ORIGINAL ARTICLE

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

H L Yilmaz, D R Yildizdas

Arch Dis Child 2003;**88**:130–134

See end of article for authors' affiliations

Correspondence to: Dr H L Yilmaz, Yeni Baraj Mah. 1 Sok. Gülek Plaza A Blok 6/9, Adana 01550, Turkey; hyilmaz@mail.cu.edu.tr

Accepted 22 August 2002

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, hypotension, bradycardia, tachypnoea, hypothermia, 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.[1–5] 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.[4 6 7] It is diluted with water before applying to plants and animals.[1 6]

When humans are exposed to amitraz, the symptoms and signs result from both xylene and amitraz.[1] Poisoning presents with numerous symptoms varying from central nervous system (CNS) depression (drowsiness, coma, and convulsion), to miosis, or, rarely, mydriasis, respiratory depression, bradycardia, hypotension, hypertension, hypothermia or fever, hyperglycaemia, polyuria, vomiting, decreased gastrointestinal motility, and intestinal distension.[1–3 8–15] Xylene may cause acute toxic signs, such as: CNS depression, ataxia, impaired motor coordination, nystagmus, stupor, coma, and episodes of neuroirritability.[4]

Amitraz is an α_2 adrenergic agonist and the observed clinical effects of amitraz poisoning resemble similar effects caused by other central acting α_2 adrenergic agonists such as clonidine.[1 2 4 8] It stimulates α_2 adrenergic receptor sites in the CNS and α_1 adrenergic and α_2 adrenergic receptor sites in the periphery.[16] It also inhibits monoamine oxidase (MAO) enzyme activity and prostaglandin E_2 synthesis.[2 9 17 18] Amitraz poisoning may occur through the oral or dermal routes and, potentially, by inhalation.[10]

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.[2 3 8–15 19–21] 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), hypotension (2 standard deviations below the age appropriate mean[22]), bradycardia, tachycardia, tachypnoea, bradypnoea below or above the appropriate average values,[23] miosis (pupils <2.5 mm[24]), mydriasis (pupils >4 mm[24]), 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/h).

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; LD, lethal dose; MAO, monoamine oxidase

Table 1 Demographic data, and clinical and laboratory findings of cases

	Cases									
	I	II	III	IV	V	VI	VII	VIII	IX	Previously reported cases in literature
Age (years)	8	3	5	4	0.83	3	2.5	2.5	3	0.41–80
Gender	Female	Male	Female	Male	Male	Male	Male	Female	Female	81 male, 56 female
Season	Summer	Spring	Summer	Spring	Summer	Spring	Summer	Spring	Spring	–
Place of poisoning	Rural	Urban (slum area)	Urban (slum area)	Urban (slum area)	Rural	Urban (slum area)	Urban (slum area)	Urban (slum area)	Rural	64/64 rural
Socioeconomic level	Low	Low	Normal	Low	Low	Normal	Low	Low	Low	–
Type of exposure	Suicidal	Accidental	Accidental	Accidental	Accidental	Accidental	Accidental	Accidental	Accidental	116 unintentional, 21 suicidal
Route of poisoning	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	99 oral, 17 dermal
Amount ingested (mg/kg)	135.9–169 (25–30 ml)	89.3–133.9 (10–15 ml)	Unknown	Unknown	89.2 (5 ml)	Unknown	104–156.2 (10–15 ml)	Unknown	Unknown	2–50 ml
Onset of symptoms (minutes)	30–60	30–60	90–120	30–60	30–60	30–60	30–60	30–60	30–60	36 (<1 hour), 19 (>1 hour), 39 (not reported) Kalyoncu *et al* reported that the time of onset of symptoms of patients with amitraz poisoning is between 5 minutes and 24 hours*
Time before arrival to hospital (minutes)	70	45	180	60	60	90	60	60	45	–**
Complaints at onset										
Vomiting	+	–	+	–	+	+	+	+	+	59/137
Dizziness	–	–	+	–	–	–	–	–	–	1/137
Disorientation	–	–	+	+	–	+	+	+	+	–
Respiratory depression	+	–	+	+	–	+	–	–	–	42/137
Abdominal pain	+	–	+	+	–	–	–	–	+	–
Convulsion	+	–	–	–	–	+	–	+	–	12/137
Drowsiness	–	+	+	+	+	+	+	+	+	87/137
Unconsciousness	+	–	+	–	–	–	+	+	+	76/137
Initial signs at physical examination										
Body temperature (°C)	36.5	36	37.5	35.8↓	35.4↓	36	36.5	36.5	35.8↓	24/137 (<36°C body temperature) 3/137 (≥38°C body temperature)
Heart rate/min	104	128	132↑	76↓	80↓	72↓	72↓	104	111	65/137 bradycardia
Respiratory rate/min	20	34↑	32↑	32↑	32	34↑	24	24	16↓	48/137 bradypnoea, 2/137 tachypnoea, 2/137 apnoea
Blood pressure (mm Hg) (systolic/diastolic)	100/70	90/60	100/60	70/50↓	60/35↓	70/40↓	60/35↓	90/55	110/70	40/137 hypotension, 6/137 hypertension
Paediatric GCS	7	13	9	14	13	13	9	9	9	–
Altered mental status	+	+	+	+	+	+	+	+	+	125/137
Unconsciousness	+	–	+	–	–	–	+	+	+	82/137
Pupil size	Miosis	Miosis	Miosis	Mydriasis	Miosis	Mydriasis	Miosis	Normal	Miosis	85/137 miosis, 11/137 mydriasis
Initial laboratory findings										
Glycosuria	+	–	+	–	+	–	+	+	+	33/102 glycosuria
Blood glucose (mg/dl)	306↑	106	293↑	90	215↑	94	200↑	231↑	324↑	84/137 hyperglycaemia, 1/137 hypoglycaemia
ALT/AST (U/l)	31/29	43/42	55/33	44/32	65/53	32/13	33/21	10/15	81/13	16/126 minimal increased ALT/AST
pH	7.408	7.300	7.370	7.380	7.350	7.305	7.360	7.350	7.380	–
pCO_2	52.6	39.9	39.2	39.1	39.4	38.4	36.7	43.0	32.0	–
pO_2	45.4	55.2	50.5	38.4	52.3	55.4	62.4	60.1	42.0	–
Urinary output	Increased	Normal	Normal	Normal	Normal	Normal	Increased	Increased	Increased	29/116 polyuria
Atropine (0.02 mg/kg/dose)	–	–	–	–	3 doses	2 doses	1 doses	–	–	Used for 65/137 cases
Mechanical ventilation	–	–	–	–	–	–	–	–	–	17/137
Recovery of CNS depression (hours)	28	4	7	12	11	22	21	24	6	2–48
Hypothermia during hospitalisation	–	–	+	–	–	–	–	–	–	–
Hypotension during hospitalisation	+	–	–	–	+	+	–	–	+	–
Tachycardia during hospitalisation	–	+	–	–	–	–	–	–	–	–
Bradycardia during hospitalisation	+	–	+	–	+	–	–	–	–	–
Length of stay in the PICU (days)	3	2	2.5	2	2	3	2	3	3	1–5
Predicted outcome	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured	2/137 died

*Kalyoncu *et al* reported the time of onset of symptoms of the patients with amitraz poisoning concerning skin exposure was between 5 minutes and 24 hours, and the ones with oral exposure was between 5 minutes and 6 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.

Table 2 Signs and possible mechanism of action in amitraz poisoning

Signs	Mechanism of action
Hypotension	Central α_2 adrenoceptor agonist stimulates presynaptic receptors and causes hypotension, and diminishes peripheral sympathetic tone, lowering the blood pressure[1 16] with augmentation by the depressive effects of xylene[4]
Bradycardia	Central α_2 adrenoceptor agonist effect whose action results in diminished peripheral sympathetic tone with a lowering of heart rate[1 41] In the animal study conducted by Cullen and Reynoldson,[16] both yohimbine (α_2 adrenergic antagonist) and prazosin (α_1 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 Xylene contributes to bradycardia by its depressive affect on the central nervous system[4]
Miosis and mydriasis	While the low doses of α_2 adrenergic agonists induce miosis (presynaptic effect), the higher doses cause mydriasis (postsynaptic effect)[42–44]
Bradypnoea	Bradypnoea occurs by inhibition of response against CO_2 via direct effect of the agent on respiratory centre[42 43]
Altered mental status	α_2 adrenoceptor stimulation causes sedation and unconsciousness[4 35] Xylene may also induce altered mental status[1 4 45]
Hypothermia	The animal study conducted by Hugnet and colleagues[35] showed that hypothermia could be related to the α_2 agonist activity of amitraz because it was reversed by low doses of atimepazole, a potent α_2 antagonist, within 10 minutes after injection
Vomiting	It is not probably an effect due to α_2 adrenergic agonist activity as it has not been noted in animal experiments with amitraz alone.[4] It is probably due to the petroleum distillates mixed with amitraz in commercial preparations[1 4]
Convulsion	Neurotoxic and proconvulsant effects are triggered by α_2 receptors partially[18]
Polyuria	α_2 adrenoceptor stimulation decreases antidiuretic hormone (ADH) and renin secretion, inhibition of ADH effect, and enhanced diuresis by increased glomerular filtration rate[43]
Gastrointestinal hypomotility	α_2 adrenoceptor stimulation causes hypomotility[46 47]
Hyperglycaemia	α_2 adrenoceptor stimulation reduces insulin secretion and causes hyperglycaemia.[36] The animal study conducted by Abu-Basha and colleagues[48] showed that amitraz inhibited insulin and stimulated glucagon secretion from the perfused rat pancreas, and inhibited insulin secretion

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 impaired consciousness. Eight patients presented with drowsiness, 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 were observed 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.

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 (5 μg/kg/min) as a second line therapy and recovered in two 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.[1 10] The minimal toxic dose previously reported was 3.57 mg/kg.[2] There have been two deaths reported in humans. One ingested 6 g amitraz; the dose in the other was not known.[25 26] Studies in animals showed the oral LD_{50} as 523–800 mg/kg in rats and >1600 mg/kg in mice.[27] The dermal LD_{50} was <1600 mg/kg for rats and >200 mg/kg for rabbits.[27]

Table 2 describes the symptoms and the mechanisms of amitraz poisoning. Except for those reported by Kalyoncu and colleagues,[28] previous authors[2 3 8 11 19–21] 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] Kalyoncu and colleagues[28] reported hyponatraemia in three cases. Rarely there is a minimal increase in the level of serum ALT and AST.[8 10 13] No abnormality has been reported in the blood gasses 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,[8] 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.

Seventeen of 137 cases (12.4%) suffered severe respiratory depression requiring mechanical ventilation for less than 24 hours.[1 3 8 10 13] The resolution time for CNS depression was reported to be 2–48 hours in the previous reports.[2 3 8 19–21] Except for the two fatal cases, all, including our patients, were discharged uneventfully in less than a week.

Some other poisoning types can present with similar symptoms and signs which might lead to diagnostic confusion. These are caused by opioids, organophosphates, and centrally acting α_2 adrenergic agonist drugs, particularly clonidine. Sedative hypnotics such as barbiturates, benzodiazepines, phenothiazines, and tricyclic antidepressants may sometimes display similar signs and symptoms. Therefore, physicians should inform their diagnosis by combining the information obtained from the patients/parents/babysitter about the exposure history, observing the specific symptoms of poisoning and using the toxicological screening and more specific measurements.

As there is not a specific antidote for amitraz poisoning, management should be supportive and symptomatic. Particular attention must be given to monitoring and evaluation of the respiratory, cardiac, and central nervous systems. Since the sedative effects of α_2 agonists are dose dependent, increased intake 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.[1] 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.[1 3 11 13]

If present, seizures should be controlled by administering lorazepam or diazepam.[1 3 9] 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.[1 9] Although the effects of activated charcoal and cathartics have not been studied, they may still be considered for treatment.[1]

Using atropine is controversial.[2 3 8 10 12 28] However, most studies reported that using atropine for those with both miosis and bradycardia resolved the problem.[3 8 19–21] Atropine is a first line therapy for the bradycardia that occurs from vagal stimulation and atrioventricular blocks, but not for that related to other mechanisms.[29] According to some animal studies α_2 adrenergic drugs cause bradycardia by stimulating the dorsal motor nucleus of the vagal nerve.[30–32] Hsu and colleagues[33] claimed that atropine (0.045 mg/kg intravenously) increased heart rate and prevented amitraz induced bradycardia in animals. Cullen and Reynoldson[34] showed that pressor 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 using 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_2 adrenergic receptor antagonists have been tried without success. However, in some experiments on animals α_2 adrenergic antagonists such as yohimbine and atimepazole have been effective in reversing most of the clinical and laboratory signs of amitraz poisoning.[35 36] These two agents might be considered for humans only in severe cases not responding to the usual measures.[11]

Clonidine is a central α_2 adrenoceptor agonist which induces similar poisoning effects to amitraz.[2 8] Naloxone has been used successfully in clonidine overdose.[37] Two animal studies have looked specifically for the effects of naloxone on respiratory and CNS depression, but it did not prove to be successful.[38 39] 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.[40]

Authors' affiliations
H L Yilmaz, D R Yildizdas, Cukurova University Medical School, Turkey

REFERENCES

1 **Ellenhorn MJ**, ed. *Ellenhorn's medical toxicology: diagnosis and treatment of human poisoning*. Baltimore: Williams & Wilkins, 1997:1729–31.
2 **Jorens PG**, Zandijk E, Belmans L, *et al*. An unusual poisoning with the unusual pesticide amitraz. *Hum Exp Toxicol* 1997;**16**:600–1.
3 **Yaramis A**, Soker M, Bilici M. Amitraz poisoning in children. *Hum Exp Toxicol* 2000;**19**:431–2.
4 **Jones RD**. Xylene/amitraz: a pharmacologic review and profile. *Vet Hum Toxicol* 1990;**32**:446–8.
5 **Al-Qarawi AA**, Al-Damegh MS, Adam SEI. Effects of amitraz given by different routes on rats. *Vet Hum Toxicol* 1999;**41**:355–7.
6 **Leikin JB**, Paloucek FP, eds. *Poisoning & toxicology compendium with symptoms index*. Ohio: Lexi-Comp Inc., 1998:642.
7 **US Department of Health and Human Services**, Public Health Service. *Toxicological profile for xylenes (update)*. Atlanta, GA: Agency for Toxic Substances and Disease Registry (ATDSDR), 1995.
8 **Aydin K**, Per H, Kurtoglu S, *et al*. Amitraz poisoning in children. *Eur J Pediatr* 2002;**161**:349–50.
9 **Garnier R**, Chataigner D, Djebbar D. Six human cases of amitraz poisoning. *Hum Exp Toxicol* 1998;**17**:294.
10 **Aydin K**, Kurtoglu S, Poyrazoğlu MH, *et al*. Amitraz poisoning in children: clinical and laboratory findings of eight cases. *Hum Exp Toxicol* 1997;**16**:680–2.
11 **Leung VK**, Chan TY, Yeung VT. Amitraz poisoning in humans. *J Toxicol Clin Toxicol* 1999;**37**:513–14.
12 **Harvey PW**, Cockburn A, Davies WW. Commentary on "an unusual poisoning with the unusual pesticide amitraz" with respect to the pharmacology of amitraz. *Hum Exp Toxicol* 1998;**17**:191–2.
13 **Ulukaya S**, Demirag K, Moral AR. Acute amitraz intoxication in human. *Intensive Care Med* 2001;**27**:930–3.
14 **Kennel O**, Prince C, Garnier R. Four cases of amitraz poisoning in humans. *Vet Hum Toxicol* 1996;**38**:28–30.
15 **Ros JJ**, van Aken J. [Poisoning with amitraz, an agricultural anti-ectoparasitic agent]. *Ned Tijdschr Geneeskd* 1994;**138**:776–8.
16 **Cullen LK**, Reynoldson JA. Central and peripheral alpha-adrenoceptor actions of amitraz in the dog. *J Vet Pharmacol Ther* 1990;**13**:86–92.
17 **Florio JC**, Sakate M, Palermo-Neto J. Effects of amitraz on motor function. *Pharmacol Toxicol* 1993;**73**:109–14.
18 **Gilbert ME**, Mack CM. Enhanced susceptibility to kindling by chlordimeform may be mediated by local anesthetic action. *Psychopharmacology* 1989;**99**:163–7.
19 **Atabek ME**, Aydin K, Erkul I. Different clinical features of amitraz poisoning in children. *Hum Exp Toxicol* 2002;**21**:13–16.
20 **Doganay Z**, Aygun D, Altintop L, *et al*. Basic toxicological approach has been effective in two poisoned patients with amitraz ingestion: case reports. *Hum Exp Toxicol* 2002;**21**:55–7.
21 **Ertekin V**, Alp H, Selimoglu MA, *et al*. Amitraz poisoning in children: retrospective analysis of 21 cases. *J Int Med Res* 2002;**30**:203–5.
22 **Barkin RM**, ed. Appendix A-2: Vital signs and ancillary ventilatory support. *Pediatric emergency medicine: concepts and clinical practice*. St Louis: Mosby, 1997:1177.
23 **Fitzmaurice LS**. Approach to multiple trauma. In: Barkin RM, ed. *Pediatric emergency medicine: concepts and clinical practice*. St Louis: Mosby, 1997:226.
24 **Elder DS**, Scott GI, eds. *System of ophthalmology, Vol. XII: Neuro-Ophthalmology*. St Louis: Mosby, 1971:605.

25 **Bonsall JL**, Turnbull GJ. Extrapolation from safety data to management of poisoning with reference to amitraz (a formamide pesticide) and xylene. *Hum Toxicol* 1983;**2**:587–92.
26 **Crosby AD**, Geller RJ. Human effects of veterinary biological products. *Vet Hum Toxicol* 1986;**28**:569–71.
27 **US Environmental Protection Agency**. *EPA Fact Sheet No. 147, Amitraz*. Washington, DC: US EPA, 1987.
28 **Kalyoncu M**, Dilber E, Okten A. Amitraz intoxication in children in the rural Black Sea region: analysis of forty-three patients. *Hum Exp Toxicol* 2002;**21**:269–72.
29 **Anon**. Pediatric advanced life support. *Resuscitation* 2000;**46**:343–99.
30 **Sanders KH**, Jurna I. Effects of urapidil, clonidine, prazosin and propranolol on autonomic nerve activity, blood pressure and heart rate in anaesthetized rats and cats. *Eur J Pharmacol* 1985;**110**:181–90.
31 **Tsuchiya Y**, Hosokawa T, Kasuya Y. Involvement of alpha 2-adrenergic receptors in the vagal reflex-induced tracheal constriction. *J Pharmacobiodyn* 1990;**13**:30–5.
32 **Robertson HA**, Leslie RA. Noradrenergic alpha 2 binding sites in vagal dorsal motor nucleus tractus solitarius: autoradiographic localization. *Can J Physiol Pharmacol* 1985;**63**:1190–4.
33 **Hsu WH**, Lu ZX, Hembrough FB. Effect of amitraz on heart rate and aortic blood pressure in conscious dogs: influence of atropine, prazosin, tolazoline, and yohimbine. *Toxicol Appl Pharmacol* 1986;**84**:418–22.
34 **Cullen LK**, Reynoldson JA. Cardiovascular responses to amitraz in the presence of autonomic antagonists and agonists. *Arch Int Pharmacodyn Ther* 1988;**296**:45–56.
35 **Hugnet C**, Buronrosse F, Pineau X, *et al*. Toxicity and kinetics of amitraz in dogs. *Am J Vet Res* 1996;**57**:1506–10.
36 **Smith BE**, Hsu WH, Yang PC. Amitraz-induced glucose intolerance in rats: antagonism by yohimbine but not by prazosin. *Arch Toxicol* 1990;**64**:680–3.
37 **Nichols MH**, King WD, James LP. Clonidine poisoning in Jefferson County, Alabama. *Ann Emerg Med* 1997;**29**:511–17.
38 **Schaffer DD**, Hsu WH, Hopper DL. The effects of yohimbine and four other antagonists on amitraz-induced depression of shuttle avoidance responses in dogs. *Toxicol Appl Pharmacol* 1990;**104**:543–7.
39 **Roberts MC**, Argenzio A. Effects of amitraz, several opiate derivates and cholinergic agents on intestinal transit in ponies. *Equine Vet J* 1986;**18**:256–60.
40 **Ozanne-Smith J**, Day L, Parsons B, *et al*. Childhood poisoning: access and prevention. *J Paediatr Child Health* 2001;**37**:262–5.
41 **Costa LG**, Olibet G, Murphy SD. Alpha 2 adrenoceptors as a target for formamidine pesticides: in vitro and in vivo studies in mice. *Toxicol Appl Pharmacol* 1984;**3**:319–28.
42 **Querioz-Neto A**, Zamur G, Goncalves SC, *et al*. Characterization of the antininociceptive and sedative effect of amitraz in horses. *J Vet Pharmacol Ter* 1998;**21**:400–5.
43 **Mase M**, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anaesthesia. *Anaesthesiology* 1991;**74**:581–605.
44 **Hsu WH**, Kakuk TJ. Effect of amitraz and chloroineform on heart rate and pupil diameter in rats: mediated by α2-adrenoreceptors. *Toxicol Appl Pharmacol* 1984;**73**:411–15.
45 **Riihimaki V**, Savolainen K. Human exposure to m-xylene. Kinetics and acute effects on the central nervous system. *Ann Occup Hyg* 1980;**23**:411–22.
46 **Hsu WH**, Lu ZX. Amitraz-induced delay of gastrointestinal transit in mice: mediated by α2-adrenoreceptors. *Drug Dev Res* 1984;**4**:655–60.
47 **Hsu WH**, McNeel SV. Amitraz-induced prolongation of gastrointestinal transit and bradycardia in dogs and their antagonism by yohimbine: preliminary study. *Drug Chem Toxicol* 1985;**8**:239–53.
48 **Abu-Basha EA**, Yibchok-Anun S, Hopper DL, *et al*. Effects of pesticide amitraz and its metabolite BTS 27271 on insulin and glucagon secretion from the perfused rat pancreas: involvement of alpha2D-adrenergic receptors. *Metabolism* 1999;**48**:1461–9.