Amitraz Poisoning: An Emerging and yet Underestimated Poison—A Review

Sidhant Sachdeva, Gurinder Mohan, Parminder Singh

ABSTRACT

Background: Amitraz is a member of the formamidine family of pesticides. Its structure is 1,5-di-(2,4-dimethylphenyl)-3-methyl-1,3,5-triazapenta-1,4-diene. It is used as an agricultural insecticide for fruit crops and as an acaricide for dogs and livestock. Awareness about amitraz, its toxicity, and its management remains poor among physicians, which is probably the reason for underreporting of amitraz intoxication in remote rural areas. In this systematic review on amitraz intoxication, we focus on demographics, toxicokinetics, mechanisms of toxicity, clinical features, and treatment modalities in amitraz poisoning.

Materials and methods: EmBase and Medline databases were searched for the following terms: “amitraz,” “intoxication,” “poisoning,” and “toxicity.” Case reports, case series, and original articles describing human cases of amitraz poisoning were included.

Results: A total of 251 articles were retrieved after excluding citations common to the two databases. A total of 63 articles described human cases. The clinical manifestations vary from central nervous system (CNS) depression (drowsiness, coma, and convulsions), miosis or mydriasis, respiratory depression, bradycardia, hypotension, hyperthermia or hypothermia, hyperglycemia, polyuria, vomiting, and reduced gastrointestinal motility. Only six reported deaths have been reported (case fatality rate, 1.9%). The proposed lethal dose of the toxin was reported to be 200 mg/kg. Around 33% of patients developed respiratory failure and 20% of them needed mechanical ventilation.

Interpretation and conclusion: Amitraz poisoning occurs in either accidental or suicidal manner and is more common in children than adults. There is no specific antidote for this toxin till date. It has an excellent prognosis with supportive management.

Keywords: Amitraz, Organophosphate/carbamate, Poison.


INTRODUCTION

Amitraz is a member of the formamidine family of pesticides. Its structure is 1,5-di-(2,4-dimethylphenyl)-3-methyl-1,3,5-triazapenta-1,4-diene. It is used as an agricultural insecticide for fruit crops and as an acaricide for dogs and livestock. It is most commonly marketed as a 12.5–50% aqueous solution and has to be diluted in water in a 1:100–1:1000 ratio before use. In most of the preparations, xylene is used as a solvent. Tetrachloroethylene and mixtures of petroleum products containing predominantly aromatic hydrocarbons are the other solvents commonly used. It is classified as “Class III—slightly toxic” and a group C “possible” human carcinogen. The first human case of poisoning was reported in 1983.

Amitraz is available without a physician’s prescription in all leading chemist shops under variety of trade names. In India, the most common brand name is “Ridd.”

Amitraz is pharmacologically active with an alpha-2-agonist action. The stimulatory effect on alpha 2 receptors is mainly responsible for neurotoxic and proconvulsant effects. It also acts by inhibiting MAO activity and PGE2 synthesis. Amitraz poisoning commonly occurs through oral or dermal routes and potentially by inhalation. The clinical manifestations vary from central nervous system (CNS) depression (drowsiness, coma, and convulsions), miosis or mydriasis, respiratory depression, bradycardia, hypotension, hyperthermia or hypothermia, hyperglycemia, polyuria, vomiting, and reduced gastrointestinal motility. Awareness about amitraz, its toxicity, and its management remains poor among physicians, which is probably the reason for underreporting of amitraz intoxication in remote rural areas. Also, it is commonly confused with organophosphate/carbamate (OPC) poisoning. India has reported several cases over the past few years. Review articles on amitraz have also been published by Yilmaz and Yildizdas and Proudfoot. In this systematic review on amitraz intoxication, we focus on demographics, toxicokinetics, mechanisms of toxicity, clinical features, and treatment modalities in amitraz poisoning.

MATERIALS AND METHODS

EmBase and Medline databases were searched for the following terms: “amitraz,” “intoxication,” “poisoning,” and “toxicity.” Case reports, case series, and original articles describing human cases of amitraz poisoning were included. A total of 251 articles were retrieved after excluding citations common to the two databases. A total of 63 articles described human cases.

Twenty articles were excluded as four were abstracts, and articles that were published in a language other than English. The search hence yielded 41 articles.
Initial Review of Studies
The initial database generated from the electronic searches was compiled and the full text of each selected citation was obtained and reviewed in detail.

Data Abstraction
The data collected were recorded on a standard data extraction form. The following items were extracted: (1) publication details (title, authors, and year of publication); (2) route (oral, dermal, or other) and manner (accidental, suicidal, and therapeutic misadventure) of poisoning; (3) country; (4) females and children (≤13 years of age) reported in the study; (5) time of onset of symptoms; (6) quantity of poison consumed; (7) signs and symptoms reported; (8) inotropic support, mechanical ventilation, and specific treatment (gastric lavage, activated charcoal, atropine, and others) offered to patients; (9) extubation or weaning, discharge from ICU or hospital, and recovery of sensorium; and (10) death.

RESULTS
Epidemiology
A majority (56.5%) of the patients were children and there was no gender predilection (51.3% males and 48.7% females) among the cases. The commonest route of exposure to the poison was by ingestion (91.9%) followed by the percutaneous route (7.4%) and rarely by inhalation and intravenous injection of the toxin.26,35 The manner of poisoning was accidental (56.5%) in the majority followed by suicidal ingestion (30%). Few (16) patients had intentional percutaneous exposure as in some regions in Turkey, amitraz had been used to treat scabies and pediculosis in humans.37 In 8.4% of the patients, the manner of poisoning was unreported. One homicidal poisoning was reported.44

Toxicokinetics
Most of the studies reported an onset of symptoms within 3 hours. With oral ingestion, appearance of symptoms was earlier, and the recovery was delayed as compared to percutaneous exposure.37 The duration of action is short and the elimination half-life in serum is only 4 hours, the major terminal metabolite being 3-methyl-4-amino benzoic acid, which is excreted by the kidneys.1,7

Dose–response Relationship
The amount of poison consumed ranged from 63 mg to 100 g. Ten studies reported a dose of more than 12 g. The proposed lethal dose of the toxin is 200 mg/kg.34,44 Therefore, with an average adult weight of 60 kg, a dose of 12 g is supposedly lethal. Death was reported in only two patients in the 10 studies with an intake of more than 12 g amitraz. The exact dose and clinical course was available only for one patient and the death was attributable to the poisoning itself as reported by Hu et al.36 A 53-year-old female who had consumed 100 g of the poison and developed refractory torsades de pointes.

Clinical Features
The clinical characteristics of the poisoning cases reported are shown in Table 1. The toxic effects of the compound on various organs of the human body have been summarized below.

Effects on the Nervous System
CNS depression manifesting as sleepiness, drowsiness, or complete loss of consciousness depending on the dose of the toxin consumed42 was the most common neurological abnormality. The duration of CNS depression had a positive correlation with the amount of amitraz taken. Most patients regained consciousness by 48 hours possibly due to the short elimination half-life of the toxin. Alternative causes should be looked for if altered sensorium persists beyond this duration. Cerebral edema in brain imaging was documented in two studies.5,24 Seizures occurred in <33% of the cases.

Amitraz exposure caused constriction of pupils at lower doses but dilation at higher doses (Table 2).4,12,13,20,23,26,31,34,35,37,42,45–52 The same patient can have both miosis and mydriasis at different times. Ataxia, hallucinations, and hypotonia were rarely reported neurological defects.

Effects on the Cardiovascular System
Cardiovascular manifestations occur mainly due to the stimulation of presynaptic α2-adrenergic receptors (Table 2).12,45,47,48 Bradycardia was the most common cardiovascular manifestation observed in more than 33% of the patients. Hypotension occurred in a smaller
Table 2: Systemic effects of amitraz and their underlying mechanisms

<table>
<thead>
<tr>
<th>Effects</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Altered sensorium (CNS depression)</td>
<td>Simulation of the central α2-adrenergic receptors and contributed by xylene solvent</td>
</tr>
<tr>
<td>Miosis</td>
<td>Presynaptic α2-adrenergic stimulation (low doses)</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>Postsynaptic α2-adrenergic stimulation (at higher doses), atropine administration</td>
</tr>
<tr>
<td>Seizures</td>
<td>Stimulation of the central α2-adrenergic receptors</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Inhibition of insulin secretion and stimulation of glucagon secretion</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Stimulation of the dorsal motor nucleus of the vagal nerve through presynaptic α2-adrenergic agonist action</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Simulation of the central presynaptic α2-adrenergic receptors with diminution of peripheral sympathetic tone</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Inhibition of response to CO₂ by direct effect on respiratory center</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Inhibition of prostaglandin synthesis</td>
</tr>
<tr>
<td>Raised transaminases</td>
<td>Reduced hepatic glutathione activity by amitraz, although xylene may be a potential cause</td>
</tr>
<tr>
<td>Polyuria</td>
<td>Decreased ADH secretion and inhibition of its renal effect, hyperglycemia, and excessive fluid administration</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Due to the solvent</td>
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</tbody>
</table>

The clinicians were unfamiliar with amitraz in 89% of the instances in a report from a poison information center. Recovering the poison container and discerning the active compound in the preparation should be encouraged among clinicians. Three most common features of this poisoning are altered sensorium, miosis, and bradycardia, which can often mislead physicians into diagnosing the patient with OPC poisoning. Features that point toward amitraz poisoning as opposed to OPC toxicity include presence of hyperglycemia, hypothermia, and reduced gastrointestinal motility. The absence of fasciculations and a hypersecretory state (salivation, lacrimation, perspiration, and diarrhea) also point against OPC poisoning. Features that point toward OPC poisoning include presence of increased cancer risk in humans. Amitraz has been found to have teratogenic effect in frogs, but there is no human data.

Effects of the Gastrointestinal System and Liver

Vomiting was reported in most of the patients. Asymptomatic transaminits may occur usually with a normal bilirubin. Dry mouth, decreased intestinal motility, and abdominal distension were rarely reported. One case of Ogilvie's syndrome (acute colonic pseudo-obstruction) was also reported (Table 1).

Effects of the Respiratory System

Respiratory depression occurred in majority of the cases (Table 1) in the form of bradypnea, respiratory acidosis, or respiratory arrest due to direct effect of the poison. Aspiration pneumonia was also reported in a small proportion of patients.

Effects on Metabolism and Homeostasis

Hyperglycemia, a distinctive feature of this poisoning was observed in 50% of the patients. Hypoglycemia and glycosuria were rarely reported. Hypothermia occurred commonly while fever was rare. Polyuria may also occur.

Management was mainly supportive as there is no specific antidote and mainly depended on cardiovascular, respiratory, and CNS stability. Around 33% of patients developed respiratory failure and 20% of them needed mechanical ventilation; however, most got extubated within 48 hours (within 24 hours in our case). Intravenous fluids and vasopressors/inotropes were administered as per the need. One debatable point in the treatment was the use of atropine. While majority of the literature states that atropine is effective precisely in symptomatic bradycardia and atrioventricular blocks, some authors believe that it can be used in bradycardia induced by other mechanisms such as amitraz toxicity.

Discussion

The results of this systematic review suggest that amitraz poisoning is not a widely reported intoxication. It has varying clinical manifestations and carries a good prognosis. Turkey reported a large proportion of cases of amitraz poisoning (15 articles, 220 cases). Six reports on amitraz poisoning have been published from India in the last 6 years. A large number of cases (69 patients) have been reported from South Africa. Toxic exposure in humans may occur by inhalation, ingestion, or by skin contact. Animal studies show that absorption from the gut occurs at a high rate. Amitraz concentrations are measurable in the plasma within 2 hours of ingestion. Amitraz is primarily metabolized rapidly in vivo to produce two metabolites: 2,4-dimethyl formanilide (BTS-27919) and an active metabolite N′-(2,4-dimethylphenyl)-N-methyl-formamidine (BTS27271), resulting in a rapid onset of symptoms. It also acts as a MAO inhibitor and an inhibitor of PGE2; however, the role of these actions in poisoning is unclear. Amitraz has been classified as a "possible" human carcinogen by the US EPA as it is shown to increase the risk of lymphoreticular malignancies and liver adenoma/carcinoma in mice. However, there are no reports of increased cancer risk in humans. Amitraz has been found to have teratogenic effect in frogs, but there is no human data.

There is no specific antidote for amitraz poisoning and treatment is mainly supportive. Monitoring of respiratory, cardiovascular, and CNS functions is required.
removed and the skin should be washed with soap and water in case of skin exposure. To avoid the risk of aspiration, endotracheal intubation should be done early in unconscious patients.

Intravenous fluids and inotropes must be administered promptly in patients with shock. Clinical benefit of gastric lavage and activated charcoal has not been established. Organic solvents in the formulation increase the risk of aspiration if gastric lavage is attempted. Therefore, it should be performed only in cases of massive ingestion after endotracheal intubation. Activated charcoal is safer but the clinical benefit is again uncertain. Role of atropine is controversial. It has been shown to improve bradycardia in many of the patients, while in some patients, dopamine was used for the treatment of bradycardia. Atropine is effective only in patients with symptomatic bradycardia in amitraz poisoning and is usually not required for those with only asymptomatic bradycardia or miosis. Although there is no antidote, few animal studies have demonstrated that α₂-adrenergic antagonists such as yohimbine or methyldopa can reverse most of the clinical and laboratory signs of amitraz poisoning. However, these drugs have not been used in human poisoning. Patients may sometimes receive naloxone for the mistaken diagnosis of OPC poisoning. Although naloxone has been used successfully for clonidine poisoning (α₂-adrenergic agonist), it has proven to be ineffective in amitraz poisoning. Amitraz poisoning carries a good prognosis with a low case fatality rate. The probable reason for the low case fatality rate was that the compound was most commonly available in a 12.5% solution. The dose and route of exposure to the poison seem to be the most important factors affecting the clinical course and prognosis. Since there are no randomized trials, no conclusions can be drawn on the ideal management strategy for this poisoning.

**Conclusion**

Amitraz poisoning occurs in either accidental or suicidal manner and is more common in children than adults. Majority of the cases have been reported from Turkey, though there has been a recent rise in the number of cases reported from South Africa and India. There is no specific antidote for this toxin till date. It has an excellent prognosis with supportive management.

**References**


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