Systematic Review

Indian J Med Res 144, September 2016, pp 348-358
DOI: 10.4103/0971-5916.198723

Quick Response Code:

Amitraz, an underrecognized poison: A systematic review

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Received June 30, 2014

***Background & objectives*: Amitraz is a member of formamidine family of pesticides. Poisoning from amitraz is underrecognized even in areas where it is widely available. It is frequently misdiagnosed as organophosphate poisoning. This systematic review provides information on the epidemiology, toxicokinetics, mechanisms of toxicity, clinical features, diagnosis and management of amitraz poisoning.**

***Methods*: Medline and Embase databases were searched systematically (since inception to January 2014) for case reports, case series and original articles using the following search terms: 'amitraz', 'poisoning', 'toxicity', 'intoxication' and 'overdose'. Articles published in a language other than English, abstracts and those not providing sufficient clinical information were excluded.**

***Results*: The original search yielded 239 articles, of which 52 articles described human cases. After following the inclusion and exclusion criteria, 32 studies describing 310 cases (151 females, 175 children) of human poisoning with amitraz were included in this systematic review. The most commonly reported clinical features of amitraz poisoning were altered sensorium, miosis, hyperglycaemia, bradycardia, vomiting, respiratory failure, hypotension and hypothermia. Amitraz poisoning carried a good prognosis with only six reported deaths (case fatality rate, 1.9%). Nearly 20 and 11.9 per cent of the patients required mechanical ventilation and inotropic support, respectively. The role of decontamination methods, namely, gastric lavage and activated charcoal was unclear.**

***Interpretation & conclusions*: Our review shows that amitraz is an important agent for accidental or suicidal poisoning in both adults and children. It has a good prognosis with supportive management.**

Key words Amitraz - intoxication - morbidity - overdose - pesticide - poisoning - toxicity

Amitraz, chemically 1,5 di-(2,4-dimethylphenyl)-3-methyl-1,3,5-triazapenta-1,4-diene is a member of the formamidine family of pesticides[1]. It is used as a veterinary ectoparasiticide (acaricide) for dogs and livestock, and as an agricultural insecticide for fruit crops[2]. It has been available for use since 1974[3], and is marketed under various trade names. It is supplied as a 12.5-50 per cent aqueous solution to be diluted in water in 1:100-1:1000 ratio before use. Xylene is used as a solvent in most of the preparations[4]. Other solvents include tetrachloroethylene and mixtures of petroleum products containing predominantly aromatic hydrocarbons[5]. The United States Environmental Protection Agency (US EPA) classifies oral amitraz exposure as 'Class III- slightly toxic' and a group C 'possible' human carcinogen[6]. The first human case of poisoning was reported in 1983[7] though amitraz is widely available in many regions worldwide.

This incongruity is probably attributable to under-reporting of amitraz intoxication in remote rural areas, as awareness about amitraz, its toxicity and its management remains poor among physicians[5]. In addition, it is often misdiagnosed as organophosphate/carbamate (OPC) poisoning[5,8]. A sizeable number of cases of human intoxication with amitraz have been reported over the past three decades. There have been several reports from India in the past five years[9-11]. Yilmaz and Yildizdas had reviewed 137 cases of amitraz poisoning in 2003[12]. Proudfoot published a narrative review on amitraz poisoning in 2003[13].Veale *et al*[5] presented the worldwide demographic data of amitraz poisoning in 2011, but they did not elaborate on the details of clinical features and management. This systematic review on amitraz intoxication describes the demographics, toxicokinetics, mechanisms of toxicity, clinical features and treatment modalities used in amitraz poisoning.

Material & Methods

Search strategy: Medline and EmBase databases (since inception to January 23, 2014) were searched using the following search terms: 'amitraz', 'poisoning', 'toxicity', 'intoxication', and 'overdose'. Citations describing human cases of amitraz poisoning including case reports, case series and original articles were included. The cross references of these articles were searched for more relevant articles. Articles published in a language other than English, those presented only as an abstract and those not providing sufficient clinical information, were excluded.

Initial review of studies: The initial database generated from the electronic searches was compiled in the reference manager package Endnote (version X7; Thomson Reuters, New York, USA), and all duplicate citations were eliminated. The citations were first screened by both the authors and disagreement was resolved by discussion. This database was then screened again to include only relevant articles. The full text of each selected citation was obtained and reviewed in detail.

Data abstraction: Data were recorded on a standard data extraction form. The following items were extracted: (*i*) publication details (title, authors and year of publication); (*ii*) country where the study was conducted; (*iii*) number of females and children (≤13 yr of age) reported in the study; (*iv*) route (oral, dermal or other) and manner (accidental, suicidal, and therapeutic misadventure) of poisoning; (*v*) amount of poison consumed; (*vi*) time of onset of symptoms; (*vii*) clinical symptoms and signs reported; (*viii*) life support (mechanical ventilation and inotropic support) and specific treatment (including gastric lavage, activated charcoal, atropine and others) offered to patients; (*ix*) time to recovery of sensorium, extubation/weaning and discharge from intensive care unit (ICU) or hospital; and (*x*) death, if any.

Results

The initial search retrieved a total of 239 articles after excluding citations common to the two databases. Fifty two articles describing human cases were found. Twenty articles were excluded due to the following reasons: (*i*) four were abstracts[14-17]; (*ii*) four had insufficient clinical details of cases[18-21]; (*iii*) one report described cases, the details of whom were included in a later paper with a larger sample size[22,23]; and (*iv*) 11 articles (33 patients) were published in a language other than English. The search thus yielded 32 studies reporting 310 cases of amitraz poisoning (Table I)[1,3-5,7-12,23-44]. Three cases from the series described by Bonsall and Turnbull[7] were excluded due to lack of clinical data.

Epidemiology: There was no gender predilection (51.3% males and 48.7% females) among the cases. A majority (56.5%) of the patients were children. The predominant route of exposure to the poison was by ingestion (91.9%) followed by the percutaneous route (7.4%). One patient had exposure by inhalation, while another patient presented with intravenous injection of the toxin[27,36]. The manner of poisoning was accidental (56.5%) in the majority while 30 per cent of the patients presented with suicidal ingestion. Sixteen patients had intentional percutaneous exposure as in some regions in Turkey, amitraz had been used to treat scabies and pediculosis in humans[38]. The manner of intoxication was unknown or not reported in 8.4 per cent of the patients. One homicidal poisoning was also reported[35]. No peculiarities of this poisoning were found in the subgroups of females and children.

Toxicokinetics: Majority of studies included (22/32, 68.8%) reported an onset of symptoms within three hours (Table I). The duration of action is short as the elimination half-life in serum is only four hours, the major terminal metabolite being 3-methyl-4-aminobenzoic acid, which is excreted by the kidneys[1,7]. Appearance of symptoms was earlier, and the recovery was delayed with oral ingestion as compared to percutaneous exposure[38].

Table I. Details of studies included in this systematic review of amitraz poisoning

Author	Year	Country	No. of individuals	No. of females	Children	Age	Number in whom the amount of poison has been mentioned	Amount	Onset of symptoms
Bonsall and Turnbull[7]	1983	NR	1*	0	0	74 yr	1	6 g	1 h
Jones[4]	1990	USA	1	0	1	3 yr	1	2 g	NR
Kennel *et al*[39]	1996	France	4	1	1	15 months - 82 yr	1	12.5 g	NR
Jorens *et al*[1]	1997	Belgium	1	0	0	45 yr	1	250 mg	1 h
Leung *et al*[40]	1999	PR China	1	0	0	33 yr	1	4 g	<1 h
Yaramis *et al*[44]	2000	Turkey	11	4	11	2.5-6 yr	0	NA	30-90 min
Ulukaya *et al*[43]	2001	Turkey	10	5	5	4-34 yr	2	6.3 g	<1 h - several hours
Atabek *et al*[26]	2002	Turkey	14	6	14	2-5 yr	0	NA	30-150 min
Aydin *et al*[23]	2002	Turkey	24	8	24	2-6 yr	0	NR	30-120 min
Doganay *et al*[33]	2002	Turkey	2	0	0	35-80 yr	2	1.8-12.5 g	<3 h
Ertekin *et al*[35]	2002	Turkey	21	8	21	5 months - 9 yr	0	NR	30-180 min
Kalyoncu *et al*[38]	2002	Turkey	43	19	43	10 months - 13 yr	0	NA	5 min-24 h
Caksen *et al*[30]	2003	Turkey	8	3	8	1-4 yr	8	1.3-1.9 g	1-4 h
Yilmaz and Yildizdas[12]	2003	Turkey	9	4	9	10 months - 8 yr	4	89-169 mg/kg	30-120 min
Agin *et al*[24]	2004	Turkey	7	2	7	2-6 yr	2	3.1-3.8 g	30-150 min
Aslan *et al*[25]	2005	Turkey	1	1	0	36 yr	0	NA	<3 h
Elinav *et al*[8]	2005	Israel	1	0	0	54 yr	1	3.8 g	30 min
Gursoy *et al*[36]	2005	Turkey	1	1	0	22 yr	1	0.8 g	1-2 min
Avsarogullari *et al*[27]	2006	Turkey	23	14	0	16-78 yr	13	1.9-12.5 g	30-120 min
Beyaztas *et al*[29]	2006	Turkey	1	0	0	46 yr	1	12.5 g	120 min
Demirel *et al*[32]	2006	Turkey	45	35	1	4-97 yr	45	0.6-12.5 g	<1 h in 28, >1 h in 17
Vucinic *et al*[3]	2007	Serbia	1	0	0	72 yr	1	10 g	30 min
Hu *et al*[37]	2010	Taiwan	1	1	0	53 yr	1	100 g	<1 h
Shitole *et al*[9]	2010	India	3	3	1	2-40 yr	3	3.8 g	90-150 min
Chakraborty *et al*[31]	2011	India	1	0	0	18 yr	1	6.3 g	150 min
Eizadi-Mood *et al*[34]	2011	Iran	1	1	0	22 yr	1	40 g	<1 h

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Author	Year	Country	No. of individuals	No. of females	Children	Age	Number in whom the amount of poison has been mentioned	Amount	Onset of symptoms
Veale *et al*[5]	2011	South Africa	69	33	28	NR	5	0.6-12.5 g	2-3 h
Batra *et al*[28]	2012	India	1	0	0	42 yr	0	NR	NR
Mwita[41]	2012	Kenya	1	1	0	25 yr	0	NR	NR
Sweta *et al*[10]	2013	India	1	1	0	15 yr	1	18.8 g	NR
Varma *et al*[11]	2013	India	1	0	1	13 yr	1	15.6 g	<30 min
Rajesh *et al*[42]	2014	India	1	0	0	14 yr	1	63 mg	NR
Total			310	151	175	5 months - 97 yr	99	63 mg-100 g	1 min-24 h

*Details of all cases not available. NR, not reported

Dose-response relationship: The amount of poison consumed was reported in 99 (31.9%) cases (Table I). It ranged from 63 mg to 100 g. A dose of more than 12 g was reported in ten studies. The proposed lethal dose of the toxin is 200 mg/kg[35,45]. Accordingly, with an average adult weight of 60 kg, a dose of 12 g is supposedly lethal. Of those ten studies with an intake of more than 12 g amitraz, death was reported in only two patients. The only death for which the information on the exact dose and clinical course was available and the death was attributable to the poisoning itself was the patient reported by Hu *et al*[37].This patient was a 53 yr old female who had consumed 100 g of the poison and developed refractory torsades de pointes. The amitraz level in the serum of this patient was 0.78 mg/ml, while that of BTS-27271, a metabolite of amitraz was 0.49 mg/ml.

Clinical features: The clinical characteristics of the cases reported in the included studies are shown in Table II. The toxic effects of this compound on various organ systems of the human body are summarized below.

Effects on the nervous system: Central nervous system (CNS) depression was the most common neurological abnormality in this poisoning. It occurs in the form of sleepiness, drowsiness, or complete loss of consciousness depending on the dose of the toxin consumed[43]. There was a positive correlation observed between the amount of amitraz taken and duration of CNS depression[32]. It is noteworthy that nearly all patients regain consciousness by 48 h (Table III). This is possibly due to the short elimination half-life of the toxin. If altered sensorium persists beyond this duration, alternative causes should be looked for. Cerebral oedema was documented by brain imaging in two studies[9,25]. Seizures occurred in <33 per cent of the patients (Table II). Amitraz exposure causes constriction of pupils at lower doses (in about 50% of the patients), but may cause dilation at higher doses due to different mechanisms of action (Table IV)[4,12,13,21,26,27,32,35,36,38,43,46-53]. Both miosis and mydriasis can occur in the same patient at different times. Rarely reported neurological defects include ataxia, hallucinations, and hypotonia[38,41,42].

Effects on the cardiovascular system: Bradycardia was the most common cardiovascular manifestation observed in >33 per cent of the patients. Hypotension occurred in a smaller proportion (<33%) of cases (Table II). Cardiovascular manifestations occur mainly due to the stimulation of presynaptic α_2-adrenergic receptors (Table IV)[12,46,48,49]. Hypertension was reported

Table II. Frequencies of various clinical features described in amitraz poisoning

Clinical features	References
Common (present in more than a third (33%) of patients	
Altered sensorium	1,3,5,7-12,23-44
Miosis	3,5,9-12,23-30,32-35,38,39,42-44
Hyperglycaemia	3-5,8,9,12,23-30,32,33,35,37-40,43,44
Bradycardia	1,5,8-10,12,23-40,42-44
Vomiting	8-12,24-27,29,31,32,34,35,38-40,43,44
Respiratory depression/failure	3,5,8-12,23-40,43,44
Less common (present in less than a third (33%) of patients	
Hypotension	5,8-12,23-29,32,33,35-37,39,40,42-44
Hypothermia	5,9,12,23,24,26,29,32,33,35-38,43,44
Glycosuria	3,7,9,12,23,26,35,38
Mydriasis	1,5,8,9,12,23,26,27,31,32,36-38,41
Raised transaminases	7,11,12,23,26,27,29,30,32-37,43
Polyuria	12,23,26,33,38,43
Seizures	5,9,12,23,26,32,35,38
Aspiration pneumonitis	5,26,29,32
Rare (reported in one or a few case reports)	
Ataxia	38,41
Hallucinations	41
Hypotonia	42
Hypertension	32
Atrial fibrillation	3
Ventricular arrhythmias	32,33
Torsades de pointes	37
Dry mouth	5
Decreased intestinal motility	22,26
Abdominal distension	35
Ogilvie's syndrome	25
Hypoglycaemia	32,38
Fever	32,43
Cerebral oedema	9,25
Hyponatremia	38

in one study[32]. Arrhythmias including atrial fibrillation and ventricular arrhythmias occurred, which responded to standard treatment[3,33]. Fatal torsades de pointes was reported in one case[37].

Effects on the respiratory system: Respiratory depression occurred in >33 per cent of the cases (Table II). It occurred in the form of bradypnoea, respiratory acidosis, or respiratory arrest due to direct effect of the poison. Aspiration pneumonia was reported in a small proportion of patients.

Effects on the gastrointestinal system and liver: Vomiting was reported in >33 per cent of the patients. Asymptomatic rise in liver transaminases may occur usually with a normal bilirubin. Rarely reported features include dry mouth, decreased intestinal motility, and abdominal distension[5,22,26,35]. A case of Ogilvie's syndrome (acute colonic pseudo-obstruction) was also reported[25] (Table II).

Effects on metabolism and homeostasis: Hyperglycaemia is a distinctive feature of this

Table III. Various treatment modalities and outcomes reported for amitraz poisoning

Author	Gastric lavage, N	Activated charcoal, N	Atropine, N	Mechanical ventilation, N	Inotrope, N	Time to regaining consciousness	Duration of MV	Duration of hospital/ICU stay	Death, N
Bonsall and Turnbull[7]	1	0	0	0	0	48 h	NR	NR	1
Jones[4]	0	0	0	0	0	NR	NR	NR	0
Kennel *et al*[39]	1	0	1	1	0	6-24 h	NR	NR	0
Jorens *et al*[1]	0	0	1	0	1	4 h	NA	NR	0
Leung *et al*[40]	0	0	1	0	0	12 h	NA	NR	0
Yaramis *et al*[44]	11	11	11	0	0	8.5-14 h	NA	<48 h	0
Ulukaya *et al*[43]	0	0	0	5	0	NR	2-23 h	2-5 days	0
Atabek *et al*[26]	3	3	11	4	3	6-24 h	NR	48-72 h	0
Aydin *et al*[23]	24	24	0	4	10	8-24 h	<24 h	NR	0
Doganay *et al*[33]	0	2	2	1	1	14-22 h	24 h	4-5 days	0
Ertekin *et al*[35]	21	21	13	1	0	6-28 h	NR	1-5 days	0
Kalyoncu *et al*[38]	29	9	0	0	0	2-48 h	NA	18-88 h	0
Caksen *et al*[30]	8	8	2	0	0	NR	NA	1-6 days	0
Yilmaz and Yildizdas[12]	9	9	3	0	2	4-28 h	NA	2-3 days	0
Agin *et al*[24]	5	4	4	2	0	6-20 h	4-8 h	18-62 h	0
Aslan *et al*[25]	1	1	1	0	0	12 h	NA	7 days	0
Elinav *et al*[8]	0	0	1	1	0	48 h	NR	4 days	0
Gursoy *et al*[36]	0	0	1	0	1	8 h	NA	NR	0
Avsarogullari *et al*[27]	21	21	20	5	1	NR	50±16 h	5 h-11 days	1
Beyaztas *et al*[29]	1	1	1	1	1	NR	4 days	4 days	1
Demirel *et al*[32]	0	0	35	19	11	5-24 h	2-96 h	2-15 days	0
Vucinic *et al*[3]	1	0	0	1	0	2 days	2 days	5 days	0
Hu *et al*[37]	1	0	0	1	1	NA	NR	<24 h	1
Shitole *et al*[9]	3	0	0	1	2	<5 h	7 h	18-90 h	0
Chakraborty *et al*[31]	1	0	0	0	NA	24 h	NA	NR	0
Eizadi-Mood *et al*[34]	1	1	1	1	0	20 h	17 h	NR	0
Veale *et al*[5]	0	0	0	11	0	1-4 days	1-4 days	1-6 days	2
Batra *et al*[28]	1	0	1	1	1	NR	NR	6 days	0
Mwita[41]	1	0	1	0	0	38 h	NA	6 days	0
Sweta *et al*[10]	1	1	1	1	0	NR	48 h	48 h	0

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Author	Gastric lavage, N	Activated charcoal, N	Atropine, N	Mechanical ventilation, N	Inotrope, N	Time to regaining consciousness	Duration of MV	Duration of hospital/ICU stay	Death, N
Varma *et al*[11]	1	0	1	1	1	48 h	NR	NR	0
Rajesh *et al*[42]	0	0	0	0	1	34 h	NA	5 days	0
Total	146	116	113	62	37	2 h-6 days	2 h-4 days	5 h-15 days	6
Percentage	47.1	37.4	36.5	20.0	11.9				1.9

MV, mechanical ventilation; N, number of patients; NA, not applicable; NR, not reported; ICU, intensive care unit

poisoning observed in almost half of the patients. Glycosuria was documented in a small proportion of the patients (Table II). Hypoglycaemia has been rarely reported[32,38]. Hypothermia was relatively common, while fever was rarely seen[32,43]. Polyuria may occur due to multiple mechanisms (Table IV).

About 33 per cent of the patients of amitraz poisoning developed respiratory depression (Table II) and 20 per cent of the patients required mechanical ventilation, although most of them were weaned off by 48 h (Table III). The case fatality rate was low (1.9%) with only six deaths reported among 310 cases (Table III). Only one of the six deaths could be directly attributed to the effects of the poison (Table V)[37]. One patient died 30 days after discharge possibly due to unrelated causes[7]. Two other deaths occurred due to pulmonary thromboembolism and ventilator-associated pneumonia on the third and fourth days of hospital admission, respectively; and thus, they were not attributable directly to the effects of the poison[27,42]. The causes of two of the deaths were not available[5].

Discussion

The results of this systematic review suggest that amitraz poisoning is a widely reported intoxication. It has multitudinous clinical manifestations and generally carries a good prognosis.

A large proportion of cases of amitraz poisoning has been reported from Turkey (15 articles, 220 cases). In the last five years, six reports on amitraz poisoning have been published from India[9-11,28,31,42]. A large number of cases (69 patients) have been reported from South Africa[5]. A large survey of all acute poisonings in South Africa reported that around one per cent of the 4771 consultations sought from a poison information centre were concerning amitraz[18].

Toxic exposure in humans may occur by ingestion, inhalation or skin contact. Absorption from the gut occurs at a high rate, as shown in animal studies[54,55]. Amitraz concentrations are measurable in the plasma within two hours of ingestion[1,21]. Amitraz is metabolized rapidly *in vivo* to produce two primary 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[6,7,37]. BTS-27271 acts through the octopamine receptors in invertebrates, which are responsible for its acaricidal and insecticidal activities. In vertebrates, it acts mainly on the α_2-adrenergic receptor which is structurally similar to the octopamine

Table IV. Systemic effects of amitraz and their underlying mechanisms

Effects	Mechanism
Altered sensorium (CNS depression)	Simulation of the central α_2-adrenergic receptors and contributed by xylene solvent[4,12,36]
Pupil size	Miosis: presynaptic α_2-adrenergic stimulation (low doses) Mydriasis: postsynaptic α_2-adrenergic stimulation (at higher doses), atropine administration[26,32,38,43,46]
Seizures	Stimulation of the central α_2-adrenergic receptors[12]
Hyperglycaemia	Inhibition of insulin secretion and stimulation of glucagon secretion[47]
Bradycardia	Stimulation of the dorsal motor nucleus of the vagal nerve through presynaptic α_2-adrenergic agonist action[12,46,48,49]
Hypotension	Simulation of the central presynaptic α_2-adrenergic receptors with diminution of peripheral sympathetic tone[50,51]
Respiratory depression	Inhibition of response to CO_2 by direct effect on respiratory centre[51]
Hypothermia	Inhibition of prostaglandin synthesis[52]
Raised transaminases	Reduced hepatic glutathione activity by amitraz, although xylene may be a potential cause[27,35]
Polyuria	Decreased ADH secretion and inhibition of its renal effect[8,51], hyperglycaemia and excessive fluid administration[53]
Vomiting	Due to the solvent; not been observed in animal studies using pure amitraz[13,21,27]

CNS, central nervous system; ADH, alcohol dehydrogenases

receptor[4]. It acts as an agonist on both pre- and post-synaptic α_2-adrenergic receptors[43,56]. Presynaptic receptor stimulation inhibits norepinephrine discharge, while stimulation of postsynaptic receptors leads to effects similar to α_1-stimulation[26,43]. It also acts as a monoamine synthesis inhibitor and an inhibitor of prostaglandin E2; however, the role of these actions in poisoning is unclear. Table IV shows the proposed mechanisms underlying the systemic effects of this toxin.

Amitraz has been classified as a 'possible' human carcinogen by the US EPA based on the studies on mice which have shown an increase in the risk of lymphoreticular malignancies and liver adenoma/carcinoma[6]. However, there are no reports of increased cancer risk in humans. Amitraz has been found to be teratogenic in frogs[57], but there is a lack of human data. Among human cases, a pregnant woman who consumed amitraz at 18 wk of pregnancy subsequently made a complete recovery with treatment and gave birth to a healthy neonate at term[58].

In a report from a poison information centre, the clinicians were unfamiliar with amitraz in 89 per cent of the instances[18]. Physicians should always insist on recovering the poison container and discerning the active compound in the preparation. Altered sensorium, miosis and bradycardia are three most common features of this poisoning. These features often mislead physicians into diagnosing the patient with OPC poisoning. Certain features point towards amitraz poisoning as opposed to OPC toxicity. These include presence of hyperglycaemia, hypothermia, and reduced gastrointestinal motility. Further, the absence of fasciculations and a hypersecretory state (salivation, lacrimation, perspiration, and diarrhoea) points against OPC poisoning. Smell of a solvent or a 'mothball-like' odour may be noticed on presentation in amitraz poisoning, while a garlic-like smell is encountered with OPC poisoning[3,38,59]. Besides, serum cholinesterase levels remain normal in amitraz poisoning, while these are low in OPC poisoning[5,28,42]. Gas chromatography-mass spectrometry and gas liquid chromatography have been used to detect the presence and measure the levels of amitraz and its metabolites in the serum and urine[1,3,37].

There is no specific antidote for amitraz poisoning. Management is supportive. Monitoring of respiratory, cardiovascular and CNS functions is essential[12]. In case of skin exposure, the contaminated clothing should be removed and the skin should be washed with soap and water. Endotracheal intubation should be done early in unconscious patients to avoid the risk of aspiration.

Table V. Characteristics of patients who expired after amitraz poisoning

Authors	Age	Cause of death	Brand of amitraz	Dose	Serum levels	Clinical features	MV required	Duration of stay (days)
Bonsall and Turnbull[7]	NR	NR	MITAC 20 EC	NR	NR	NR	NR	6
Avsarogullari *et al*[27]	NR	Pulmonary embolism	NR	NR	NR	NR	NR	3
Beyaztas *et al*[29]	46 yr	Septicemia due to pulmonary infection due to *Pseudomonas aurtiginosa*	kenaz	12.5 g	NR	Nausea, vomiting, dizziness, and dysphagia, lethargy, hypothermia (35°C), respiratory distress (moist crackles in his right lung), miosis	Yes	4
Hu *et al*[57]	53 yr	Refractory torsades de pointes	NR	100 g	Amitraz- 0.78 mg/mL; BTS 27271-0.49 mg/ml	Unconsciousness, bradycardia, hypotension	Yes	1
Veale *et al*[5]*	Adult	Respiratory failure	NR	NR	NR	NR	NR	NR

*Two deaths were reported in this study. MV, mechanical ventilation; NR, not reported; BTS27271, N'-(2,4-dimethylphenyl)-N-methyl-formamidine

Intravenous fluids and vasopressors/inotropes must be administered in hypotensive patients. There are no randomized controlled trials performed to date to clarify the true clinical benefit of gastric lavage and activated charcoal. In the studies included in this review, gastric lavage was performed in only 47.1 per cent of the patients (146/310) and activated charcoal was administered to only 37.4 per cent (116/310) of them (Table III). There are concerns that organic solvents present in the formulation may increase the risk of aspiration if gastric lavage is attempted[13]. Therefore, it should be performed only after endotracheal intubation, in cases of massive ingestion[12,21].

Activated charcoal is relatively safer; however the clinical benefit is again uncertain. Role of atropine is controversial. It has been shown to abrogate bradycardia in many of the patients, while in others dopamine was used for the treatment of bradycardia[1,12,23,26]. In this review, bradycardia was reported in 47.1 per cent of the patients, while only 36.5 per cent are reported to have received atropine (Table III). Yilmaz and Yildizdas[12] suggest that atropine is effective only in patients with symptomatic bradycardia in amitraz poisoning and is not required for those with only asymptomatic bradycardia and/or miosis.

Although there is no antidote, animal studies have demonstrated that α_2-adrenergic antagonists such as yohimbine and atipamezole can reverse most of the clinical and laboratory signs of amitraz poisoning[60,61]. These drugs, however, have not been used in human poisoning. Occasionally, patients receive pralidoxime for the mistaken diagnosis of OPC poisoning, which is however not recommended[27]. Naloxone used successfully for clonidine poisoning (α_2-adrenergic agonist) has proved to be ineffective in animal studies of amitraz poisoning[62,63].

Amitraz poisoning carries a good prognosis with a low case fatality rate. The most important factors affecting the clinical course and prognosis seem to be the dose and route of exposure to the poison. The possible reason for the low case fatality rate was that the compound was most commonly available in a 12.5 per cent solution. At this dilution, a large quantity needs to be consumed for a lethal effect.

There were a few limitations of this review. We did not have access to patient level data for all studies, therefore, certain factors such as the relationship of dose of poison consumed and the severity of the effects could not be analyzed for the entire patient population.

As there are no randomized trials, no conclusions can be drawn on the ideal management strategy for this poisoning.

In conclusion, the present analysis shows that amitraz poisoning occurs in either accidental or suicidal manner and is more common in children than adults. Though majority of the cases have been reported from Turkey, there has been a recent rise in the number of cases reported from South Africa and India. There is no antidote for this toxin. It has an excellent prognosis with supportive management.

***Conflicts of Interest*:** None.

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