

## ACCIDENTAL AMITRAZ INTOXICATION FOLLOWING SUBCUTANEOUS INJECTION IN A YOUNG CAT

### INTOXICAȚIA ACCIDENTALĂ CU AMITRAZ ÎN URMA INJECTĂRII SUBCUTANATE LA O PISICĂ TÂNĂRĂ

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#### ABSTRACT | REZUMAT

The present case report describes clinical features, therapeutic approach, and the successful outcome in a 6-month-old feline patient after accidental subcutaneous administration of amitraz solution. The main symptoms were depression, ataxia, cardiovascular collapse, bilateral mydriasis, and severe sinus bradycardia. Treatment consisted of an  $\alpha_2$ -adrenergic receptor antagonist as well as stabilization of the patient with oxygen supplementation and intravenous fluids. Besides, a brief overview of the current knowledge of amitraz toxicosis in cats is presented.

**Keywords:** atipamezole, feline, formamidine, toxicosis

Prezentul raport de caz descrie semnele clinice, abordarea terapeutică și evoluția favorabilă la un pacient felin în vârstă de 6 luni la care s-a administrat subcutanat accidental soluție de amitraz. Principalele simptome manifestate au fost depresie, ataxie, colaps cardiovascular, midriază bilaterală și bradicardie sinusală severă. Tratamentul a constat în administrarea unui antagonist  $\alpha_2$ -adrenergic, precum și stabilizarea pacientului prin suplimentare cu oxigen și fluidoterapie intravenoasă. În plus, este prezentat un scurt rezumat al cunoștințelor actuale despre intoxicația cu amitraz la pisici.

**Cuvinte cheie:** atipamezol, pisică, formamidină, intoxicație

Amitraz is an ectoparasiticide available in the form of powder, liquid, and spray but can also be used as a synergist and combined with other insecticides in over the counter products (11). It is not recommended to be used in cats, horses, and small breed dogs, such as Chihuahua and Pomeranian (9). Its broad-spectrum use as an acaricide and insecticide together with its highly lipid-soluble composition leads to frequent cases of intoxication in humans and animals (12), but, to the author's knowledge, toxicosis following subcutaneous administration has never been reported previously. Acute toxicity of amitraz was studied in several species, including mouse, rat, guinea pig, rabbit, dog and baboon, by oral, dermal, inhalation, intraperitoneal, and intravenous route of administration. LD50 varies between species and administration routes, with extremes of 100 mg/kg/day *per os* in dogs and 1600 mg/kg/day in mice (6). In cats, LD50 of amitraz has not been established yet. However, dosage as low as 1 mg/kg IV leads to the expression of clinical signs of toxicosis in this species (3). The present report describes clinical features, therapeutic approach, and the successful outcome in a feline patient that received an accidental subcutaneous injection of amitraz solution.

#### CASE PRESENTATION

A 6-month-old intact female Domestic short-haired cat was presented for acute collapse. On physical examination, the cat was quiet, lethargic, and unresponsive, with a body condition score (BCS) of 4/9.

Further examination revealed pale mucous membranes, prolonged capillary refill time (CRT of 4 seconds), poor pulse quality and hypothermia (37.1°C).

The cat was ataxic and presented discrete sialorrhea and bilateral mydriasis. An electrocardiogram (ECG) was performed and revealed severe sinus bradycardia (heart rate range between 65 and 97 bpm), with no other significant arrhythmias. Complete blood count showed no significant abnormalities while blood biochemistry revealed hyperglycaemia and decreased  $\gamma$ globulin concentration (Table 1). Further diagnostic workup was declined by the owner.

Besides up to date immunization schedule, the owner reported a recent visit to the primary veterinarian and purchase of an amitraz-based ectoparasiticide for dogs, which eventually was administered at home to the cat as treatment for mild pruritus, manifested within the last two weeks. Thorough history clarified that an accidental subcutaneous injection of amitraz solution was given 2 hours prior to presentation in our clinic and that symptoms had appeared within less than an hour post-administration of the drug.

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Table 1

## Summary of serum biochemistry

Analyte, unit	Result	Reference interval**
Albumin, g/dL	2.8	1.92-3.3
ALP, U/L	104.5	40-190
ALT, U/L	39.7	<60
AST, U/L	32.5	<35
Creatinine, mg/dL	1.1	0.56-1.8
GGT, U/L	8.6	<10
$\gamma$ Globulin, g/dL	*0.72	0.82-1.4
Glucose, mg/dL	*196.2	72-108
Total Protein, g/dL	6.1	5.5-7
Urea, mg/dL	56.4	30-66

\* Values outside of the reference range;

\*\* reference values of our laboratory;

ALT - alanine aminotransferase; AST - Aspartate Aminotransferase;

GGT - gamma-glutamyl transferase; ALP - Alkaline Phosphatase

Stabilization of the patient included oxygen supplementation via mask and later oxygen chamber (2-5 L/min), intravenous fluid therapy (25 ml/kg as a rapid bolus, followed by 25 ml/kg of continuous infusion), and administration of atipamezole IV (0.2 mg/kg within the first minutes, followed by 0.1 mg/kg after 30 minutes). Eight hours from admission, the cat was discharged in stable condition, with the recommendation to follow-up with the primary veterinarian for further care.

## DISCUSSION

Amitraz is a broad spectrum formamidine antiparasitic agent (19) which produces systemic toxicity and induces significant changes in all major body systems, including digestive, cardiovascular, urinary, nervous, and respiratory (4). It stimulates both  $\alpha$ 2 adrenergic receptor sites in the CNS as well as  $\alpha$ 1 adrenergic and  $\alpha$ 2 adrenergic receptor sites in the periphery, and it inhibits monoamine oxidase (MAO) enzyme activity and synthesis of prostaglandin E2 (5). In addition, it increases glucagon secretion, resulting in hyperglycaemia (9). Clinical features of toxicosis could be mainly related to its  $\alpha$ 2-adrenergic agonist activity (13), as they are identical to the ones produced by pure  $\alpha$ 2-adrenergic agonists. The central  $\alpha$ 2-agonist activity usually leads to CNS depression and hypothermia (5) but manifestations of depression or stimulation depend on dose and species involved. Higher doses have a depressive effect on activity, cardiac parameters, and breathing, with death occurring due to respiratory failure. At lower doses, CNS stimulation may occur (18). The central activity of the drug will also lead to changes in blood pressure and heart rate by  $\alpha$ 2-adrenoceptor agonism, the cause of a decreased peripheral sympathetic tone (5). The vasopressor action of amitraz on peripheral vessels owes to the above-mentioned  $\alpha$ 1 and  $\alpha$ 2 adrenoceptors and produces hypotension (20).

Experimental studies have shown that intravenous administration of amitraz in dogs and cats induces significant clinical signs among which sedation, loss of reflexes, vocalization, sialorrhea, vomiting, mydriasis as well as bradypnea, bradycardia, bradyarrhythmias, hypotension, hypothermia, and an increase in appetite and urine production (1, 2, 3). Besides, it induces hyperglycaemia, hypoinsulinemia, hypocortisolemia but no alterations of complete blood count, or liver and renal function tests (2, 3, 10).

However, the dosage and route of administration vary greatly between experimental studies. In cats, dosages of 1 mg/kg were administered intravenously and induced signs of toxicity (2, 3); administration via bathing in a 0.0125% amitraz concentration (10) or a 0.4% concentration (14) has proven to have noticeable toxic effects. In dogs, dosages as high as 100 mg/kg were administered orally (13), with potential lethal effect. The fact that amitraz is very liposoluble makes it quickly absorbed through the skin and mucous membranes (17), therefore making exposure dangerous for patients. In our case, subcutaneous administration lead to fast absorption and manifestation of symptoms. In dogs, Hugnet et al. (13) reported that, with plasma concentration around 5 mg/l, clinical signs of intoxication begin around 1h post-ingestion and are present until the concentration of the substance decreases. In our patient situation, the dose of amitraz (per kg) could not be established, but we suspect that a dosage higher than 1 mg/kg was administered, as commercially available solutions in Romania have a concentration of 12.5%. Amitraz is not licensed for use in felines but has been successfully used in the treatment of *Demodex gatoi* clinical infections. The recommended drug concentration in these cases is 0.0125 - 0.025% as a rinse, but might have side effects such as anorexia, depression, and diarrhea (15).

Treatment of amitraz intoxication in cats includes administration of  $\alpha$ 2-adrenergic receptor antagonists

such as yohimbine or atipamezole, the latter being faster-acting and more potent compared with yohimbine for reversing amitraz effects, due to its higher affinity for the  $\alpha_2$ -adrenergic receptors (2). In addition, yohimbine is more unspecific and might have several side effects such as hypotension and reflex tachycardia due to  $\alpha_1$  blockade (16). A total dose of 0.3 mg/kg IV of atipamezole was found to be effective in our case, which resulted in complete resolution of the clinical signs, similar to a previous experimental study by Andrade et al. (2) that has shown significant improvement after a single administration of 0.2 mg/kg IV. In dogs, a low dose of atipamezole administered intramuscularly (50  $\mu$ g/kg) induced complete resolution of the clinical symptoms within 10-20 minutes and can be repeated after 3-4 hours if needed (13). Non-specific treatment guidelines suggest removal of dog collar and bathing in case of transdermal administration of amitraz, as well as the use of gastric lavage and charcoal administration following ingestion (11), but there are no such suggestions for the present case, where the subcutaneous route is incriminated. In humans, amitraz poisoning currently involves supportive and symptomatic treatment, due to lack of a specific antidote (8). Published reports were successfully treated with gastric lavage, activated charcoal, vasopressors and inotropic agents, intravenous fluids and assisted ventilation, and showed an excellent prognosis with a very low case fatality rate (1.9%) (7). Information on prognosis in cats is lacking from current literature, but extrapolating from our case we can suggest a good prognosis, provided that administration of atipamezole and supportive care is offered.

### CONCLUSIONS

This report shows that accidental amitraz intoxication following erroneous subcutaneous administration is a possible clinical case scenario and proves that atipamezole is an effective treatment in reversing its clinical signs. This case raises awareness of the importance of prescription drug regulations as well as their administration solely in veterinary practice.

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