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Case Report

Neonicotinoid Poisoning Presenting As Methemoglobinemia – An Unusual Presentation

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Abstract
Neonicotinoids are considered a class of insecticides that are less toxic to human beings than organophosphates, carbamates, pyrethroids and organochlorides. Neonicotinoids are developed and launched in the market in the absence of direct human toxicity data. Human toxicity is extrapolated from animal studies, whose relevance is unclear.Despite its widespread use, very few cases have been reported. We report an unusual case of thiamethoxam poisoning- a 2nd generation neonicotinoid insecticide presenting as methemoglobinemia.

Keywords : Neonicotinoids, Brown peripheral blood, Methemoglobinemia, Methylene blue, Ascorbic acid.

Introduction

Poisoning is one of the major public health issues in developing countries.[1] Poisoning with insecticides like organophosphates and carbamates is the major cause of serious poisoning, sometimes even resulting in death. Because of this, a new insecticide called Neonicotinoids has been created.[2] Neonicotinoids are used to combat various pests, fleas and also against household pests.[3] Neonicotinoids have low toxic value in humans as they interact less with nicotinic receptors in vertebrates and have less penetration to the blood-brain barrier. For this reason, they have been used increasingly across the world. However, ingestion at large doses has been associated with severe poisoning.[4] One such rare case has been reported here.

Case details

A 53-year-old female presented to casualty with complaints of vomiting and altered sensorium. There was an alleged history of unknown substance ingestion followed by gastric lavage and primary management in a local hospital three days back. There was no other significant history. There was no history of a fall or head trauma. She had no comorbidities in the past. She had no psychiatric illness. There was no history of similar attempts in the past. She was not an alcoholic or substance abuser. Upon examination, she was confused, agitated and disoriented with a GCS scale of 13/15. She had tachycardia with a pulse rate of 116/min, dyspnea with a respiratory rate of 26/min and spo2 around 76% in room air. Cardiovascular and respiratory system examination didn't show any remarkable findings otherwise. She was immediately shifted to Medicine ICU with oxygen support. Upon arrival in the ICU, she was drowsy and agitated with a GCS score of 12/15; she was also pale, cyanosed, tachycardic, tachypnoeic, and her pupils were mid dilated and normally reacting to light. Later after a thorough enquiry, the nature of the substance was found to be Thiomethoxane- A 2nd generation Neonicotinoid insecticide. Conservative management was started initially, and the patient was put on CPAP with 100% FiO2. Upon drawing blood for routine investigation, it was found to be muddy brown. ABG was done, which showed PaO2 106.3 mmHg with 100% O2, while the pulse oximeter showed 86%. This led to high suspicion of methaemoglobinaemia, and blood samples were sent to estimate the

methaemoglobin levels, which later revealed the diagnosis.

Routine blood investigation showed leukocytosis, normal renal function test, mild unconjugated hyperbilirubinemia, and elevated LDH levels. X-ray chest didn't show any obvious abnormality. RT-PCR for Covid-19 was negative. Standard treatment for acute methaemo globinaemia (i.v methylene blue and ascorbic acid) was proposed immediately. Unfortunately, methylene blue was not available at the hospital, and hence ascorbic acid was given at a higher dose (1 gram every 6^{th} hourly). The patient was deteriorating despite the above treatment. The patient could not be salvaged and succumbed to death despite all efforts.

Discussion

Neonicotinoids are one of the environmental substances that are used in agriculture, horticulture, and forestry as a pesticide.[3] At present, Neonicotinoids are used in 120 countries under various trade names.[5] Various substances include

- First-generation- Imidacloprid, Nitenpyram, Acetamiprid, Thiacloprid.
- Second generation- Thiamethoxam Clothianidin
- Third generation- Dinotefuran, Sulfoxaflor, Cycloxaprid.[5]

Respiratory tract intoxication is negligible as these molecules are non-volatile. However, secondary swallowing of inhaled aerosols can occur.[6] Peak plasma concentration is achieved in 2 hours.[7] Metabolism of neonicotinoids occurs through a variety of cytochrome isoenzymes.[8] The insecticidal activity results from agonist activity at postsynaptic nicotinic receptors for acetylcholine.[9] However, the interaction is much less in vertebrates rendering them less toxic.[4] Clinical symptoms upon accidental ingestion include

1. Neurological- sleepiness, vertigo, ataxia, tinnitus, confusion, hallucinations, delirium, seizures, coma
2. Eye- irritation, lid oedema, keratitis, corneal ulcer, and corneal perforations
3. Skin- irritation, 1^{st} to 3^{rd}-degree burns
4. Muscle - myalgia, fasciculations, extreme cramps, rhabdomyolysis, compartment syndrome, CPK >10,000 microL/L
5. Blood- hemolysis, methaemoglobinaemia, coagulation disorders, anaemia, leucopenia, thrombocytopenia
6. Liver- AST, ALT: 2 – 50 times normal based on severity and clinical signs of liver failure.[10]

Thiamethoxam intoxication cases are rarely reported, and hence symptoms are less known. Vinod et al. noted a case manifesting nausea, vomiting, agitation, and multiple episodes of generalized tonic-clonic seizures within the first two hours of ingestion. Subsequently, the patient developed coma, hypotension, renal failure, metabolic acidosis, rhabdomyolysis, and succumbed to death after 36 hours of ingestion.[11] Diagnosis is based on the patient's medical history and clinical symptoms. No specific laboratory parameters are available.[6] Management of acute poisoning is symptomatic and supportive. Skin and mucosal exposures are decontaminated as early as possible. Gastric lavage is not helpful due to the risk of inhalational pneumonia. If the patient is comatose and has respiratory distress, ventilatory support and hemodynamic support are to be provided.[4] Oximes are ineffective and contraindicated as they have weak inhibitory effects on acetylcholinesterase activity and, in turn, increase nicotinic effects.[6] Haemofiltration is ineffective as the severity of poisoning is not proportional to plasma concentration.[12] For methemo globinemia, intravenous methylene blue 1-2 mg/kg is the first line of treatment and should be infused in asymptomatic patients if levels are more than 30% and in symptomatic patients if the levels are more than 20%.[13] Methylene blue is converted in vivo by the Endogenous enzyme, NADPH-dependent methemoglobin reductase, to leucomethylene blue, reducing methemoglobin to haemoglobin. Vitamin C can be used in high doses.[14] N-acetyl cysteine, ketoconazole, and cimetidine are experimental treatments in methemoglobinemia yet. Patients who do not improve require exchange transfusions.[15]

Conclusion

Neonicotinoids act selectively on insects. However, they are not free of human toxicity. The number of neonicotinoid poisonings has been increased in the last ten years. Respiratory, cardiovascular, neurological, rhabdomyolysis have been reported as potentially fatal complications.[12] This case report highlights that delayed methemoglobinemia can also be one of the fatal complications associated with neonicotinoid poisoning, which is not usually seen. Proper medical history and clinical examination help in the early identification of complications and adequate management, which is life-saving. In our case, the non-availability of the timely medical history of the substance ingested and the non-availability of first-line medication were detrimental factors for the patient's survival. This report of thiamethoxam toxicity sensitizes physicians to an emerging cause of poisoning and highlights the need to carefully review its toxicity profile.

Conflicts of interest/Competing interests: None

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Figure 1: Muddy brown colour blood

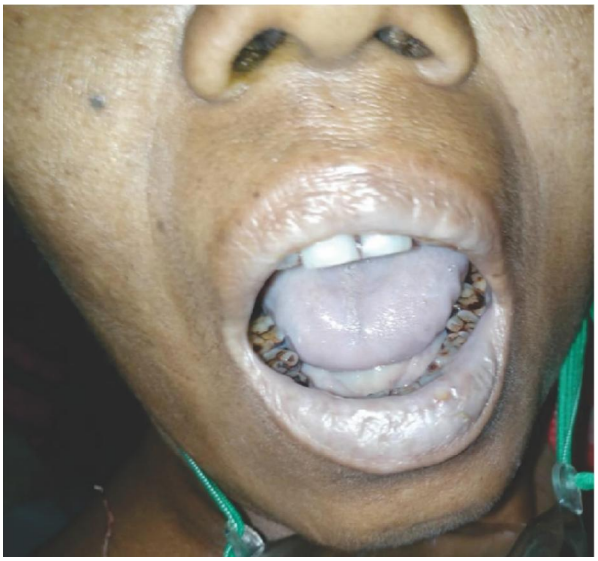

Figure 2: Cyanosis

Table 1: Investigations

Parameters	Values
Hb	6.8 gm/ dl
ESR	5 mm / hr
WBC	16,800 /cu.mm
RBC	2.6 million /cu.mm
PCV	19.4 %
MCV	72.9 fl
MCH	25.6 pg
MCHC	35.1 gm / dl
Reticulocyte count	8.0 %
LDH	559
Urea	21.50 mg / dl
Creatinine	0.53 mg / dl
Sodium	136.5 mmol / l
Potassium	3.55 mmol / l
Total protein	6.36 gm / dl
Albumin	3.00 gm / dl
Globulin	3.35 gm / dl
Total bilirubin	2.43 mg / dl
Unconjugated bilirubin	1.69 mg / dl
Conjugated bilirubin	0.29 mg / dl
AST	85 u / l
ALT	35 u / l
ALP	44 u/ l
GGT	40 u / l
TSH	1.75 miu /ml
Po2	106.3
Pco2	25.4
Ph	7.495
CHCO	319.1
Pf index	506.3

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