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Amitraz poisoning in a cat

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ABSTRACT: A 4-month-old male Himalayan cat presented with clinical signs of acute lethargy and motor incoordination after being treated with amitraz for parasite control. On clinical examination, the patient was lethargic and ataxic with severe pulicosis, hypothermia, pale mucous membranes, bradycardia, weak femoral pulses, hyperglycemia, and bilateral mydriasis. Blood tests revealed non-regenerative hypochromic microcytic anemia. Serum alanine levels were elevated tenfold. The patient received supportive treatment with atipamezole (an α2-adrenergic antagonist) at a dose of 0.1 mg/kg intramuscularly. After 24 h of hospitalization and constant monitoring, the patient recovered and was discharged. The published literature showed that the active ingredient amitraz is effective in the treatment of some parasitic diseases in cats, such as scabies and demodicosis; therefore, it is still used for this purpose. Given the small therapeutic margin of this insecticide, veterinarians should caution owners about its potential toxicity. This report emphasized the significance of amitraz intoxication in feline species and the success of the treatment, which should be initiated in the first hour after intoxication.
Key words: intoxication, insecticide, formamidine, felines, atipamezole, amitraz.

Intoxicação por amitraz em um gato

RESUMO: Um gato da raça Himalaia, macho, com quatro meses de idade, apresentou sinais clínicos de letargia aguda e incoordenação motora após ser medicado com amitraz para controle de parasitas. No exame clínico, o paciente se apresentava letárgico e atáxico, com pulicose grave, hipotermia, mucosaspálidas, bradicardia, pulso femoral fraco, hiperglicemia e midríase bilateral. O exame de sangue revelou anemia microcítica hipocrômica não regenerativa. Os níveis séricos de ALT estavam 10x elevados. O paciente recebeu tratamento de suporte e administração de atipamezol (antagonista α2-adrenérgico) na dose de 0,1 mg/kg por via intramuscular. Após 24 horas de internação e acompanhamento constante, o paciente se recuperou e recebeu alta. Dados publicados na literatura demonstram que o princípio ativo amitraz é eficaz no tratamento de algumas doenças parasitárias em gatos como sarna e demodicose e, portanto, ainda é utilizado para esta finalidade. Dada a pequena margem terapêutica deste inseticida, os veterinários devem informar os proprietários sobre o seu potencial de toxicidade. O objetivo deste relato é enfatizar a importância da intoxicação por amitraz na espécie felina e o sucesso do tratamento, que deve ocorrer nas primeiras horas após a intoxicação.
Palavras-chave: intoxicação, inseticida, formamidina, felinos, atipamezole, amitraz.

A four-month-old male Himalayan cat weighing 2.7 kg presented with acute lethargy and ataxia. The patient had shown severe pulicosis, prompting the owners to apply an insecticide containing amitraz as the active ingredient at a concentration of 126 mg/mL, without veterinary recommendations. The product was diluted in warm water according to the manufacturer's recommendations, and the animal was bathed with this solution. After a few minutes, while still being bathed, the patient started showing signs of lethargy, weakness, and tachypnea. At that time, the patient was urgently transferred to the feline medicine service at the veterinary teaching hospital of the University of Rio Grande do Sul (UFRGS), Brazil, where he received emergency care 1 h after the onset of clinical signs.

On clinical examination, the patient was lethargic, with a large number of fleas and flea feces present on the fur and skin, a wet coat, and the strong odor of the product used in his bath. The cat had severe hypothermia (rectal temperature: 34.7 °C), pale mucous membranes, bradycardia (heart rate: 96 bpm), weak femoral pulses, hyperglycemia (398 mg/dL), systolic blood pressure of 100 mmHg, and bilateral mydriasis.

At first, the patient was administered extensive warm baths in order to remove the toxic

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product and avoid greater cutaneous absorption. After that, the patient was dried and warmed up to recovery body temperature. The patient was administered atipamezole[b] (0.1 mg/kg, IM) and Ringer's lactate solution (2 ml/kg/h) at body temperature through a peripheral venous line. After treatment, the patient's physiological parameters returned to normal, as shown in table 1.

Blood work-up revealed non-regenerative hypochromic microcytic mild anemia (erythrocytes: 6.09 x10^{12}/L; reference interval 5 - 10.5[a] x 10^{12}/L; hemoglobin: 6.7 g/dL; reference interval 8 - 15 g/dL[a]; hematocrit: 21%; reference interval 24 - 45%[a]). Biochemical tests revealed elevated serum alanine aminotransferase (ALT) activity (932 IU/L; reference interval <83 IU/L[a]).

Six hours after initiation of treatment, the patient became alert and active and began to eat. Hospitalization was requested for vital sign monitoring and supportive treatment with fluid therapy and acetylcysteine (70 mg/kg, IV). After 24 h, the patient was discharged with a prescription of silymarin (30 mg/kg, PO) and the owners were advisedon the use of safer insecticides (active ingredients, doses, route of administration, and frequency of use) and given recommendations for a 7-day follow-up for clinical reassessment and routine blood tests. The owners did not bring the patient for further examinations, but stated that the patient was fine during phone contact.

The climatic conditions of Brazil, being a tropical country, favor the development of ectoparasites, and as a result, parasitism occupies a prominent place among the diseases that affect domestic animals (BENNETT, 1974).

In Brazil, amitraz is widely used in veterinary medicine for the control of ectoparasites, such as fleas, ticks, lice, and mites (GUPTA, 2012). It is available in various commercial preparations as a powder, pour-on, emulsifiable liquid, or even as a spray (GUPTA, 2012). The most common forms of applications include baths, immersion and sprinkling (GUPTA, 2012). Oral poisoning often occurs in cats due to the grooming behavior of the species (GUNARATNAM et al., 1983).

Table 1 - Values of physiological parameters of the hospitalized patient at 0, 4, 8, and 12 h after treatment.

	0 h	4 h	8 h	12 h
Rectal temperature (C°)	34.7	37	38.2	38.9
HR (bpm)	96	140	190	200
RR (breaths/min)	36	40	36	36
Mucous membranes	Pale	Pale	Pale	Pale
CRT (s)	<2"	<2"	<2"	<2"
SBP (mmHg)	100	100	110	140
Blood glucose (mg/dL)	398	115	125	---
Hydration	NH*	NH*	NH*	NH*

A study by XAVIER et al. (2002) showed that the use of these products is one of the most common causes of intoxication in dogs and cats in Brazil; amitraz intoxication corresponds to 25% of cases, in the form of pesticides for domestic use, along with organophosphates (39.9%) and carbamates (37.7%) (XAVIER et al., 2002).

Although, the present case shows an intoxication via cutaneous absorption, a previous report has described intoxication by amitraz through a different route. A recent retrospective study showed that 5.17% of dogs taken to four veterinary clinics in Thailand were intoxicated with amitraz. In this case, the dogs showed tachycardia, tremors, and ataxia, which is expected in dogs that receive an oral amitraz concentration greater than 100 mg/kg (LORSIRIGOOL et al., 2022). This demonstrated that amitraz is a product that is widely used worldwide, and its toxicity may occur regardless of the route of administration. In cat patients, it is important to recognize not only the cutaneous absorption but also the possibility of oral intake via grooming (GUNARATNAM et al., 1983).

Although, amitraz is an old insecticide and there are now much safer and more effective drugs recommended as a frontline treatment for ectoparasites, the literature suggests that amitraz is effective in the treatment of mange and demodicosis in dogs and cats and; therefore, is still widely used and prescribed by veterinarians (GUPTA, 2012). However, there is a lack of precise guidelines on their toxic potential, which permits the incorrect use of the products and, consequently, intoxication (ANDRADE et al., 2007a).

Currently, most manufacturers no longer recommend the use of products with amitraz for cats because of the greater sensitivity of the species (GUPTA, 2012). There are several studies regarding species-related amitraz toxicity in cats (ANDRADE et al., 2006; ANDRADE, 2007b). For instance, some reports have shown that cats tend to get intoxicated at much lower doses of amitraz than dogs (GUNARATNAM et al., 1983). No reasonable explanation for this phenomenon is available yet. It is important to highlight that even though cats are known to be more vulnerable to amitraz toxicity and most manufacturers do not recommend its use in cats, the product used by the owner was labeled for use in cats according to the package leaflet.

Due to its high lipid solubility, when ingested or, as in the case of the reported patient, through dermal exposure, it is quickly absorbed, becoming potentially dangerous, which explains the speed with which the patient showed clinical signs after exposure (GUPTA, 2012). Its penetration occurs even with intact skin, but it is observed that in patients with inflamed skin or with skin lesions, such as that caused by the presence of fleas in the patient of this report,the absorption is even faster (SARTOR et al., 2011).

The deleterious effect of amitraz in mammals is due to the interaction of its active metabolite, N-2,4-dimethyl-phenyl-N'-methylformamidine, with α2-adrenergic receptors, leading to the inhibition of the monoamine oxidase (MAO) enzyme (HSU, 1996). This enzyme is responsible for the degradation of some neurotransmitters, such as noradrenaline and serotonin, causing CNS depression. In addition, the postsynaptic adrenergic system is stimulated, promoting less sympathetic activity, which causes sedation, loss of reflexes, lethargy, motor incoordination, excitability and aggression, and mydriasis (HSU, 1996; ANDRADE, 2007b; LORSIRIGOOL et al., 2022). The CNS depression phase may be preceded by a transient phase of excitation and aggression (CULLEN & REYNOLDSON, 1987).

High doses of amitraz stimulate α2-adrenergic receptors present in various tissues of the body, generating the main clinical signs of poisoning such as sedation, incoordination, respiratory depression, seizures, bradycardia, hypotension, hypothermia, transient hyperglycemia, polyuria, mydriasis, and gastrointestinal signs such as emesis and constipation (GUPTA, 2012). The patient presented with many of these signs when he presented for veterinary care.

The degree of sedation in intoxicated animals varies according to the dose absorbed by the body (HUGNET et al., 1996). The patient in this report arrived for care in the lateral decubitus position and was lightly sedated—a common presentation in cats intoxicated by amitraz, according to a study carried out by ANDRADE et al. (2007b).

The heart rate of cats is usually altered, with bradycardia being a clinical sign frequently observed during physical examination (ANDRADE et al., 2007b). This change is due to the activation of presynaptic α2 receptors in the sympathetic nervous system. Thus, it decreases the release of dopamine and noradrenaline and there is a reduction of the sympathetic tone in the cardiac muscle (HSU & KAKUK, 1984). This action can also lead to hypotension, but this was not observed in the patient, unlike that observed in a study by ANDRADE et al. 2007b and described by other authors (GUPTA, 2012; CULLEN & REYNOLDSON, 1990).

The blocking action on the sympathetic nervous system and increase in vagal tone can also induce arrhythmias, especially sinus arrhythmia and atrioventricular block (ANDRADE et al., 2007b). Unfortunately, the patient did not undergo electrocardiography.

Cats are more susceptible to hypothermia when they are under the effect of α2-adrenergic agonists, such as amitraz, and some anesthetics (MICHELL, 1994). This is because substances such as amitraz affect the thermoregulatory center in the hypothalamus, which explains why the patient's temperature was 34.7 °C when the patient arrived at the hospital for care (HSU, 1996). In addition, the fact that the patient was taken to the service while still wet after the bath performed by the owners, may have contributed to the loss of body heat and consequent hypothermia.

The respiratory rate (RR) can also be affected by central α2-adrenergic action. There is evidence that these receptors act by inhibiting respiratory neurons located in the ventral portion of the brain and that high concentrations of α2-adrenergic agonists can reduce the sensitivity of the respiratory center to increases in the partial pressure of carbon dioxide (PCO_2) (CULLEN & REYNOLDSON, 1990). However, patients from these two studies did not show significant differences in RR, similar to the patient in the present report (ANDRADE et al., 2007b; MARAFON et al., 2010).

Transient hyperglycemia is observed in animals poisoned by amitraz, as seen in our patient. These values are due to the inhibition of insulin release, mediated by α2-adrenergic receptors (α2D subtype) present in the pancreatic islets (ABU-BASHA et al., 1999). Because of these changes, amitraz is highly contraindicated in patients with diabetes mellitus (ANDRADE et al., 2007a).

One of the most notable clinical signs observed during the physical examination was bilateral mydriasis. This finding is in agreement with the studies carried out by HSU & KAKUT (1984), who studied the effects induced by amitraz on the pupillary diameter in rats, and in subsequent studies carried out by ANDRADE et al. 2007b with cats. According to researchers, this insecticide causes dose-dependent mydriasis mediated by postsynaptic α2-adrenoceptors.

The biotransformation of amitraz occurs in the liver, and its metabolites are excreted via

biliary and urinary routes (HUGNET et al., 1996). Although, studies have shown no changes in the serum concentration of ALT after the use of amitraz in controlled doses (GUNARATNAM et al., 1983; ANDRADE et al., 2007b), the patient had high levels of serum enzyme activity, which may be related to exposure to high concentrations of the product (126 mg/mL). In a study in which rats were subjected to chronic and higher exposure to the drug, increased serum levels of ALT, significant post-mortem histopathological changes in the liver, including moderate vacuolar degeneration of periportal hepatocytes, and renal changes, such as mild-to-moderate generalized tubular degeneration, were observed (OMOJA et al., 2016). However, any possible chronic liver disease should also be considered, since the exposure to amitraz was acute.A new biochemical test for ALT enzyme control was requested after the patient's treatment and recovery. As the owners did not return for review after the patient's clinical improvement, the control exam was not performed and; therefore, we could not confirm that the increase in ALT was due to the toxic effect of amitraz.

The patient presented with hypochromic microcytic anemia, as observed on complete blood count, which may be related to flea infestation and consequent chronic blood loss. Large concentrations of ectoparasites that chronically feed on the host's blood, as in the case reported, can result in iron-deficiency anemia (NELSON et al., 1977). In these cases, it is common to find a decreased mean corpuscular volume or microcytic cell subpopulation as erythrocytes tend to undergo divisions to obtain complete hemoglobin content and, thus, smaller erythrocytes with less hemoglobin appear (THRALL, 2012).

Most poisonings generate acute clinical signs, especially in cats, and the diagnosis is based on a history of exposure, as reported by the owners in this case. The clinical signs related to the stimulation of α2-adrenergic receptors and complementary examinations, such as serum biochemistry and ECG, were added to the diagnosis (GUPTA, 2012).

The main clinical signs of poisoning are evident during the critical (peak plasma) period, which is between 120 and 240 min after exposure to the product(MARAFON et al., 2010). Another study cited that in dogs the clinical presentation of intoxication by amitraz through the oral route occurred around 60 minutes (HUGNET, 1996). Ideally, the antidote (α2-adrenergic antagonist) should be administered within this period to have a greater probability of successful resolution of intoxication (MARAFON et al., 2010).

Emergency therapy recommended for cases of cutaneous poisoning is decontamination by removing excess products from the skin (GRAVE & BOAG, 2010). Therefore, bathing with warm soapy water was promptly instituted for the intoxicated cat in this report. In addition to correcting the temperature, glucose, and insulin levels, continuous monitoring of the cardiovascular, respiratory, and central nervous systems is recommended (GRAVE & BOAG, 2010). In patients with severe hypothermia, it is of prime importance to establish warming. Intravenous fluid therapy is also recommended in cases of hypotension, with the aim of increasing blood perfusion to the organs, as was instituted in this case (LEE, 2013).

The use of α2-adrenergic antagonists (atipamezole and yohimbine) has been shown to reverse the toxic effects of amitraz (GUPTA, 2012). After administration of atipamezole, the patient showed rapid improvement in clinical signs, corroborating the literature, which suggests that the clinical effects of amitraz can be controlled approximately 20 min after administration of the reversing drug (GUPTA, 2012). In cats, signs of bradycardia, mydriasis, and sedation respond better to atipamezole than to yohimbine because of its greater affinity for α2-adrenergic receptors (ANDRADE et al., 2006).

During hospitalization, the patient received acetylcysteine every 6 hours, during the 2 days it remained hospitalized, because of its antioxidant and cytoprotective effects (McMICHAEL, 2007), as an increase in serum ALT activity was detected in the blood test. He was discharged from the hospital with a prescription to continue with silymarin orally because of its ability to protect hepatocytes by stabilizing their membranes, which is also the reason for its frequent use in the treatment of liver diseases (HAKOVÁ & MIŠÚROVÁ, 1993); in addition, it protects hepatocytes against the toxic effects of many substances and also stimulates the cell regeneration process (SCHOSSLER et al., 1998).

The prognosis for animals with mild-to-moderate poisoning is considered good as they may show mild signs and recover spontaneously. Those who are severely intoxicated or concomitantly have other diseases, such as diabetes and cardiomyopathy, have a poor prognosis (ANDRADE et al., 2007b). GUNARATNAM et al. (1983) and GUPTA (2012) concluded that amitraz at low doses can cause toxic effects. However, a more recent study by ANDRADE et al. (2007a) concluded that if the product is used topically, through a therapeutic bath, and at the appropriate concentration, it is safe for healthy cats.

Owing to the serious consequences that this intoxication can cause and considering the low therapeutic index of the product, owners should

receive veterinary advice on the toxicity of amitraz. In addition, the correct dilution of the product and mandatory use of protective gloves during handling and application must be clarified to owners (GUPTA, 2012).

In this case, amitraz was acquired and used by the owners without the guidance of a veterinarian, leading to severe symptoms. Considering the risks that this intoxication can cause, it is extremely important that owners be instructed on the proper use of insecticidal substances commercialized freely to avoid intoxication. In addition, veterinarians must be prepared to deal with any case of poisoning that becomes a veterinary emergency.

FOOTNOTES

a. LACVet, Laboratório de Análises Clínicas UFRGS, Porto Alegre, Brazil.
b. Antisedan, Orion Pharma, Zoetis, Kalamazoo, Mich.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

All authors critically reviewed and approved the final version of the manuscript.

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