affects all vital organs like the gastrointestinal tract, renal, hepatic, nervous system, cardiovascular, and neuromuscular systems leading to Multi Organ Dysfunction Syndrome (MODS) [1-15]. Inadequate history regarding the deliberate intoxication, distinct clinical presentation, and unavailability of diagnostic facility to detect and estimate the agent makes it a major concern in poisoning as it mimics organophosphorus poisoning at presentation in the emergency room (ER) [1]. Here, we present a case of 2, 4-D poisoning and the challenges faced in management by successfully using various management techniques with a brief review on the varied clinical presentations and the treatment measures provided with the outcome of various reported cases.

CASE PRESENTATION

A 41-year-old farmer was referred to us from a regional health center with an alleged history of suicidal ingestion of herbicide 2,4 D (2,4 D amine salt 58%) of approximately ~100 ml, following which he was brought to the ER. He had apparently ingested the toxin mixed with alcohol about 10-12 hours prior and had been found poorly responsive at home by family members. He has been treated with charcoal gastric lavage and IV fluids at the community hospital before referral. He developed altered sensorium, two episodes of vomiting, which were non-projectile/non-bilious/non-blood tinged, and one episode of involuntary defecation during the

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transit time to the hospital. There was no history of seizures, breathlessness, chest pain, or involuntary micturition. He has no other prior medical conditions and was not on any medication. On presentation in the ER, his vitals were: pulse rate 161bpm, respiratory rate 27cpm, blood pressure 91/63 mmHg, room air saturation of 96%, temperature 36.8^{0}C with Glasgow Coma Scale (GCS) of 9/15 (E2V2M5), and blood sugar of 130mg/dl. Bilateral pupils were equal (2mm) and reactive. Electrocardiography (ECG) revealed sinus tachycardia, short PR segment, and right axis deviation. Arterial blood gas (ABG) revealed high anion gap metabolic acidosis with elevated lactate. The urine analysis revealed 1+ protein with 6-10 RBCs/HPF. Gastric lavage was performed again in the ER, and the patient was admitted to the intensive care unit for further management. Conservative management with fluid therapy, cardiac monitoring, and sodium bicarbonate alkaline diuresis were provided. The toxicology screening for barbiturates was negative, serum cholinesterase levels were within normal limits. We were not able to measure the serum level of the 2,4 D compound due to the non-availability of the test even at the nearby Poison referral center. The patient continued to be drowsy (GCS 12/15), conscious, but disoriented, and irritable after four cycles of forced alkaline diuresis (FAD). However he did not have respiratory depression and maintained O2 saturations with mask O2. Complete blood count, liver function tests, and creatine phosphokinase (CPK) were within normal range. However, it was noted that there was persistent mild hypokalemia, and renal function parameters were worsening (Figure 1) with decreased urine output, suggestive of nephrotoxic acute kidney injury. Serial ECGs revealed no hypokalemia changes. Intravenous potassium correction was provided. From day 8, hemodialysis was initiated. He was delirious for the most part of the first 10 days of his hospital stay. However, after 14 days with supportive measures, regular hemodialysis (HD), and the addition of steroids at 0.5 mg/kg/day, his general sensorium (GCS 15/15) and renal parameters improved (Figure 1). He was discharged after 3 weeks in the hospital with a serum creatinine of 2.0 mg/dl and was off hemodialysis. Two-weeks later, during follow-up, he had clinically recovered, and serum creatinine was 1.3 mg/dl.

DISCUSSION

In the early 1940s, 2, 4-D, an auxin analog, was used as a chemical regular for the growth of the plant; later, this compound was used as an herbicide with broad spectrum effect as a weedicide and herbicide. It is the third most frequently used herbicide in the United States and is used very commonly in agricultural practices worldwide, including in India [1-15]. With the code name Agent Orange, it was even used as a defoliant in the Vietnam War [9]. Few cases of chronic cutaneous/inhalational occupational exposure and deliberate oral poisoning have been reported [1-15]. Following oral ingestion, it is readily absorbed, distributed widely over the tissues, and excreted unchanged in the urine. 2,4-D is a weak acid, and by de-ionizing and fat binding, the distribution is wide. It is estimated that 90% of the compound undergoes renal excretion, which depends on urine output and pH [13]. Analysis of 15 previously published articles (Table 1) revealed that this poisoning has been primarily reported in males. In our case, the patient had consumed approximately 100ml. Plasma level estimation is performed by gas-liquid chromatography with electron capture. The degradation of 2, 4-D leads to the formation of toxic compounds like chlorophenols or dioxins. These toxic compounds disrupt the cell membrane, acetyl coenzyme, mitochondria, and DNA by free radicals. This disruption causes the release of caspases and thereby causes apoptosis. 2,4-D impairs the electron

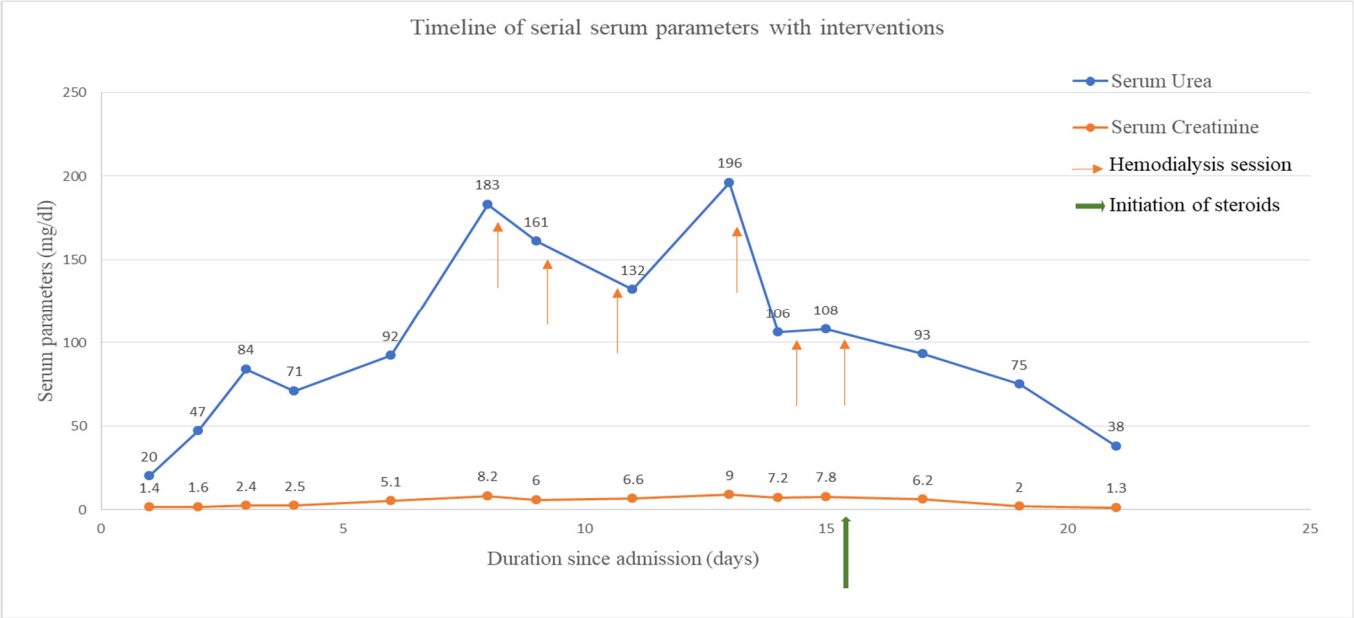

Figure 1. Graphical image depicting the correlation between renal parameters and interventions employed during the hospital stay duration

transport chain with uncoupling of oxidative phosphorylation, causing depletion of ATP [1,2,11-13].In toxic doses due to systemic absorption and widespread distribution, it affects almost all vital organs, leading to MODS. Gastrointestinal (GI) tract damage due to the corrosive effect causes oral ulcers/burning mouth, nausea, vomiting, throat pain, abdominal pain, and diarrhea [1, 2, 4-6, 8-14]. At higher doses, agitation and confusion develop following GI symptoms. In addition to GI fluid loss, direct myocardial inhibition and peripheral vasodilation cause hypotension [3,4,7]. Cardiotoxicity manifests with hypotension, elevation of creatine kinase MB (CK-MB), and electrocardiogram changes like sinus tachycardia, T-wave inversion, ventricular fibrillation, and occasionally bradycardia [2-5,7,12]. Central nervous system depression causes miosis, seizures, loss of consciousness, fasciculation, impaired coordination, drowsiness, nystagmus, paralysis, hallucination, ataxia, and coma [1-3, 5-15]. By inhibition of chloride channels, muscular involvement manifests as muscular weakness, muscular fibrillation, myotonia, loss of tendon reflex, or rhabdomyolysis with elevated CPK [1-5, 11,12]. Sometimes, involvement of localized proximal muscle group or pharyngeal muscle weakness manifesting with nasal regurgitation/impaired deglutition or hoarseness of voice is noted. Involvement of the respiratory group muscle causes respiratory distress [1, 4, 14]. Elevated liver enzymes indicate hepatotoxicity [1,4,8], with rare hepatic necrosis [1]. Nephrotoxicity is a serious concern [1-3, 8, 9, 11,15] that develops later after presentation, which almost occurs secondary to rhabdomyolysis. Early initiation of alkaline diuresis not only augments the elimination of toxins but also prevents nephrotoxicity [1, 4-6, 8, 10,11,13]. The worsening toxin-induced acute kidney injury/acute renal failure should be promptly managed by hemodialysis [3], as it helps in the elimination of 2,4-D. HD avoids the need for excess administration of intravenous fluid to eliminate the toxins or to alter the urine pH [3]. As per Durakovic et al. [3], hemodialysis is considered more effective than urine

Table 1. Table of published studies of 2, 4 D poisoning

Author Name, Year of Publication	Journal	No. of Cases	Age	Sex	Amount of Consumption	Serum Level of 2,4 D	Outcome
Bhalla et al 2008	*Emerg Med J*	4	22 25 31 28	F F F M	NA	NA	3 died within 24 hours, 1 survived
Demissie et al 2022	*Int Med Case Rep J*	1	32	Female	30 ml	NA	Death (Day 3)
Durakovic et al 1992	*Arch Toxicol*	4	51 80 24 50	All male	400ml 100m 200ml 100-200ml	NA; 177mg/100ml 122.5mg/100ml 37mg/100ml	All 4 survived
Friesen et al 1990	*Drug safety*	1	61	Female	150-200 ml (history of vomiting following consumption)	392 mg/L	Extubated after 22 hours of admission, shifted to wards on day 3
Hiran et al 2017	*Asia Pac J Med Toxicol*	1	33	Female	70 ml	NA	Survived (discharged on day 10)
Jearth et al 2015	*Indian J Crit Care Med.*	1	19	Male	3 teaspoons	NA	Survived (discharged on day 5)
Jorens et al 1995	*Eur J Emerg Med*	1	60	Male	480 g^{-1}	192 mg l^{-1}	Death (4.5 hours)
Kancir et al 1998	*J Toxicol Clin Toxicol.*	1	55	Female	Unknown quantity	NA	Death (Day 15)
Keller et al 1994	*Forensic Sci Int*	1	49	Male	500g/l	389 mg/l in PM	Death (Day 3)
Kumar 2019	*Indian J Crit Care Med.*	1	17	Male	150 ml	NA	Survived
Pannu et al 2018	*Trop Doct*	2	25 29	Male, Female	NA	NA	Both survived
Rajendran et al 2021	*Cureus*	1	65	Male	50 ml	NA	Survived
Singla et al 2017	*Int J Contemp Pediatr*	1	14	Male	50 ml	NA	Death
Wells et al 1981	*Clin Toxicolo*	2	26 21	Male male	75ml 25ml	79.6mg/L 118mg/L	Survived Survived
Teshome et al 2023	*Research square*	1	20	Male	Unknown quantity	NA	Death (7 hours of ER stay)

alkalinization alone, even if the 2,4-D clearance values from urine alkalinization and high urine flow are comparable.

Based on current evidence published so far, 10 cases resulted in death, while 13 patients from the 23 documented in 15 published studies survived (Table 1). It is challenging to comment on the appropriate treatment and prognosis of 2,4D poisoning due to its rarity. The first challenge in the management of this poisoning is the misdiagnosis of 2, 4-D poisoning, as the presentation almost mimics commonly reported OP poisoning. Secondly, the non -availability of plasma concentration estimation techniques in most centres hinders early detection. Finally, managing this lethal toxin is difficult without a specific antidote. In our case, the patient presented relatively early, and we were able to do gastric lavage with some removal of the toxin and institution of renal replacement therapy for nephrotoxic AKI improved prognosis and aided survival.

CONCLUSION

2, 4-D poisoning remains a significant clinical challenge due to its non-specific presentation. This article contributes to the limited available literature on this potentially fatal condition highlighting the successful management of a severe case through a multi-modal approach involving alkaline diuresis, hemodialysis, and potentially corticosteroids. Further research is needed to elucidate the pathophysiology of 2,4-D toxicity and to develop specific antidotes.

Conflict of interest: None declared
Funding and Support: None

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