Amitraz poisoning, an emerging problem: epidemiology, clinical features, management, and preventive strategies

H L Yilmaz, D R Yildizdas

Background: Amitraz is a pharmaceutical, veterinary, and agricultural product which is used worldwide under numerous generic names as an acaricide and insecticide. Because of its widespread use amitraz poisoning has come emerged as a cause of childhood poisoning during the past decade, particularly more in certain countries such as Turkey.

Aims and Methods: To report the clinical features, the management, and the preventive strategies of amitraz poisoning in nine children, and review the previously reported 137 cases in humans.

Results: Five male and four female children aged 10 months to 8 years were admitted to our department. The estimated ingested dose ranged between 89.2 and 163 mg/kg and estimated time from ingestion to presentation was 30–120 minutes. The initial signs and symptoms were impaired consciousness, drowsiness, vomiting, disorientation, miosis, mydriasis, hypertension, bradycardia, tachyphoea, hyperthermia, and generalised seizures. Hyperglycaemia, glycosuria, and minimal increase in transaminase levels were observed. None required mechanical ventilation. CNS depression resolved spontaneously within 4–28 hours in all. The length of hospital stay was two to three days; all had a good outcome.

Conclusion: This review details preventive measures and management strategies of amitraz poisoning, including the importance of following patients closely in the intensive care unit, monitoring their respiratory, cardiovascular, and central nervous systems since they may occasionally experience serious cardiopulmonary side effects.

Amitraz is a synthetic compound with insecticide and acaricide properties used worldwide on both animals and crops to control pests. Its wide spectrum makes it appropriate for numerous conditions varying from red spider mites on fruit crops to ticks, lice, or keds on livestock.\(^1\) Commercial formulations of amitraz generally contain 12.5–20% of the drug in organic solvents, especially xylene, which is also used as a solvent in paints, cleaners, and glues.\(^1\) It is diluted with water before applying to plants and animals.\(^2\)

When humans are exposed to amitraz, the symptoms and signs result from both xylene and amitraz.\(^2\) Poisoning presents with numerous symptoms varying from central nervous system (CNS) depression (drowsiness, coma, and convulsion), to miosis, or, rarely, mydriasis, respiratory depression, bradycardia, hypertension, hypertension, hyperthermia or fever, hyperglycaemia, polyuria, vomiting, decreased gastrointestinal motility, and intestinal distension.\(^1\) Xylene may cause acute toxic signs, such as: CNS depression, ataxia, impaired motor coordination, nystagmus, stupor, coma, and episodes of neuroirritability.

Amitraz is an \(\alpha\) adrenergic agonist and the observed clinical effects of amitraz poisoning resemble similar effects caused by other central acting \(\alpha\) adrenergic agonists such as clonidine.\(^1,2,4\) It stimulates \(\alpha\) adrenergic receptor sites in the CNS and \(\alpha\) adrenergic and \(\alpha\) adrenergic receptor sites in the periphery.\(^6\) It also inhibits monoamine oxidase (MAO) enzyme activity and prostaglandin E\(_2\) synthesis.\(^5\) \(\alpha\) and \(\alpha\) adrenergic poisoning may occur through the oral or dermal routes and, potentially, by inhalation.\(^9\)

Many cases have been reported in animals but only 137 human cases have been reported in journals indexed in Index Medicus (Medline), EMBASE, and Science Citation Index Expanded to date. Amitraz poisoning has increased in recent years. Among the 137 cases reported, 119 are children.\(^1,3,5,16-20\) There is a high incidence in rural areas of Turkey among families raising animals, probably because of the easy availability of the product without prescription.

We report our experience with nine paediatric cases and review the clinical features, management, and preventive strategies.

PATIENTS AND METHODS

Nine children poisoned with amitraz were admitted to Cukurova University Medical Faculty, Department of Pediatric Emergency Medicine between 1995 and 2002. The proprietary name of the ingested veterinary formulation, which contains 12.5% amitraz, is Kenaz, and all parents brought with them Kenaz bottles. We made the diagnosis according to a compatible exposure history and clinical findings. We reviewed their medical charts and detailed demographic data, intoxication route, ingested dose, onset and duration of effects, clinical and laboratory presentations, management, and outcome.

The major clinical signs were as follows: hypothermia (central body temperature <36°C), hypertension (2 standard deviations below the age appropriate mean\(^25\)), bradycardia, tachycardia, tachyphoea, bradypnoea below or above the appropriate average values,\(^27\) miosis (pupils <2.5 mm\(^2\)), hyperglycaemia (serum glucose >6.66 mmol/l (>120 mg/dl)), increased transaminase levels (serum transaminase level >50 IU/l (reference range 15–40 IU/l)), polyuria (urinary output >3 ml/kg).

We searched Medline, EMBASE, and SCI-Expanded (Web of science v4.3.1) up to July 2002 using the terms: amitraz

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CNS, central nervous system; ECG, electrocardiogram; GCS, Glasgow coma score; ID, lethal dose; MAO, monoamine oxidase
### Table 1: Demographic data, and clinical and laboratory findings of cases

<table>
<thead>
<tr>
<th>Cases</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
<th>IX</th>
<th>Previously reported cases in literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>0.83</td>
<td>3</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Season</td>
<td>Summer</td>
<td>Spring</td>
<td>Summer</td>
<td>Spring</td>
<td>Spring</td>
<td>Rural</td>
<td>Spring</td>
<td>Spring</td>
</tr>
<tr>
<td>Socioeconomic level</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Type of exposure</td>
<td>Accidental</td>
<td>Accidental</td>
<td>Accidental</td>
<td>Accidental</td>
<td>Accidental</td>
<td>Accidental</td>
<td>Accidental</td>
<td>Accidental</td>
</tr>
<tr>
<td>Amount ingested (mg/kg)</td>
<td>135.9–169 (25–30 ml)</td>
<td>89.3–133.9 (10–15 ml)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>89.2 (5 ml)</td>
<td>Unknown</td>
<td>104–156.2 (10–15 ml)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Time before arrival to hospital (minutes)</td>
<td>70</td>
<td>45</td>
<td>180</td>
<td>60</td>
<td>60</td>
<td>90</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Complaints at onset</td>
<td>Vomiting</td>
<td>Dizziness</td>
<td>Disorientation</td>
<td>Respiratory depression</td>
<td>Abdominal pain</td>
<td>Convulsion</td>
<td>Drowsiness</td>
<td>Unconsciousness</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>36.5</td>
<td>36</td>
<td>37.5</td>
<td>35.8</td>
<td>35.4</td>
<td>36</td>
<td>36.5</td>
<td>36.5</td>
</tr>
<tr>
<td>Time before arrival to hospital (minutes)</td>
<td>30–60</td>
<td>30–60</td>
<td>90–120</td>
<td>30–60</td>
<td>30–60</td>
<td>30–60</td>
<td>30–60</td>
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<td>30–60</td>
<td>90–120</td>
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<td>30–60</td>
<td>30–60</td>
<td>30–60</td>
<td>30–60</td>
</tr>
</tbody>
</table>

**Kalyoncu et al reported the time of onset of symptoms of patients with amitraz poisoning is between 5 minutes and 24 hours**

**Kalyoncu et al reported the time before arrival to hospital for the patients with amitraz poisoning concerning skin exposure was 8–26 hours, and the ones with oral exposure was 1–15 hours.**
AND (poisoning OR intoxication OR toxicosis). We concentrated on human amitraz poisoning articles (which were fewer than those regarding animals). We also looked for further cases by contacting the producer of Kenaz (Atabay Agricultural Chemicals and Veterinary Medicines Inc., Turkey) and the National Poisons Control Center. We checked the reference lists of all the studies and medical texts related to amitraz poisoning for additional case reports, and studied the abstracts of scientific meetings, but have not used them in our analysis.

RESULTS

Five boys and four girls aged 10 months to 8 years were admitted to our department. Table 1 shows the demographic, clinical, and laboratory data. Eight poisonings were accidental and one a suicide attempt. Intoxication occurred orally in all. The 10 month old baby boy was given one dose (5 ml) of amitraz solution mistakenly by his mother who confused it with the expectorant syrup in a similar bottle.

The estimated ingested dose ranged from 89.2 to 163 mg/kg in four of the cases and was unknown for the other five cases. Estimated time between ingestion and presentation was 30–120 minutes.

The paediatric Glasgow coma scores (GCS) of the cases were 7–14 (median 9). The predominant initial symptom in all was vomiting, seven vomiting, and six were disorientated.

In the initial clinical evaluation six cases presented with miosis, two with mydriasis, and one with normal size pupils. Hypotension was present in four cases. There was bradycardia in four cases and tachypnoea in four. Three had a decreased body temperature (below 36°C). Short generalised seizures occurred in three cases; they responded to diazepam treatment.

Blood glucose was higher than 6.66 mmol/l (120 mg/dl) in six cases who also had glycosuria. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels increased minimally in three cases but all recovered to normal within two days. Urinary output was increased (>3 ml/kg/h) in four cases. Blood urea nitrogen, creatinine, serum sodium and potassium concentrations, and ECG were normal in all cases. None required mechanical ventilation support.

Table 2 Signs and possible mechanism of action in amitraz poisoning

<table>
<thead>
<tr>
<th>Signs</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>Central α2 adrenoceptor agonist stimulates presynaptic receptors and causes hypotension, and diminishes peripheral sympathetic tone, lowering the blood pressure [10] with augmentation by the depressive effects of xylene.</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Central α2 adrenoceptor agonist whose action results in diminished peripheral sympathetic tone with a lowering of heart rate. [6] In the animal study conducted by Cullen and Reynoldson, both yohimbine (α1 adrenergic antagonist) and prazosin (α2 adrenergic antagonist) partially inhibited the bradycardia produced by amitraz. Thus, it might be concluded that both adrenoceptor subtypes appear to be stimulated to produce bradycardia.</td>
</tr>
<tr>
<td>Miosis and mydriasis</td>
<td>While the low doses of α2 adrenergic agonists induce miosis (presynaptic effect), the higher doses cause mydriasis (postsynaptic effect). [13] Xylene contributes to bradycardia by its depressive effect on the central nervous system.</td>
</tr>
<tr>
<td>Bradypnoea</td>
<td>Bradypnoea occurs by inhibition of response against CO₂ via direct effect of the agent on respiratory centre. [42] [43] Xylene may also induce altered mental status.</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>α2 adrenoceptor stimulation causes sedation and unconsciousness. [12] [20] Xylene induces unconsciousness in animals.</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>The animal study conducted by Hugnet and colleagues showed that hypothermia could be related to the α1 agonist activity of amitraz because it was reversed by low doses of atimepazole, a potent α1 antagonist, within 10 minutes after injection.</td>
</tr>
<tr>
<td>Vomiting</td>
<td>It is not probably an effect due to α2 adrenergic agonist activity as it has not been noted in animal experiments with amitraz.</td>
</tr>
<tr>
<td>Convulsion</td>
<td>Neurotoxic and proconvulsant effects are triggered by α2 receptors partially.</td>
</tr>
<tr>
<td>Polyuria</td>
<td>α2 adrenoceptor stimulation decreases antidiuretic hormone (ADH) and renin secretion, inhibition of ADH effect, and enhanced diuresis by increased glomerular filtration rate.</td>
</tr>
<tr>
<td>Gastrointestinal hypotonicity</td>
<td>α2 adrenoceptor stimulation causes hypomotility.</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>α2 adrenoceptor stimulation reduces insulin secretion and causes hyperglycaemia. [28] The animal study conducted by Abu-Basha and colleagues showed that amitraz inhibited insulin and stimulated glucagon secretion from the perfused rat pancreas, and inhibited insulin secretion.</td>
</tr>
</tbody>
</table>

All cases received gastric lavage and activated charcoal. Six patients with hypotension received intravenous fluid repletion, with four improving and two requiring dopamine infusion for four hours. Atropine was used in cases V, VI, and VII, who had both bradycardia and hypotension. Cases VI and VII responded to the medication but case V required dopamine infusion for four hours. Atropine was used in cases V, VI, and VII, who had both bradycardia and hypotension. Cases VI and VII responded to the medication but case V required dopamine infusion for four hours. Atropine was used in cases V, VI, and VII, who had both bradycardia and hypotension. Cases VI and VII responded to the medication but case V required dopamine infusion for four hours. Atropine was used in cases V, VI, and VII, who had both bradycardia and hypotension. Cases VI and VII responded to the medication but case V required dopamine infusion for four hours.

During hospitalisation one child developed fever (38.5°C). CNS depression resolved spontaneously within 4–28 hours (median 12 hours) in all patients. The length of hospital stay was two to three days. All the patients had good outcomes with no long term morbidity.

DISCUSSION

Amitraz is a pharmaceutical, veterinary, and agricultural product which is sold and used worldwide under numerous generic names.\[^{11}\] It can cause poisoning in animals and humans when ingested, inhaled, or after skin exposure.\[^{11}\] The minimal toxic dose previously reported was 3.57 mg/kg.\[^{11}\] There have been two deaths reported in humans. One ingested 6 g amitraz; the dose in the other was not known.\[^{11}\] \[^{25}\]\[^{28}\] Studies in animals showed the oral LD₅₀ as 523–800 mg/kg in rats and >2000 mg/kg in mice.\[^{27}\]\[^{28}\] The dermal LD₅₀ was <1600 mg/kg for rats and >2000 mg/kg for rabbits.\[^{27}\]\[^{28}\] Table 2 describes the symptoms and the mechanisms of amitraz poisoning. Except for those reported by Kalyoncu and colleagues,\[^{28}\] previous authors\[^{1\}\] and colleagues\[^{28}\] reported the onset and the duration of action for oral poisoning as 30–180 minutes, compatible with our results (table 1). However, Kalyoncu and colleagues\[^{28}\] reported that it was 5 minutes to 6 hours, and that onset and the duration of action for dermal exposure was 5 minutes to 24 hours. Although the levels of BUN, creatinine, and serum sodium and potassium usually do not change,\[^{10}\]\[^{11}\] Kalyoncu and colleagues\[^{28}\] reported hyponatraemia in three cases. Rarely there is a minimal increase in the level of serum ALT and AST.\[^{10}\] \[^{11}\] No abnormality has been reported in the blood gases except for the study by Kalyoncu and colleagues.\[^{28}\] They reported respiratory alkalosis in two cases, respiratory acidosis in three cases, and metabolic acidosis in five cases. In the study by Aydin and colleagues,\[^{7}\] non-specific ST changes were reported in the ECGs of seven children with
no history of cardiac disease who recovered completely in 24 hours. We did not observe any changes in ECG in our cases.

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If history of the respiratory, cardiovascular, and central nervous system is suspected, naloxone may lead to severe effects on the body systems causing coma and respiratory failure.13 The clinical presentations of our cases were relatively mild and did not require intubation or mechanical ventilation. Supportive measures include oxygen, supporting the blood pressure, and perfusion by administering fluids and/or vasopressors.13 Inotropic agents (dopamine or noradrenaline) should be added as a second line therapy, but dopamine might potentiate MAO inhibiting drugs, so dosage should be as low as possible.13 If present, seizures should be controlled by administering lorazepam or diazepam.13 We do not recommend gastric lavage, unless the dose is massive, because of the presence of petroleum distillate in amitraz formulations. It should be performed after endotracheal intubation in order to avoid inhalation or aspiration pneumonitis, which should be checked by baseline chest x ray and follow up films in 6–24 hours.13 Although the effects of activated charcoal and cathartics have not been studied, they may still be considered for treatment.13

Using atropine is controversial.13 However, most studies reported that using atropine for those with both bradycardia and bradycardia resolved the problem.13–15 Atropine is a first line therapy for the bradycardia that occurs from vagal stimulation and atroventricular blocks, but not for that related to other mechanisms.13 According to some animal studies atropine adrenergic drugs cause bradycardia by stimulating the dorsal motor nucleus of the vagal nerve.19–22 Hsu and colleagues claimed that atropine (0.045 mg/kg intravenously) increased heart rate and prevented amitraz induced bradycardia or miosis in animals. Cullen and Reynolds10 showed that presor responses to amitraz were slightly enhanced by atropine while bradycardia was reduced by it. In our study we used atropine on three of our patients who had bradycardia hypotension, and miosis together and two of them recovered. The third case, a 10 month old baby, was given three doses of atropine which did not eliminate bradycardia; dopamine (5 µg/kg/min) had to be added to the therapy. We conclude that atropine is effective when there is only symptomatic bradycardia in amitraz poisoning. However, asymptomatic bradycardia or miosis does not require atropine use.

To date there has been no specific antidote reported for amitraz poisoning in humans; several α, adrenergic receptor antagonists have been tried without success. However, in some experiments on animals α1 adrenergic antagonists such as yohimbine and atimepazole have been effective in reversing most of the clinical and laboratory signs of amitraz poisoning.15–16 These two agents might be considered for humans only in severe cases not responding to the usual measures.15–16 Clonidine is a central α2 adrenergic agonist which induces similar poisoning effects to amitraz.16 Naloxone has been used successfully in clonidine overdose.17 Two animal studies have looked specifically for the effects of naloxone on respiratory and CNS depression, but it did not prove to be successful.17–18 Further investigation is needed to clarify its effectiveness.

A total of 84.6% of amitraz poisoning cases have been reported to occur accidentally and mainly among children. This emphasises the importance of taking serious precautions against this drug. We believe that action by producers, regulatory authorities, and national poisons control centres can minimise amitraz poisoning. For example: containers could be redesigned as childproof packages with striking and clear warning labels; public education should be expanded on primary prevention of poisoning using media sources; and there should be new legislation for safety caps on poison containers.16–18

Authors’ affiliations
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