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CASE REPORT

Accidental human poisoning with a neonicotinoid insecticide, imidacloprid: A rare case report from rural India with brief review of literature

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Abstract Acute pesticide poisoning is an important public health problem worldwide and accounts for a significant number of deaths occurring each year. Most of these fatalities are due to poisoning with organophosphorus insecticides which are an integral part of agriculture within this region of Asia. Due to their very high intrinsic toxicity, continuous efforts are done to develop newer pesticides of low toxicity and high potency. Invariably such compounds are released into the market without appropriate data on direct human toxicity. Human toxicity is often extrapolated from toxicological studies in animals, the relevance of which remains poorly defined. Imidacloprid is a neonicotinoid insecticide belonging to the chloronicotinyl nitroguanidine chemical family. It acts on the nervous system through an acetylcholine receptor blockade and is considered nontoxic to humans based on the available literature. Routinely it is used to kill fleas present on pet animals, termites and bees. We report a case that presented with severe gastrointestinal symptoms along with respiratory distress and neuropsychiatric features following accidental inhalational exposure to imidacloprid. Patient recovered from the effects of poisoning with supportive and symptomatic treatment. According to the best of our knowledge this is the first report of acute inhalational intoxication with imidacloprid in India.

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1. Introduction

Acute pesticide toxicity is extremely common in developing countries of the Asia–Pacific region, particularly in setting 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. Among different pesticides, organophosphates are most commonly used but being highly toxic, new compounds with high potency but with least

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toxicity, are being developed continuously. Imidacloprid is one such newer insecticide and is the first of the chemical class of neonicotinoids to be developed for commercial use.[1] Other common examples of this group include Acetamipid, Clothianidin, Dinotefuran & Thiacloprid. Imidacloprid was developed with the aim of combining compounds of high potency against insects but with low mammalian toxicity and favorable persistence. On the basis of animal studies, it is classified as a "moderately toxic" (class II by WHO and toxicity category II EPAV). It is not banned, restricted, canceled, or illegal to import in any country.[2] It was first registered for use as a pesticide in the US by the United States Environmental Protection Agency (USEPA) in 1994 and is currently one of the best-selling insecticides.[3] It has very high potency and systemic action against piercing and sucking pests.[4] In addition it may be applied to structures, soil, and as seed treatment.[5,6] Imidacloprid has a wide variety of uses and it is advised to always read and follow the instructions on the label when applying pesticide products. Imidacloprid [1-(6-chloro-3-pyridylmethyl)-n-nitroimidazolidin-2-ylideneamine, CAS No.-138261-41-3] belongs to a relatively new class of the insecticidal chemical family; the chloronicotinyl nitroguanidine group of compounds [Fig. 1].

2. Mode of action

Imidacloprid is designed to be effective by contact or ingestion.[5] Imidacloprid acts on several types of post-synaptic nicotinic acetylcholine receptors in the nervous system.[7,8] In insects, these receptors are located only within the central nervous system. Following irreversible binding to the receptors, nerve impulses are spontaneously discharged at first, followed by failure of the neuron to propagate any signal.[9,10] Sustained activation of the receptor results from the inability of acetyl cholinesterases to break down the pesticide.[8] 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.[10] However, the binding affinity of imidacloprid at the nicotinic receptors in mammals is much less than that of insect nicotinic receptors.[11]

2.1. Toxicity

Imidacloprid is very low in toxicity via dermal exposure[12] and moderately toxic if ingested[13]; but upon inhalation, its toxicity is variable. Its dust is considered slightly toxic but the aerosol form is highly toxic.[13] The LC_{50} for inhalation is 0.05 mg/L of aerosol form & acute oral LD_{50} for moderate toxicity is 50–500 mg/kg.[14]

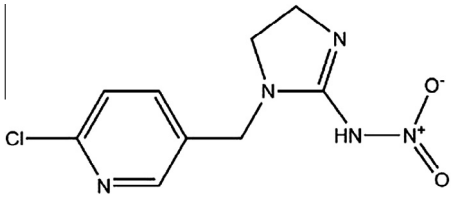

Figure 1 Structural formula of Imidacloprid.

2.1.1. Animal toxicity

Very high oral dose may lead to lethargy, vomiting, diarrhea, salivation, muscle weakness and ataxia.[12] Other features at high doses are uncoordinated gait, tremors, and reduced activity.[15] On acute exposure the signs of toxicity appear and disappear rapidly, with most resolving within 24 h of the exposure. If a lethal dose has been administered, death occurs within 24 h.[16]

2.1.2. Human toxicity

There is a dearth of literature about human toxicity from imidacloprid. Few case reports of attempted suicides described signs of toxicity such as drowsiness, dizziness, vomiting, disorientation, and fever.[17,18] A 69-year-old woman who ingested a formulated product containing 9.6% imidacloprid suffered severe cardiac toxicity with complaints of disorientation, sweating, vomiting, increased heart and respiratory rates and died 12 h after the exposure.[19] A 24-year-old man who accidentally inhaled a pesticide containing 17.8% imidacloprid while working on his farm was disoriented, agitated, incoherent, sweating and breathless following the exposure.[20]

3. Fate in the body

3.1. Absorption

In experimental studies among animals (in rats); it has shown rapid absorption (92%), with a peak plasma concentration within approximately 2.5 h and is followed by a rapid disposition phase.[21] Little systemic absorption was seen following dermal exposure in pets. Studies using human intestinal cells, found that imidacloprid was rapidly absorbed at a very high rate of efficiency. It was concluded that an active transport system was involved.[22]

3.2. Distribution

In experimental research one hour after its single oral dose, it was detected throughout the body with the exception of fatty tissues and the central nervous system.[23] Studies examining the distribution of imidacloprid in humans could not be found.

3.3. Metabolism

It is rapid, extensive and primarily occurs in the liver where only 10–16% of a dose is excreted unchanged.[21] Mammals metabolize imidacloprid in two major pathways. In the first pathway, it is broken by oxidative cleavage to 6-chloronicotinic acid and imidazolidine. Imidazolidine is excreted in the urine, and 6-chloronicotinic acid undergoes further metabolism via glutathione conjugation to form mercaptonicotinic acid and hippuric acid.[21] In another pathway, it is metabolized by hydroxylation of the imidazolidine ring and produces 5-hydroxy and olefin derivatives.[15] Potentially, individual variation in cytochrome P450 isoenzymes involved in oxidative imidacloprid metabolism may contribute to variable toxicity.[24]

3.4. Management

There are no specific antidotes for neonicotinoid poisoning in mammals.[24] On the basis of clinical experience and available

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studies, symptomatic and supportive care is all that is required for the management of patients with acute imidacloprid poisoning. Treatment with oximes such as pralidoxime is expected to be either ineffective or contraindicated.[25]

4. Case report

A 60 year old male farmer was brought to the casualty services of a hospital in a state of altered sensorium with previous history of having 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 uneasiness and difficulty in respiration. Later on he developed nausea, vomiting, abdominal cramps, muscle twitching for which he took some treatment by a local general practitioner but could not be relieved and was referred to a higher center. On arrival he was drowsy, had dyspnea and was unable to stand unsupported. There was no significant co-morbid medical illness & relatives also denied consumption of any drug, poison or medications except for the fumigation. The relatives also showed the empty container of insecticidal spray "HOTSHOT" which was being used by the patient. On inspection it mentioned the constituent as imidacloprid 17.80 SL (Fig. 2).

On physical examination his vitals were normal with oxygen saturation of 60%. There was no pallor, cyanosis or injury marks. Scattered coarse 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 leucocytosis with normal hemoglobin level, RBC and platelet counts. Serum electrolytes, random blood sugar, and renal function were found to be normal but liver functions were deranged with SGOT & SGPT levels as 79 and 67 IU/L, respectively. Chest X-ray was hazy but the ECG was normal. A provisional diagnosis of 'suspected imidacloprid poisoning' was kept, gastric lavage was done and sample was collected for toxicological analysis as routine for all cases of suspected poisoning. The patient was treated symptomatically along with a 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. 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 not collected by the police for toxicological examination since due to the presence of reliable history, presence of the empty container and presenting complaints it was labeled as a case of accidental inhalation and therefore no legal action was required to be taken.

Figure 2 Empty Container of Imidacloprid.

5. Discussion

Acute agrochemical poisoning is a leading cause of mortality and morbidity in the Asia–Pacific region and is mostly due to exposure to organophosphates (most common in India), organochlorines, and aluminum phosphide compounds which are an integral part of agriculture within this region and are readily available at very cheap prices. Due to their intrinsic toxicity, new chemicals of high potency and low toxicity continue to be developed e.g. Imidacloprid, Pendimethiline, and Pencycuron etc., but they are released to the market without appropriate data on direct human toxicity. Instead, human toxicity is often extrapolated from toxicological studies in animals, the relevance of which is poorly defined.[26] Imidacloprid acts as a competitive inhibitor at nicotinic acetylcholine receptors in the nervous system resulting in impairment of normal nerve function.[27] It has a higher binding strength to insect nerve receptors than to mammalian receptors and is reported to have very low toxicity to human beings. It generally demonstrates low human lethality even in large ingestions. Substitution of imidacloprid for organophosphorus compounds in areas where the incidence of self-poisoning is high may reduce such mortalities.[25] For imidacloprid, regarded as safe for human beings, toxicity can occur through inhalation exposure as in the present case. Few case reports of attempted suicides have been described.[17,18] Till date neuropsychiatric symptoms in imidacloprid poisoning have been reported in one case with inhalational exposure mainly due to central nicotinic stimulation.[19] Cardiovascular manifestations like tachycardia, bradycardia, arrhythmia, and cardiac arrest were also described in different case reports.[17] There is a paucity of information about human toxicity. In some of them, the authors concluded that the other ingredients in the formulated product were more likely to account for many of the observed signs.[17,18]

In a prospective case series of 68 cases in Srilanka, it was found that the majority developed mild gastrointestinal disorders and other symptoms. Only one case required mechanical ventilation for respiratory failure but there were no deaths.[25] It was demonstrated that imidacloprid self-poisoning resulted in mostly minor toxicity and was nonfatal. It seems favorable compared to outcomes with other insecticides, particularly organophosphorus compounds which commonly have a case fatality between 5% and 30%.[28,29]

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6. Conclusion

Imidacloprid is generally less toxic to humans causing mild symptoms. However all the precautions must be taken during its handling. In the case of acute toxicity, respiratory failure and reduced level of consciousness are the most serious but uncommon complications. Care should be taken so that these may not get confused with/mistaken as an organophosphorus compound. Substitution of imidacloprid for organophosphorus compounds in highly affected areas may save a number of precious lives. As the clinical consequences of poisoning with newer pesticides like imidacloprid are not very well described therefore such information is valuable for clinicians, regulatory authorities and public at large. Clinical outcomes rely on early recognition, prompt referral and aggressive management. Awareness programs about its toxicity should be implemented at different levels.

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