



AN UNUSUAL CAUSE OF METHEMOGLOBINEMIA : INDOXACARB POISONING

KEYWORDS

DR.V.PAVAN TEJA

JUNIOR RESIDENT,
DEPARTMENT OF MEDICINE
GANDHI MEDICAL COLLEGE,
SECUNDERABAD

DR.THRILOK C BINGI

ASSISTANT PROFESSOR,
DEPARTMENT OF MEDICINE,
GANDHI MEDICAL COLLEGE
SECUNDERABAD, TELANGANA,
INDIA

DR.B.S.V.MANJULA

PROFESSOR AND HOD
DEPARTMENT OF MEDICINE
GANDHI MEDICAL COLLEGE
SECUNDERABAD, TELANGANA,
INDIA

DR.RUSHENDRA VEMULA

ASSISTANT PROFESSOR, DEPARTMENT OF MEDICINE, GANDHI MEDICAL COLLEGE
SECUNDERABAD, TELANGANA

ABSTRACT *The latest generation of insecticides includes an oxadiazine insecticide DPX-JW062 (Indoxacarb) which is active against lepidopteran pests. Indoxacarb is an oxadiazine pesticide developed by DuPont is a broad-spectrum insecticide with activity on codling moth, white apple leafhopper, pandemic leafroller, and lacanobia fruit-worm. It acts on sodium channels and blocks the flow of sodium ions. Very few cases are reported from India. We report a case of 35 year old female with Indoxacarb poisoning presented with cyanosis due to methemoglobinemia. She improved after giving methylene blue and supportive management .*

INTRODUCTION:

Indoxacarb is the International Organization for Standardization (ISO) approved name for a new oxadiazine insecticide, methyl (S)-N-[7-chloro-2,3,4a,5-tetrahydro-4a-(methoxycarbonyl)-indeno[1,2-e][1,3,4]oxadiazin-2-ylcarbonyl]-4-(trifluoromethoxy)carbanilate[1]. Contact with the substance can take place through ingestion, physical contact, inhalation. In insects, this compound is rapidly cleaved to its decarbomethoxylated JW062 metabolite DCJW which, appears to be a potent blocker of sodium-dependent action potentials in lepidopteran (*Manduca sexta*) larval motor nerve preparation. Indoxacarb and its decarbomethoxylated metabolite, DCJW, are known to block voltage-gated Na(+) channels in insects and mammals. The result is impaired nerve function, feeding cessation, paralysis and death.

CASE REPORT:

A 35 year old female came to emergency department with a history of suicidal consumption of insecticide with composition of Indoxacarb. Patient was conscious and complained of respiratory difficulty. On examination had central cyanosis, pupils were bilateral 3mm in size reacting to light, pulse rate was 114beats/min, blood pressure was 90/70. On systemic examination, there were no cardiac murmurs, no radio radial or radio femoral delay. Pulse oximetry was connected and it showed 83% of saturation. Patient was immediately kept on I.V fluids and oxygen supplementation of 6lit/min. Blood samples were drawn which was chocolate brown in colour. Arterial blood gas analysis revealed PH-7.2, PaCo₂-32mm of Hg, PaO₂-255mm of Hg, HCo₃-17. The symptoms of Indoxacarb was enquired from Poison Information Centre (AIIMS) which showed a possibility of methemoglobinemia secondary to Indoxacarb poisoning. As there is non-availability of quantifying methemoglobin levels, but under high suspicion of methemoglobinemia due to cyanosis, chocolate brown color of blood, O₂ saturation gap between ABG and pulse

oximeter, we started treating as methemoglobinemia. Injection Methylene blue 150 mg diluted in 100 ml saline (dose 2 mg/kg, preparation 1%) was given over a period of 10 min intravenously. Inj. Ascorbic acid (Vitamin C) 500 mg in 5% dextrose was also started at a rate of 100 ml/h. Within two hours of giving Methylene blue, patient started improving in terms of respiratory difficulty and cyanosis with an increased SpO₂ value to 90% on pulse oximeter. Repeat ABG analysis showed pH 7.3, PaCO₂ 34mmHg, PaO₂ 290mmHg, HCO₃ 20.3. She was continued with oxygen inhalation and kept on maintenance dose of Inj. Methylene blue at a dose of 1 mg/kg and ascorbic acid 500 mg in 5% dextrose were continued at 12-h intervals. The next day SpO₂ value rose to 92%; ABG analysis revealed pH 7.34, PaCO₂ 36, PaO₂ 340, HCO₃ 22. On 3rd day her ABG and saturations became normal.

Thus our patient was managed successfully with methylene blue and other supportive/symptomatic treatment for methemoglobinemia which was probably secondary to Indoxacarb.

DISCUSSION:

Indoxacarb is a broad-spectrum non-organophosphorus oxidiazine insecticide widely used in farming. Indoxacarb is the first commercial insecticide of the oxadiazine group. Indoxacarb is typically a 75:25 mixture (DPX-MP062) of its two enantiomers (stereoisomers) – with one enantiomer responsible for the insecticidal activity. The acute oral LD50 is 1800 mg/kg and the acute dermal LD50 is >5000 mg/kg^[2]. It has high affinity for the inactivated state of the Na(+) channels. They specifically inhibit sodium channel function by binding selectively to slow-inactivated (non-conducting) sodium channel states^[3].

It is readily absorbed after oral ingestion and extensively metabolized by the liver. Toxicity results in neurological, hematological effects and lung damage. Impaired nerve

function, feeding cessation, paralysis and death in insects, rats and mice. "Lung noise" is observed and indicates the development of acute lung injury and high permeability pulmonary edema [4]. However, in humans, the effects are mainly hematological as per the toxicity cases reported so far. Methemoglobinemia is the most common complication with which patients presented so far with features of cyanosis and falling O₂ saturations.

Methemoglobin is generated by oxidation of the heme iron moieties to ferric state, causes bluish-brown muddy color resembling cyanosis. It has got very high affinity to oxygen and oxygen is not delivered to the tissues (oxygen dissociation curve shifted to the left). Methemoglobinemia [5] should be suspected in patients with hypoxic symptoms who appear cyanotic, though PaO₂ levels on ABG analysis are sufficiently high to fully saturate the hemoglobin. Symptoms like skin color changes and blood color changes occur at levels up to 15%. As levels rise above 15%, neurologic and cardiac symptoms arise as a consequence of hypoxia. Levels higher than 70% are usually fatal. The characteristic chocolate brown appearance of freshly drawn blood can be a critical clue.

The possible mechanism for hematological manifestations due to Indoxacarb poisoning were studied in mice. Indoxacarb decreased the haemoglobin content, leukocyte and erythrocyte counts in mice. These effects could be due to adverse effects of insecticide on bone marrow or direct destruction of blood cells^[6]. On reviewing the literature, the trifluoromethoxyaniline (IN-P0036) metabolite has been identified as the likely metabolite causing oxidative damage to red blood cells in laboratory animals exhibiting hemolytic anemia after indoxacarb exposures.^[7]

This is confirmed by in vitro studies on rat, dog and human erythrocytes. A reduction in erythrocyte count, hemoglobin and/or EVF, with increases in MCV and MCH, indicative of mild hemolysis was observed.^[8]

There is **no antidote** for indoxacarb poisoning. Treatment consists in preventing further exposure together with **supportive and symptomatic measures**. Methemoglobinemia is treated with Methylene blue, 1-2 mg/kg, administered slowly. If cyanosis persists, the dose may be repeated at an hourly interval to a maximum of 7 mg/kg/day. The maintenance dose of methylene blue is 1 mg/kg twice or three times a day. Other supportive measures include the administration of vitamin C and correction of the metabolic abnormalities.

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