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Case Report

Neonicotinoid insecticides: an emerging cause of acute pesticide poisoning

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ABSTRACT

Neonicotinoids are a new class of insecticides widely applied for crop protection. Information on human exposures to neonicotinoids is limited. The most common routes of exposure were ingestion (51%), dermal (44%), and ocular (11%). These insecticides act as agonists at nicotinic acetylcholine receptors, which cause insect paralysis and death the high specificity for receptors in insects was considered to possess highly selective toxicity to insects and relative sparing of mammals. However, an increasing number of cases of acute neonicotinoid poisoning have been reported in recent years. Present study report three cases presented to us with acute neonicotinoid poisoning with different manifestations including acute myocardial infarction, central nervous system (CNS) depression, and acute kidney injury, who recovered subsequently with supportive care. A detailed literature review found that respiratory, cardiovascular and certain neurological presentations are warning signs of severe neonicotinoid intoxication. Supportive treatment and decontamination are the practical methods for the management of all neonicotinoid-poisoned patients.

Keywords: Imidacloprid, Insecticide, Thiamethoxam, Neonicotinoid

INTRODUCTION

The neonicotinoids are a commercially important class of insecticides, with increased usage in recent years due to their favorable safety profiles, the restrictions placed on other insecticides and their utility for resistance management.[1] Representatives of this class are used to control insect pests in a variety of agricultural, commercial, residential, and veterinary settings, with insecticidal activity attributed to the activation of post-synaptic nicotinic acetylcholine receptors (nAChR) in insects.[2] There are currently seven members in the class of neonicotinoid insecticides: imidacloprid, acetamiprid, clothianidin, thiacloprid, dinotefuran, nitenpyram and thiamethoxam. These seven neonicotinoids have distinct structural features compared with nicotine that result in enhanced selectivity for insect nAChRs. Also, the amino nitrogen atom in nicotine is ionized, while in the neonicotinoids, the corresponding nitrogen atom is not ionized but bears a partial positive charge.

The specificity of the neonicotinoid insecticides for the nAChR subtype that occurs in insects, combined with poor penetration of the mammalian blood–brain barrier, rapid metabolism, and low application rates contributes to high margins of human safety associated with commercial uses.[3-5] By comparison, nicotine is more toxic to mammals than insects, due to a higher affinity for mammalian nAChRs and greater penetration across the blood-brain barrier in mammals.

The mortality rates of neonicotinoid poisoning in two large studies were 0-2.9%, which is much lower than that of other insecticides.[6-7] However, severe intoxication and even death after exposure to neonicotinoid were reported.[6] The exact mechanisms of neonicotinoid poisoning are still unknown, and physicians are unaware of the warning signs that could indicate the development of severe morbidity or poor outcome.

CASE REPORT

Case 1

A 50-year-old man with a history of lumbar vertebrae fracture with paraparesis, bed ridden since 3 yrs. with severe depression admitted in emergency department of SMS hospital with allied history of attempting suicide by ingesting approximately 40ml of pesticide 3 hours before his arrival at the emergency department, he retched and vomited persistently. The pesticide was "GAUCHO600 FS" which contain 48% w/w imidacloprid in the solvent Glycerin Propane-1,2-diol, isothialozone (Figure 1).

Figure 1: Pesticide "GAUCHO600 FS".

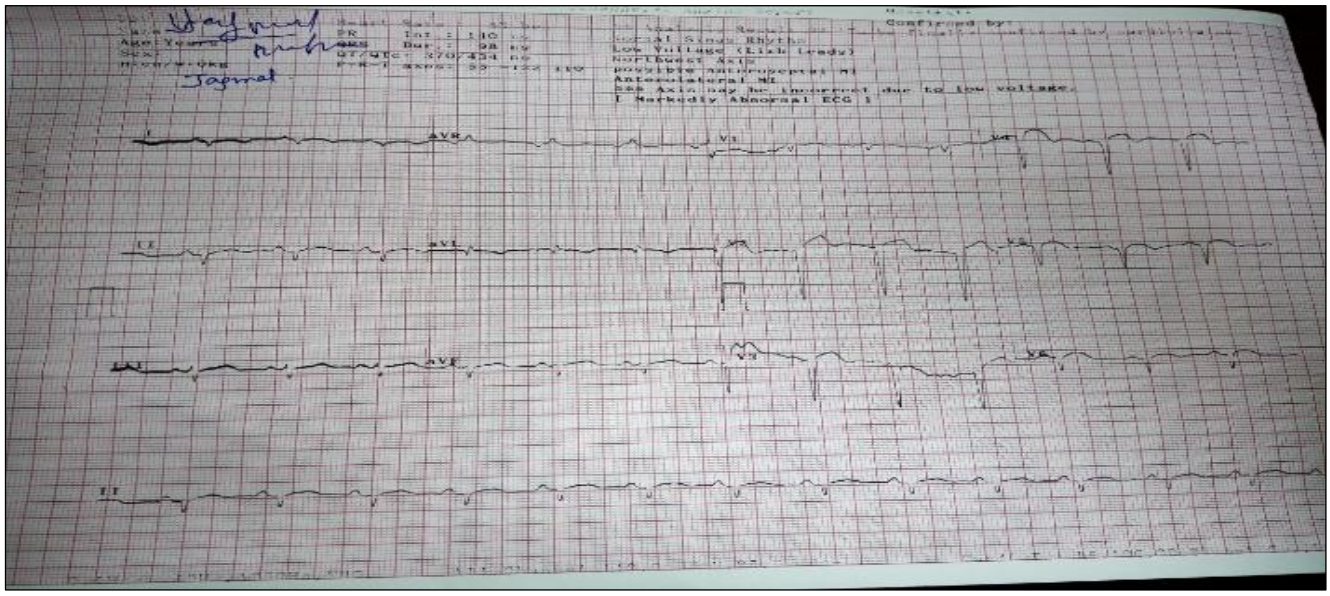

Figure 2: ECG showing ST elevation in anterior chest lead.

On arrival patient complain of chest pain, dyspnea, diaphoresis with vital signs were as follows: body temperature, 36.8°C; pulse, 94 beats/min.; respiratory rate, 24/min.; and blood pressure, 110/80 mmHg. Patient had no h/o hypertension, diabetes. No h/o smoking and alcohol intake. A physical examination revealed a drowsy with dyspnea, diaphoresis with systemic examination normal except coarse crepititions present on bilateral basal chest.

An ECG (Figure 2) shows ST elevation in anterior chest lead with reciprocal changes, Tropt was positive, CPKMB 248 U/L, 2D echo shows RWMA with LVEF of 35% (Figure 3) CAG was normal. Other laboratory investigations are within normal limit. A plain radiograph of the chest shows congestive changes. A provisional diagnosis of 'suspected neonicotinoid poisoning' was kept, gastric lavage was performed, and a sample was collected for toxicological analysis as a routine practice for all cases of suspected poisoning. The patient was managed conservatively with vasodilators, antiplatelets and antithrombotic. Patient improved symptomatically with improving ECG changes and discharged on oral medications with advice for regular follow up.

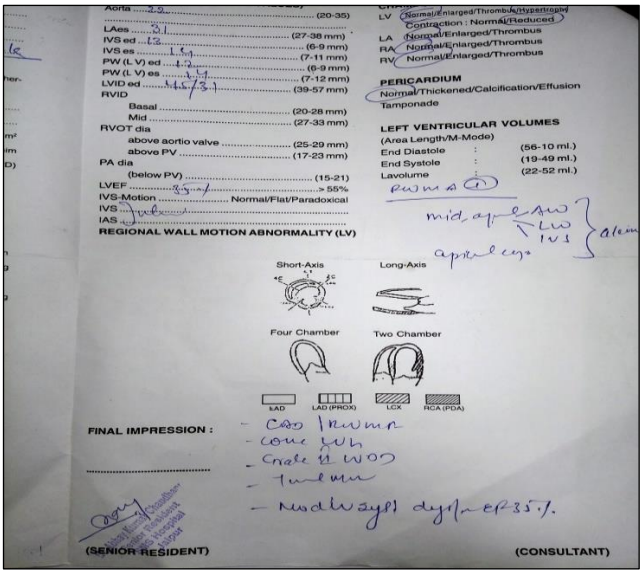

Figure 3: 2D echo report showing RWMA in midapical region with LVEF of 35%.

Case 2

A 20-year-old male was brought to the casualty services of a hospital in a state of altered sensorium with a history of having had an acute episode of intractable vomiting since last 3-4 hrs. According to his relatives, he intentionally consumes 50ml of some insecticide 4 hour prior to admission. The relatives also showed the empty container of insecticidal spray ‘‘CAPCADIS’’which was being used by the patient. Upon inspection of the container, it mentioned the constituent of the insecticide as being thiomethoxam 75 % w/w (Figure 4).

He felt unwell and had difficulty breathing. Later on he developed nausea, vomiting, abdominal cramps, and muscle twitching for which he followed a treatment plan prescribed by a local general practitioner, but after which he was not get relieved and he was thereafter referred to our health center. Upon arrival, he was drowsy, had dyspnea and was unable to stand unsupported. There was no significant co-morbid medical illness,

On physical examination, his vitals were normal with oxygen saturation of 90%. There was no pallor, cyanosis or injury marks. Scattered fine crepitations were present on chest auscultation. On neurological examination he was drowsy, having Glasgow Coma Scale (GCS) of 8/15 (E2, M3, and V3) with no focal neurological deficit. Investigations showed that he had mild leukocytosis with normal hemoglobin levels, RBC and platelet counts. Serum electrolytes, random blood sugar, liver function and renal function were found to be normal. Chest X-ray was hazy but the ECG was normal.

A provisional diagnosis of ‘suspected neonicotinoid poisoning’ was kept, gastric lavage was performed and a sample was collected for toxicological analysis as a routine practice for all cases of suspected poisoning. The patient was treated symptomatically along with good supportive and general nursing care in the absence of any specific antidote. After a few hours the patient regained consciousness and started developing neuropsychiatric manifestations like agitation and delirium. After 12–14 h, the neuropsychiatric manifestations subsided. MRI brain with contrast was also normal (Figure 6).

Figure 4: Insecticide ‘‘CAPCADIS’’.

Case 3

A 47-year-old male farmer was brought to the casualty services of a hospital with history of having had an acute episode of intractable vomiting and watery diarrhea for about 5–6 h. According to his relatives, he was spraying the pesticides in his fields, and after an hour, he felt unwell and had difficulty breathing. Later on, he developed nausea, vomiting, abdominal cramps, and muscle twitching for which he followed a treatment plan prescribed by a local general practitioner, but after which he was not relieved, and he was thereafter referred to our health center. There was no significant co-morbid medical illness, and relatives also denied consumption of any drugs, poison or medications except for the use of pesticide fumigation. The relatives also showed the empty container of insecticidal spray ‘‘WILLOXAM’’ which was being used by the patient. Upon inspection of the spray, it mentioned the constituent of the insecticide as being thiomethaxom 25% w/w (Figure 5).

On arrival patient complain of, dyspnea, with decreased urine output. His vital signs were as follows: body temperature, 36.8°C; pulse, 86 beats/min.; respiratory rate, 24/min.; and blood pressure, 110/80 mmHg. Patient had no h/o hypertension, diabetes. No h/o smoking and alcohol intake.

A general physical examination and systemic examination within normal limit except mild crepititions present on bilateral basal chest. On laboratory investigation CBC suggestive of mild leukocytosis and

RFT was deranged (urea-110mg/dl, creatinine-4.87mg/dl with Crcl of 19.89ml/min) with metabolic acidosis in ABG.

Figure 5: Insecticidal spray ''WILLOXAM''.

Nephrology reference was taken for AKI, advised conservative management. Patient improved in 3 days clinically with improved output and decreasing RFTs.

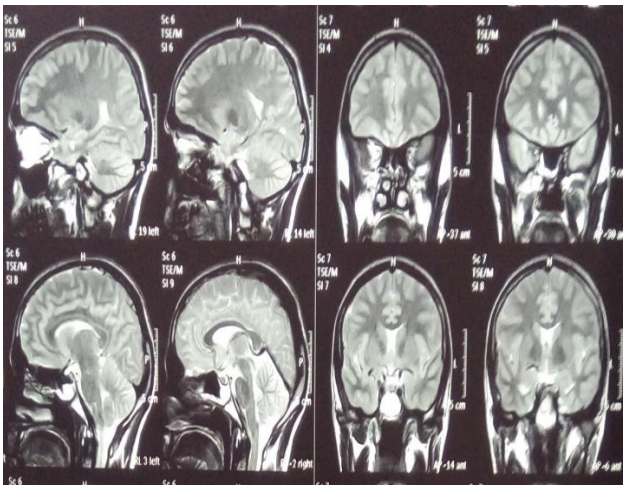

Figure 6: Normal MRI brain with contrast.

On the second day his respiratory function and oxygen saturation improved and chest crepitations disappeared. Later he was discharged upon further improvement. The gastric lavage sample was collected by the police for toxicological examination.

DISCUSSION

Acute pesticide toxicity is extremely common in developing countries of the Asia–Pacific region, particularly in settings of low education and poor regulatory frameworks. India is an agricultural country with a large rural population (60–80%), where pesticides are freely available and are used extensively and quite frequently for self-poisoning. New compounds like neonicotinoids with high potency but with least toxicity are being developed continuously. There are currently seven members in the class of neonicotinoid insecticides: imidacloprid, acetamiprid, clothianidin, thiacloprid, dinotefuran, nitenpyram and thiamethoxam.

Imidacloprid is the first of the chemical class of neonicotinoids to be developed for commercial use. On the basis of animal studies, it is classified as ''moderately toxic'' (class II by WHO and toxicity category II EPAV). It is not banned, restricted, canceled, or illegal to import in any country.[8]

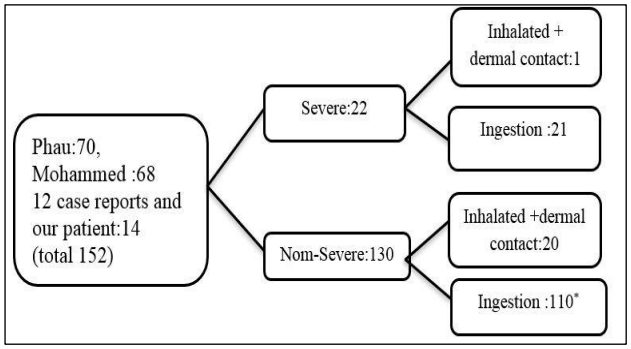

Figure 7: The study population and routes of neonicotinoid poisoning. *One non-severe case was poisoned via both ingestion and subcutaneous injection.

These compounds can be absorbed via ingestion, dermal or inhalational route, and there is more severe poisoning with oral ingestion than other routes. A study by Phau DH et al.[9] included 70 cases, but only 50 cases with detailed records of clinical presentations were evaluated. Another study conducted in Sri Lanka included 68 patients, but the symptoms were described for only two severe cases.[10] In addition, we noted the clinical features in 14 of the intoxicated cases presented in the 12 case reports as well as the present case (Figure 7).

Imidacloprid acts on several types of post-synaptic nicotinic acetylcholine receptors in the nervous system .[11] In insects, these receptors are located only within the central nervous system.[12] Mammalian nicotinic receptors are made up of a number of subtypes and are present at neuromuscular junctions as well as in the central nervous system in contrast to insects.[13] However, the binding affinity of imidacloprid at the nicotinic receptors in mammals is much less than that of insect nicotinic receptors.[14]

Neonicotinoid acts on nicotinic acetylcholine receptors in the nervous system. It initially stimulates the agonized receptors and interferes with the transmission of neuronal impulses by fatigue.[15-16] The effect influences the central nervous system and results in dizziness, drowsiness, disorientation and coma. The autonomic nervous system is stimulated through a similar mechanism, first with diaphoresis, mydriasis, tachycardia and elevations of blood pressure.

The clinical outcomes, as modified from the American Association of Poison Control Center data collection system, were classified as non-severe and severe.[17] The poisoned patients who exhibited signs or symptoms that were life-threatening or resulted in significant disability or disfigurement (e.g. status epilepticus, respiratory failure, ventricular tachycardia with hypotension, cardiac or respiratory arrest, disseminated intravascular coagulation, massive haematemesis or melena) were categorized as severe. Other clinical presentations were categorized as non-severe.

Here we reported three cases of neonicotinoid poisoning presented with different manifestations. In first case, patient presented as acute myocardial infarction with significant ECG changes and RWMA in 2D echo with normal CAG suggestive acute coronary spasm leading to this acute event after imidacloprid poisoning. Autonomic nervous system stimulation may lead to coronary spasm and cardiac ischaemia, followed by nervous system paralysis. As a result, poisoned patients may present with arrhythmia, hypotension and bradycardia.[18]

Second patient presented in altered sensorium followed by neuropsychiatric manifestations like agitation and delirium. It act on nicotinic receptors in central nervous system and interfere with neuronal transmission and lead to disorientation, coma and death. Agarwal and Srinivas reported neuropsychiatric manifestations and rhabdomyolysis with imidacloprid and both patients improved with supportive management.[19] Viradiya K and Mishra A also reported severe neuropsychiatric symptoms with respiratory failure following ingestion of imidacloprid and recovery with symptomatic treatment.[20]

Third patient presented with acute kidney injury with metabolic acidosis. Neonicotinoid cause rhabdomyolysis which may lead to acute renal failure.[19] A study of effects of thiamethoxam on male rats shows that there is acute and chronic tubular lesions with hyaline changes in the renal tubular epithelium.[21]

There are no specific antidotes for neonicotinoid poisoning in mammals.[22] On the basis of clinical experience and available studies, symptomatic and supportive care is all that is required for the management of patients with acute neonicotinoid poisoning.

CONCLUSION

Neonicotinoids is generally less toxic to humans causing mild symptoms. However, all the precautions must be taken during its handling. Care should be taken so that these may not get confused with an organophosphorus compound. Respiratory, cardiovascular and certain neurological presentations (dyspnea/apnea, coma, tachycardia, hypotension, mydriasis and bradycardia) are warning signs of severe neonicotinoid intoxication. Supportive treatment and decontamination are the current practical management methods for all neonicotinoid-poisoned patients.

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