INVITED ARTICLE

Neonicotinoid Poisoning and Management

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Abstract

Neonicotinoids are a newer class of insecticides, which act on postsynaptic nicotinic acetylcholine esterase receptors. Its use is gradually increasing over recent years due to its better safety profile compared to other commonly used pesticides like organophosphates, organochlorides, carbamates, and pyrethroids. The better toxicological profile is attributed to more selectivity for insects compared to mammals and decreased penetration through the blood–brain barrier. Common symptoms of self-poisoning described are dizziness, hypertension, tachycardia, nausea, vomiting, eye irritation, dermatitis, and oral mucosal lesions. Mortality due to poisoning is less than 3%. Till date, there is no specific antidote for neonicotinoid poisoning and management of poisoning is symptomatic and supportive.

Keywords: Acute poisoning, Insecticide, Neonicotinoid.

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Introduction

Acute pesticide poisoning is an important cause of intentional self-poisoning in India. The World Health Organization (WHO) estimates around 3,00,000 deaths per year due to pesticide poisoning in the Asia-pacific region.[1] Among various pesticides, organophosphates are the major cause of self-poisoning death in southern and central India[2] and aluminum phosphide is the major cause in some parts of northern India.[3] Other pesticides used for self-poisoning are organochlorides, carbamates, and pyrethroids. Due to high mortality of these compounds, there has been a constant search for newer pesticides with a favorable safety profile. Neonicotinoids are a newer class of insecticides with increasing usage in recent decades because of their favorable toxicological profile. Neonicotinoids have very high margin of safety because of specificity of the insecticides for nicotinic acetyl choline receptors (nAChRs) in insects than mammals combined with rapid metabolism and poor penetration to the blood–brain barrier. The mortality due to neonicotinoid poisoning is 0–2.9%,[4,5] which is very much less than that of other pesticides.

Classification

Neonicotinoids are a newer class of pesticides used in the agricultural industry for crop protection, horticulture, and fleas control. In 1972, the first neonicotinoid nithiazine was developed but was never commercialized. Imidacloprid, a chloronicotinyl neonicotinoid, is the first agent in the group to be used as a commercial pesticide. Its use is gradually increasing over years and is currently one of the best-selling insecticides all over the world. Other members of this group are thiamethoxam, clothianidin, thiacloprid, acetamiprid, dinotefuran, nitenpyram, imidaclothiz, flonicamid, sulfoxaflor, and cycloxaprid. The classification of this group is shown in Table 1.

Mechanism of Action

Neonicotinoids are neurotoxins that act as agonists in postsynaptic nAChRs of the nervous system mainly on the parasympathetic system and some of the sympathetic system. They bind irreversibly to the receptors that initially stimulate and then block Na^+/K^+ channels leading to blockade of transmission of nervous influx.

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Neonicotinoids have little or no effect on nAChRs of the peripheral nervous system (α1γα1δβ1 subtype) and are selective for receptor subtypes in the vertebrate brain (α4β2 and α7). The insecticidal activity is due the effect of the agents on nAChRs of insects. Their more insect toxic effect compared to the mammal is due to their affinity for the insect-specific receptor subtype (α4β2 in insects), absence of the blood–brain barrier, and predominance of the receptors in the central nervous system. The better safety profile in humans is due to the wider distribution of the receptors in the neuromuscular junction where the neonicotinoid affinity is low and decreased penetration of these agents through the blood–brain barrier. The neonicotinoids and pyrethroids have higher selectivity factors for insects vs mammals compared to other insecticides due to their target site specificity (Table 2).

Toxicokinetics

Imidacloprid is the most commonly used insecticide of the neonicotinoid group. Animal studies has shown that oral LD50 (lethal dose in 50% of animals) of imidacloprid in rats is 475 mg/kg and the acute dermal LD50 exceeds 5,000 mg/kg. Severe intoxication occurs mainly after oral ingestion. Penetration through the skin after dermal exposure is not quantified in humans and absorption through the respiratory tract is very minimal as these compounds are nonvolatile. One of the largest studies by Mohamed et al.,[5] which included 68 patients, showed that initial oral absorption is rapid within 2 hours and plasma concentration remains elevated for 10–15 hours post ingestion indicating that absorption and/or elevation follow zero-order kinetics or are

Table 1: Classification of neonicotinoids

Generation of neonicotinoids	*Type of neonicotinoid*
First-generation neonicotinoids	Imidacloprid
	Nitenpyram
	Acetamiprid
	Thiacloprid
Second-generation neonicotinoids	Thiamethoxam
	Clothianidin
Third-generation neonicotinoids	Dinotefuran
	Sulfoxaflor
	Cycloxaprid

Table 2: Mechanism of action of major insecticides

Class	*Target*	*Selectivity factor*
Neonicotinoids	nAChR*	456
Organophosphates	AChE**	33
Carbamates	AChE**	16
Organochlorines	Na^+ or Cl^- channel	91
Pyrethroids	Na^+ channel	4,500

*Nicotinic acetyl choline receptors
**Acetylcholine esterase
Data from ref. 6

prolonged after high doses. Cytochrome P450 isoenzymes play an important role in the metabolism of imidacloprid.[7] Two pathways have been identified by which imidacloprid is metabolized. One is hydroxylation and desaturation to 5-hydroxyimidacloprid and imidacloprid olefin by CYP 3A4 isoenzymes and the second is the nitroimine reduction pathway to yield nitroso guanidine, aminoguanidine, and urea imidacloprid by CYP 1A2, 2B6, 2D6, and 2E1 isoenzymes. So, concomitant use of cytochrome enzyme inhibitors increases the toxicity. There is no distribution to fat-rich tissues and penetration through the blood–brain barrier is minimal. They are not accumulated in the body and undergo complete elimination in 48 hours.

Clinical Symptoms and Presentation

Clinical symptoms of neonicotinoid poisoning are less severe in humans because of their decreased affinity for human nicotinic receptors, rapid metabolism by cytochrome enzymes, and their limited ability to cross the blood–brain barrier. Clinical features are better described for imidacloprid that is the most commonly used insecticide in the neonicotinoid group. One of the large reports of neonicotinoid symptomatology is from the Texas Poison Center, which included 1,142 exposures during the period 2000–2012.[8] The main symptoms described in the study after exposure are dizziness, hypertension, tachycardia, nausea, vomiting, eye irritation, dermatitis, oral mucosal lesions.[8] Neonicotinoid initially stimulates the nicotinic receptors in the nervous system followed by blockade of nerve transmission by continued stimulation leading to fatigue. This effect leads to initial symptoms like headache, agitation fasciculations, seizures followed by disorientation, drowsiness, decreased muscle tone, and coma. Stimulation of receptors in the autonomic nervous system leads to tachycardia, hypertension, diaphoresis, and mydriasis. Gastrointestinal symptoms like nausea, vomiting, abdominal pain, and corrosive damage to orogastric mucosa are common. Severe clinical features like respiratory failure, ventricular fibrillation, myocardial ischemia due to coronary vasospasm, acute renal failure, and rhabdomyolysis have been reported.[4,9–13] Concomitant intoxication of imidacloprid with alcohol leading to multiorgan failure and death has been reported in a case report.[14] Solvents used in the insecticide also play a role in poisoning symptoms. The most commonly used solvent in neonicotinoid is *N*-methylpyrrolidone. Ingestion of a large amount of this solvent causes abdominal pain, oral ulceration, nausea, vomiting, dysphagia, and odynophagia.[13]

Management

Management of acute neonicotinoid poisoning is mainly symptomatic and supportive. Dermal and mucosal decontamination and removal of contaminated clothes should be done immediately as these compounds undergo absorption by the dermal and inhalational route. Gastric decontamination should be considered after large volume ingestion (over 100 mL) and if the patient presents within 1 hour. Gastric lavage and activated charcoal should be avoided if corrosive damage to the orogastric mucosa is suspected due to the solvent. Assisted ventilation and hemodynamic support should be considered in the presence of hypotension, poor glasgow coma scale (GCS<8), hypoventilation, or respiratory distress. In case of hoarseness of voice or stridor, the airway should be secured as early as possible and endoscopic evaluation of the vocal cords and airway mucosa should be done.

There is no specific antidote for neonicotinoid agents. Neonicotinoid poisoning can sometimes present with muscarinic clinical features such as excessive salivation, lacrimation, urination, bronchorrhea, miosis, and bradycardia similar to organophosphates.[15] Atropine and oximes may be administered inadvertently because of the clinical presentation. Oximes are ineffective or sometimes can cause adverse effects when administered in neonicotinoid poisoning. Oximes have weak acetyl choline esterase inhibiting activity and can cause tachycardia, hypertension, and other nicotinic symptoms if administered in the absence of organophosphate compounds. However, careful use of atropine may be justified if patients present with severe life-threatening clinical features like severe bronchorrhea leading to airway compromise or severe bradycardia.

Conclusion

Neonicotinoids are a newer class of insecticide and their use is increasing over recent years. Because of their wider application, number of poisoning is also increasing over the recent decades. Although neonicotinoids appear to be less toxic compared to other insecticides, sometimes severe complications like respiratory failure, ventricular fibrillation, and death have been reported. There is no specific antidote and management at present is supportive and symptomatic. Available evidence for toxicokinetics of neonicotinoids and management of poisoning is mainly based on animal studies, case reports, and case series. More research is required for evidence-based management of neonicotinoid poisoning.

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