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Article type: Case Report

Received: 15 September 2023

Accepted: 2 February 2024

Published online: 13 February 2024

eISSN: 2544-1361

Eur J Clin Exp Med

doi: 10.15584/ejcem.2024.2.17

Novaluron and indoxacarb induced methemoglobinemia – unveiling a rare poisoning

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ABSTRACT

Introduction and aim. In India, the utilization of agricultural pesticides for intentional self-poisoning is a prevalent method, and it is associated with substantially higher fatality rates compared to other self-poisoning approaches. Plethora, an agricultural insecticide containing novaluron (5.25%) and indoxacarb (4.5%), has recently been introduced and widely used in India and various other regions for its broad-spectrum lepidopteran control. While there have been documented cases of isolated self-poisoning involving indoxacarb, there is currently no literature reporting incidents of human poisoning specifically related to novaluron.

Description of the case. An 83-Year-old male was presented to the emergency department (ED) with a history of consumption of 50 mL of an insecticide suspension concentrate called 'PLETHORA' to commit suicide. He had one episode of vomiting and dizziness after the ingestion. There was associated cyanosis, and the patient was put on high-flow oxygen at 10 L/min through a face mask. The patient was diagnosed to have methemoglobinemia and was successfully treated with methylene blue and ascorbic acid. One hour post methylene blue injection showed a methemoglobin level of 1%, and the patient gradually improved. Patients presenting with novaluron and indoxacarb poisoning require supportive treatment as there is no specific antidote. There should be a high index of suspicion for methemoglobinemia in such patients, and timely management is necessary to prevent further complications. The patient was successfully managed and discharged after the 3rd day of admission.

Conclusion. The management of patients with novaluron and indoxacarb poisoning primarily involves supportive care, as there is currently no specific antidote available for these substances. Maintaining a high suspicion index for the development of methemoglobinemia and timely management of other complications is crucial for the best possible patient outcomes.

Keywords. emergency department, indoxacarb, methemoglobinemia, novaluron, poisoning

Introduction

The self-poisoning by agricultural pesticides is a common means of suicide in India.^{1,2} The problem is of particular concern in rural India, where a variety of highly hazardous pesticides are easily available in the home and work settings for use in routine agricultural needs.² The case fatality rates are significantly higher following these hazardous pesticides compared to other means of self-poisoning, such as with sedatives and analgesics.² The case fatality rates following agriculture pesticide poisoning in India range from 5 – 70 % across the reported studies.² There exists considerable variation across the suicide rates from pesticides among the Indian states, where states with good economic development and a higher proportion of populations engaged in agriculture documented a rising trend.² Plethora (novaluron 5.25% + indoxacarb 4.5%) is a recently introduced broad-spectrum lepidopteran insecticide for agricultural use in India and many parts of the world.³ While incidents of isolated self-poisoning by indoxacarb have been reported, currently the documented evidence of human poisoning by novaluron is rare in the existing literature.^{4,5,6} There is only one reported case of novaluron and indoxacarb combination-induced poisoning in the literature that developed acute methemoglobinemia, and there is a need to shed more light on the challenges in the management of such rare agricultural insecticide poisoning given their growing agricultural use.⁶

Aim

In this article, we present a case of self-poisoning with 'Plethora' that was presented to our emergency department (ED) with altered sensorium and cyanosis and successfully managed by a multidisciplinary team of the ED, with emphasis on the challenges encountered during treatment, culminating in the patient's discharge on the third day after presentation.

Description of the case

An 83-year-old male, presented at the ED with a history of deliberate ingestion of 50 ml of an insecticide suspension concentrate known as 'PLETHORA' (Fig. 1) in an attempt to end his life. Shortly after consuming the substance, he experienced a single episode of vomiting and dizziness. Upon inquiry, family members became aware of the incident and immediately sought medical assistance. The patient was promptly taken to a nearby local hospital, where gastric lavage was performed before being referred to our hospital.



Fig. 1. Plethora insecticide containing novaluron 5.25% and indoxacarb 4.5%

Upon arrival at our ED, the patient presented with an altered sensorium, characterized by a drowsy state and a Glasgow Coma Scale score of 13 out of 15 (E3V4M6). This altered level of consciousness is indicative of neurological impairment, affecting the patient's responsiveness and cognitive awareness. His vital signs included a pulse rate of 100 beats per minute, blood pressure of 132/82 mmHg, respiratory rate of 24 breaths per minute, and oxygen saturation of 82% on room air (Table 1).

Table 1. Vital signs of the patient during hospitalization

Sl no	Vital signs	Initial presentation	Day 1	Day 2	Day 3 (at discharge)
1	Heart rate (rate/minute)	100	72	68	75
2	Blood pressure (mm/Hg)	132/82	122/82	118/78	124/86
3	Temperature (degree Fahrenheit)	98.6	99.0	98.2	99.5
4	Respiratory rate (rate/minute)	24	18	16	16
5	Spo ₂ (% in room air)	82	92	95	96

Bilateral respiratory sounds were normal. However, the patient displayed cyanosis, prompting the administration of high-flow oxygen at a rate of 10 L/min through a face mask, which effectively maintained oxygen saturation at 88%. Arterial and venous blood samples were collected for comprehensive analysis,

encompassing blood gas analysis, complete blood count, renal function tests, and liver function tests. Notably, the blood sample exhibited a muddy brown coloration, which was observed during the collection process. These clinical observations collectively indicated a potential diagnosis of acute methemoglobinemia, subsequently confirmed by arterial blood gas analysis revealing a significantly elevated partial pressure of oxygen (PO₂) of 224.7 mmHg and an abnormally high methemoglobin value of 35%.

Simultaneously, blood samples were sent for testing to rule out the possibility of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Meanwhile, the patient received intravenous administration of 500 mg of ascorbic acid, supplemental oxygen, and fluid therapy. Considering that the G6PD values fell within the normal range, an intravenous injection of methylene blue (50 mg, corresponding to 1 mg/kg of a 1% solution) in saline solution was administered over 5 minutes. Following the administration of methylene blue, the patient displayed the characteristic development of apple-green urine. One hour after the methylene blue injection, the methemoglobin (MetHb) level decreased to 1%, and the patient exhibited gradual improvement, with renal parameters returning to normal. Although the initial renal function tests displayed deranged results, including urea levels of 46 mg/dL, creatinine levels of 1.66 mg/dL, and a urea/creatinine ratio of 27.7, the urine output remained within the normal range (Table 2). The patient was observed in the hospital for another 48 hours along with supportive management measures and discharged on the third day of presentation. The authors attest that the manuscript adheres to the standards of CARE guidelines for clinical case reporting. Written informed consent was obtained from the patient for publication in the journal.

Table 2. Laboratory data during hospitalization

Parameters	Initial presentation	Day 1	Day 2	Day 3 (at discharge)
pH	7.320	7.430	7.365	7.401
PaO ₂ (mmHg)	224.7	110.5	96	99.1
PaCO ₂ (mmHg)	35	30.5	36	35
Base excess (mmol/L)	- 4.3	-1.9	-1.4	-1.6
Bicarbonate (mmol/L)	18.3	22.1	24.2	22.2
Lactate (mmol/L)	3.40	1.07	1.20	1.01
Methemoglobin (%)	35	1	0.8%	0.9%
Fractional oxyhemoglobin (%)	58.4	94	94.4	96
Sodium (mEq/L)	133	140	144	145
Potassium (mEq/L)	4.41	4.01	4.05	3.68
Chloride (mEq/L)	99	–	105	110
Blood urea nitrogen (mg/dl)	21.47	–	20.73	10
Creatinine (mg/dl)	1.66	–	1.4	1.17

Discussion

Globally, pesticide mortality and morbidity associated with pesticide-related suicides pose a significant concern, particularly in developing countries like India, where agriculture plays a central role in livelihoods.² Each pesticide compound exhibits variations in toxicokinetics and/or dynamics, often necessitating specific medical management.² Novaluron, classified as a benzoylphenylurea compound, acts as a chitin synthesis inhibitor.⁷ It is reported to possess lower acute toxicity towards mammals and reduced risks to non-target organisms and the environment, distinguishing it from other insecticides.⁷ To date, there have been no documented cases of isolated novaluron poisoning, although animal studies have demonstrated elevated levels of methemoglobin upon exposure to the compound and one reported case of poisoning by novaluron and indoxacarb combination product.^{6,8}

Indoxacarb 4.5% belongs to the oxadiazine class and functions by blocking sodium channels in the insect nervous system.^{4,5} Several reports have indicated methemoglobinemia following indoxacarb ingestion.^{4,5} Methemoglobinemia occurs when the ferrous (Fe²⁺) ions of heme undergo oxidation to the ferric (Fe³⁺) state, impairing the oxygen-carrying capacity of hemoglobin.^{4,5} This process causes a leftward shift in the oxygen-dissociation curve and compromised tissue oxygenation. The metabolism of indoxacarb in the body likely involves the cleavage of the parent compound and the production of aniline metabolites and aromatic compounds capable of generating methemoglobin through metabolism.^{4,9} In the present case, the presence

of cyanosis and the observation of muddy brown-colored blood during sampling raised a strong suspicion of methemoglobinemia, which was subsequently confirmed by arterial blood gas analysis (ABG).

The primary approach to treating Plethora poisoning is supportive care. Depending on the patient's condition, fluid resuscitation and correction of metabolic abnormalities may be necessary.⁵ The therapeutic approach to methemoglobinemia involves a systematic regimen encompassing various pharmacological interventions and supportive measures tailored to mitigate the condition's severity. Central to this strategy is the administration of methylene blue (MB), a paramount antidote utilized at a loading dose of 1–2 mg/kg over 5 minutes at intervals of 30–60 minutes, with a maximum cumulative dose not exceeding 7 mg/kg.^{4,5,10} Methylene blue acts by reducing methemoglobin through the action of the nicotinamide adenine nucleotide phosphate (NADPH) reductase enzyme, significantly decreasing the half-life of methemoglobin from 15–20 hours to 40–90 minutes.¹⁰ Concomitant administration of dextrose plays a pivotal role in this therapeutic paradigm, aiming to bolster NADPH formation, a crucial step in the reduction of methemoglobin. The addition of dextrose serves as a facilitator in the enzymatic conversion of methemoglobin back to its functional hemoglobin form. In instances where MB therapy exhibits ineffectiveness, the consideration for exchange transfusion emerges as a plausible alternative, offering a means to rapidly replace the affected blood with unaffected blood components.¹¹ In our case, after ruling out G6PD deficiency, the patient received 50 mg of methylene blue. Additional drugs, such as ascorbic acid, which can supplement NADH or NADPH, may be indicated to expedite methemoglobin reduction via NADPH reductase.^{4,5} Ascorbic acid, a component within the minor reduction pathway of methemoglobin, assumes significance as an adjunctive therapeutic option in cases where MB therapy is contraindicated or ineffective.^{10–11} The recommended dosage of ascorbic acid ranges from 1 to 3 grams administered at eight-hour intervals, contributing to the reduction of methemoglobin levels via its intrinsic properties.¹⁰ In most instances, rapid response to methylene blue treatment is observed, although some patients may require repeated doses if symptoms persist. In our patient, a favorable response was observed following methylene blue administration, evidenced by a reduction in cyanosis and improvement in ABG values. The authors acknowledge that long-standing follow-up of the index case was not available, and that could have shed more light on the long-term effects of such rare poisoning.

Conclusion

The management of patients with novaluron and indoxacarb poisoning primarily involves supportive care, as there is currently no specific antidote available for these substances. In such cases, it is crucial to maintain a high index of suspicion for the development of methemoglobinemia. Timely and appropriate management is essential to prevent the occurrence of further complications and ensure the best possible outcomes for these patients. There is a need to study the long-term health effects of such rare poisoning to determine the need for supportive management measures and continuous follow-up.

Declarations

Funding

There were no sources of support or funding.

Author contributions

Conceptualization, I.M.S. and C.R.M.; Methodology, I.M.S., C.R.M. and R.V.R.; Software, I.M.S. and R.N.S.; Validation, C.R.M., R.V.R. and R.N.S.; Formal Analysis, I.M.S. and R.N.S.; Investigation, I.M.S., C.R.M. and R.N.S.; Resources, C.R.M.; Data Curation, I.M.S. and R.V.R.; Writing – Original Draft Preparation, I.M.S., C.R.M. and R.V.R.; Writing – Review & Editing, R.V.R. and R.N.S.; Visualization, R.N.S., and C.R.M.; Supervision, I.M.S. and C.R.M.; Project Administration, C.R.M.

Conflicts of interest

There are no conflicts of interest to declare from any of the authors.

Data availability

The data pertaining to the reported case is available with the Authors.

Ethics approval

Not applicable as written informed consent was taken from the participants.

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