Too Blue To Be True": Indoxacarb Induced Methemoglobinemia- A Rare Case

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Abstract

Indoxacarb is an oxadiazine insecticide, which is a sodium channel blocker in the nervous system of insects and causes mild tremors, cessation of feeding, and death in few hours.

Here we describe a case of novaluron and indoxacarb poisoning in a suicide attempt. The patient presented with cyanosis with saturation – paO2 gapindicating methemoglobinemia and was treated with methylene blue and other supportive measures.

Keywords: *insecticide, toxin, indoxacarb, novaluron, methemoglobinemia, cyanosis, methylene blue, tissue hypoxia.*

Introduction

Indoxacarb is an oxadiazine [1] compound and a sodium channel blocker. It is a broad-spectrum insecticide [1] widely used in commercial and farm planting for the control of certain insects, i.e. moth, leaf hopper and fruit worm. Contact with the substance can take place through ingestion, physical contact, pruning, and rewetting of surfaces.

We report a case of novaluron and indoxacarb toxicity with suicidal intent, presenting as a medical emergency. Acute methemoglobinemia is an emergency requiring prompt diagnosis and treatment with methylene blue.

Case Report: A 55 year old farmer hailing from Andhra Pradesh reported to our emergency department with alleged history of a feud at home and consumption of 100 ml of an unknown insecticide as shown in

The insecticide was identified to be a combination of novaluron (5.25%) and indoxacarb (4.5%) (trade name: SENORA) with no specific antidote as per the leaflet. The patient presented to us 4 hours after the ingestion with no first aid administered. He complained of vomiting, drowsiness, headache and abdominal pain.

On arrival he had a pulse rate of 84/min, blood pressure of 110/80 mm Hg, saturation of 80% on room air and 82% on 15 litres of oxygen via Non-rebreathing mask (NRBM), respiratory rate of 22/min. He was conscious but mildly drowsy with Glasgow Coma Scale of 14/15. His pupils were 3 mm, bilaterally equal and reactive to light.

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Figure 1: Insecticide containing indoxacarb and novaluron (trade name: SENORA)

On general physical examination, the patient had central cyanosis involving tongue and mucous membranes as shown in Figure 2:

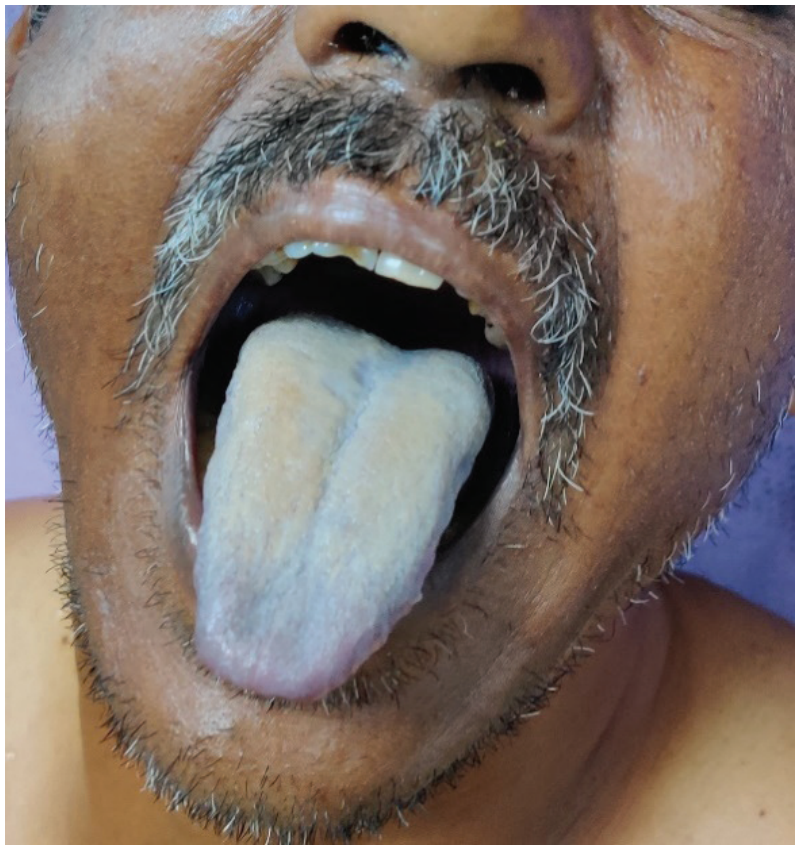


Figure 2: Central cyanosis involving tongue

On further eliciting history there was no history of congenital heart disease, fever, cough or respiratory distress in the near past or other comorbidities. His only habits were occasional ethanol consumption and smoking approximately amounting to 10 pack-years.

An arterial blood gas was obtained which showed a pH: 7.237, pCO2: 22.9, pO2: 141, Hb: 18.3, sO2: 97.8, Na: 143, K: 2.8, Cl: 109, lac: 18, HCO3: 9.4 interpreted as partially compensated metabolic with lactic acidosis with hypokalaemia.

To identify the cause of spO2 - paO2 gap and co-oximetry was ordered for.

The results came as follows: MetHB (methemoglobin) – 46.4%, COHb (carboxyhemoglobin) – 3.3%, leading us to the diagnosis of methemoglobinemia. Literature review led us to the conclusion of a rare case of methemoglobinemia caused by indoxacarb exposure.

On comparing the patient's blood gas sample to a normal patient's sample the characteristic chocolate brown colour of blood was appreciated as shown in Figure 3:

Figure 3: Classic chocolate blood coloured blood in methemoglobinemia

Our final diagnosis was methemoglobinemia secondary to pesticide ingestion: Indoxacarb and novaluron.

The patient was treated with anti-emetics and the antidote methylene blue. Thepatients weight was about 70 kg and he was treated with 70 mg of methylene blue intravenously (1mg/kg with each ml containing 10 mg of methylene blue). Saturation picked up to 94% shortly after and repeat ABG was as follows: pH 7.415, pCO2: 32, pO2: 101, HCO3: 20.1, sO2: 95.8, Na: 137, K: 3.11, Cl: 108, lac: 0.9, MetHb: 1.6.

Table 1 given belowshows the comparison between the pre and post treatment blood gas analysis.

Table 1: ABG comparison

Blood gas analysis	Pre-treatment	Post treatment
pH	7.23	7.41
pCO2	22.9	32
pO2	141	101
HCO3	9.4	20.1
sO2	97.8	95.8
Na/K/Cl	143/2.8/109	137/3.11/108
MetHb	46.4	1.6
Lactate	18	0.9

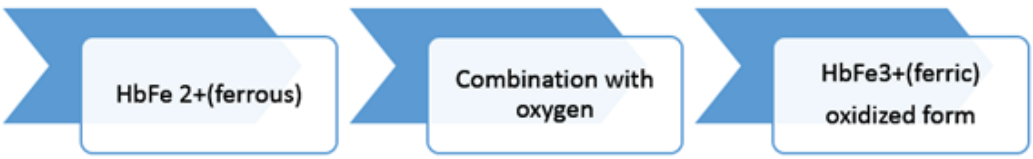
A repeat dose of 140 mg of methylene blue was given the following day as saturation dropped and MetHb levels was 24. He was also on treatment with supportive measures of vitamin c 500 mg once daily, intravenous fluids and thiamine as the patient had a history of an alcohol binge.

Final diagnosis: Indoxacarb and novaluron (pesticide) induced methemoglobinemia.

Physiology

Normal physiological process is as shown below in ***Table 2:***

Table 2: Physiological oxidization of hemoglobin



Formation of methemoglobin is as shown below in ***Table 3:***

Table 3: *Methemoglobin formation*

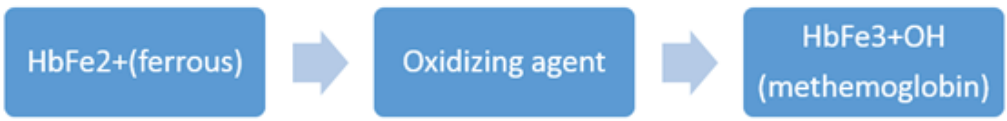


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Table 3: Methemoglobin formation

Etiology

Table 4: given below lists the most common etiologies of methemoglobinemia.

Local anaesthetics	Benzocaine, Procaine, Tetracaine, Lidocaine. [4]
Nitrates	Nitro-glycerine, Inhaled nitric oxide, Nitroprusside, Oral nitrates, Amyl nitrate. [4]
Antibiotics	Dapsone, Rifampin, Sulfonamides (e.g., sulfamethoxazole), Antimalarials (chloroquine, primaquine). [4]
Miscellaneous	Flutamide, Metoclopramide, Phenazopyridine (urinary analgesic agent-Pyridium). [4]
Environmental triggers	Pesticides, weed killers, Dyes, paints, thinner, rubber solvent. [4]

Table 4: *Etiology of methemoglobinemia*

CLINICAL FEATURES

Table 5given below illustrates symptoms with corresponding MetHb values.

Methemoglobin concentration	Percentage of total haemoglobin	Symptoms
<1.5 g/dl	<10	None
1.5-3.0 g/dl	10-20	Cyanosis
3.0-4.5 g/dl	20-30	Anxiety, headache
4.5-7.5 g/dl	30-50	Fatigue, confusion
7.5-10.5 g/dl	50-70	Coma, seizures, acidosis
>10.5 g/dl	>70	Death

Table 5: Symptoms of methemoglobinemia with corresponding values

Wright RO, Lewander WJ, Woolf AD: Methemoglobinemia: Etiology, pharmacology, and clinical management. Ann Emerg Med November 1999

CLINICAL DECISION MAKING

The Figure 7given below illustrates an algorithm to approach a patient with cyanosis.

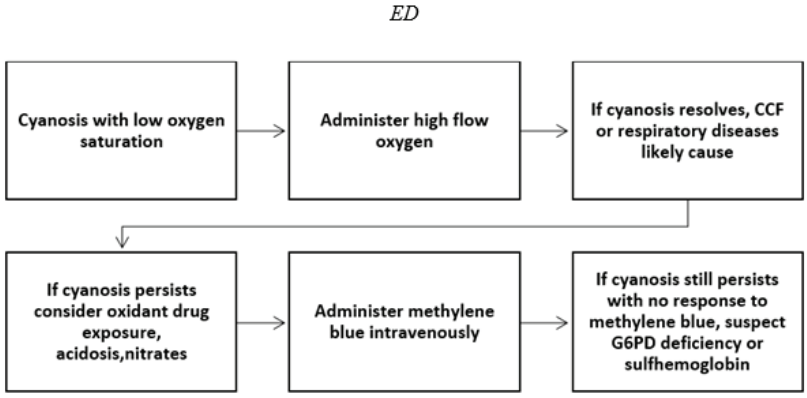

Figure 7: Approach to cyanosis in ED

Wright RO, Lewander WJ, Woolf AD: Methemoglobinemia: Etiology, pharmacology, and clinical management. Ann Emerg Med November 1999

Diagnosis

Arterial blood gas analysis

Methemoglobinemia may cause chocolate-brown discoloration of the blood. As a bedside test, if blood is dropped on a piece of white gauze, it will remain brown as it dries (in contrast, normal deoxygenated blood will absorb oxygen and become red). [5]

There is an obvious mis-match between the PaO2 (which is >>100 mm) versus the pulse oximetry (which is typically ~80-90% saturated). This is known as ***PaO2-saturation gap****, and it is indicative of some sort of hemoglobinopathy (most often methemoglobinemia).* [5]

Co-oximetry is the gold standard of detecting methemoglobinemia with spectrophotometry. Methemoglobinemia has a peak absorbance of light at 630 nm which is characteristic. [6]

Discussion

Methemoglobinemia refers to the oxidation of ferrous iron (Fe++) to ferric iron (Fe+++) within the haemoglobin molecule. [1]This reaction impedes the ability of haemoglobin to transport oxygen, leading to tissue hypoxemia. Methemoglobinemia most commonly results from exposure to an oxidizing chemical, but may also arise from genetic, dietary, or even idiopathic etiologies. [2, 3]

TREATMENT

Methylene blue

Methylene blue (MB) is a reducing agent. MB exerts its reductive effects by activating the dormant but volatile hexose monophosphate (HMP) shunt to regenerate NADPH. Dextrose should be co-administered in order to increase NADPH formation. If MB therapy is ineffective and life-threatening shock is imminent, exchange transfusion should be initiated.

Methylene blue is provided as a 1% solution (10 mg/mL). The dose is 1 to 2 mg/kg (0.2 mL/kg of a 1% solution) infused intravenously over 3 to 5 minutes. The dose may be repeated at 1 mg/kg if MB does not resolve within 30 minutes. Methylene blue should reduce MB levels significantly in less than an hour. The maximum dose is up to 7 mg/kg within 24 hours. [7]

Dextrose should be co-administered in order to increase NADPH formation. If MB therapy is ineffective, exchange transfusion should be considered. Ascorbic acid, part of the minor reduction pathway of methemoglobin, may be useful in patients in whom MB

therapy is contraindicated. The dose is 1-3 gm every 8th hourly. [8] Hyperbaric oxygen is also effective in MB levels above 50% and in patients with no response to other treatment modalities. Other agents considered were N-acetyl cysteine and high dose cimetidine in dapsone induced methemoglobinemia. [9]

Conclusion

To conclude we report a rare case of toxin (indoxacarb) induced methemoglobinemia with a MB level of 46%, treated successfully with methylene blue and ascorbic acid and discharged after 5 days of hospital stay. Early diagnosis and initiation of methylene blue aided in significantly reducing the morbidity and need for mechanical ventilation in this patient. During this pandemic of COVID-19, importance of understanding that other etiologies might present with hypoxemia and ordering for co-oximetry when appropriate is of paramount importance.

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Funding: Self.

Conflict of Interest: Nil.

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