

Canine renal cortical necrosis and haemorrhage following ingestion of an Amitraz-formulated insecticide dip

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ABSTRACT

Amitraz is a formamidine compound used in veterinary medicine as a topical dip to control ticks and mites on dogs and livestock. A 10-year-old female Scottish terrier was presented following the accidental oral administration of a dip containing amitraz. This case report describes the clinical signs, treatment and pathology of this dog. Clinical signs of toxicity from amitraz result from stimulation of alpha₂-adrenergic receptors. Amitraz is seldom fatal because the effects can be reversed by alpha₂-adrenergic antagonists. The dog recovered from the amitraz toxicity but died 5 days later from acute renal failure.

Key words: amitraz, acute renal failure, acute renal haemorrhage and necrosis, dog.

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INTRODUCTION

Amitraz (N¹-[2,4-dimethylphenyl]-N-(2,4-dimethylphenyl)iminomethyl-N-methylmethanimidamide) is a topical acaricide used in veterinary medicine for dogs and livestock^{7–9}. The commercial preparation in the present case was Ectodex (Intervet SA, Isando), a formulation of 12.5 % m/v amitraz.

Amitraz toxicity has been described in the dog^{6,9,12}. The most common form of amitraz toxicity in dogs is ingestion of amitraz-impregnated collars^{6,12}. Amitraz toxicity is seldom fatal following ingestion if treated with an alpha₂ antagonist¹². Most of the clinical signs of toxicity are related to amitraz's stimulation of alpha₂-adrenergic receptors^{3,4,6,9,15}. Dogs usually present with central nervous signs relating to depression and coma, respiratory depression, bradycardia, hypertension, mydriasis, gastrointestinal stasis, diarrhoea, vomiting, hypothermia, polyuria and hyperglycaemia^{6,13}. Death from amitraz in animals is usually the result of respiratory failure from profound central nervous system depression¹⁴.

This case study describes acute renal failure in a dog following accidental oral administration of undiluted Ectodex formulation.

CLINICAL HISTORY

A 10-year-old, female Scottish terrier weighing 16 kg was presented with amitraz toxicity. Due to a misunderstanding at a pet boarding facility, the patient was orally dosed with an estimated 10 ml of amitraz (Ectodex, Intervet SA, Isando) instead of dipped. The patient was severely agitated with generalised muscle tremors, congested mucous membranes and miotic pupils. Tachycardia (198 beats per minute (bpm)), hyperventilation (168 breaths per minute (bpm)) and hyperthermia (40.5 °C) were evident. The presence of vomitus on the patient's tongue suggested she may have vomited before arrival at the veterinary hospital.

Thoracic auscultation and abdominal palpation were normal and examination of a peripheral blood smear revealed no blood parasites. Blood glucose and electrolytes were tested on admittance with an in-house blood chemistry analyser (Vet Test 8008, IDEXX Laboratories Inc, Maine, USA). Serum potassium was within normal range but the patient was mildly hyperglycaemic (Table 1).

The patient was sponged down with cold water and was given intravenous fluids (Ringers lactate, Fresenius Kabi, Midrand) at double maintenance rate (80 ml/h) and a bolus (10 ml/kg) of hydroxyethyl starch (Voluven, Fresenius Kabi).

The mental state deteriorated rapidly. Within an hour the patient was comatose, menace and pupillary light reflexes were

absent and the patient showed no response to stimuli except deep pain. At this stage the temperature had dropped to 35.1 °C and the mucous membranes had become mildly cyanotic. The patient was placed on a warm circulating water heating pad and wrapped in blankets. Oxygen was supplemented via a nasal cannula and a urinary catheter was inserted to monitor urine production. Urine specific gravity was measured with a refractometer and was greater than 1.040. Urine dipstick parameters were normal. The hypothermia took 8 hours to resolve.

As the risk of iatrogenic aspiration pneumonia was considered high, gastric lavage and treatment with activated charcoal was not carried out⁶. Anti-emetic therapy was started using metoclopramide (Clopamon, Fresenius Kabi) at 0.5 mg/kg i/v tid. Atipamizole (Antisedan, Novartis) was given at 0.06 mg/kg i/m every 5 hours as well as prophylactic antibiotics, cefazolin (Izaceph, Fresenius Kabi), at 20 mg/kg bid i/v.

Four hours after admission, heart rate (124 bpm) and respiratory rate (42 bpm) had improved. Systolic blood pressure (SBP), measured oscillometrically (Dinamap, Johnson & Johnson, Midrand), was 129 mm Hg and mean arterial pressure (MAP) was 95 mm Hg. Peripheral oxygen saturation was measured with a pulse oximeter placed on the tongue and remained above 95 %. Artificial tears (Teargel, Novartis, Isando) were applied to the corneas every 4 hours and the patient was turned every hour.

Three hours later, thoracic auscultation revealed bilateral pulmonary rales. Pulmonary oedema and acute respiratory distress syndrome (ARDS) were suspected. The fluid rate was dropped to 30 ml/h, a second bolus (10 ml/kg) of hydroxyethyl starch was administered and furosemide (Furosemide, Fresenius Kabi) at 2 mg/kg s/c was given twice, 2 hours apart. Response to treatment was dramatic. The pulmonary oedema resolved, furosemide was discontinued and the fluid rate slowly increased over 13 hours to 80 ml/h (twice maintenance requirements). The higher fluid rates were necessary to maintain adequate blood pressure to preserve

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Table 1: Serum chemistry and electrolyte values.

Parameter	Units	Day 1	Day 2	Day 4	Reference values*
Electrolytes					
Na ⁺	mmol/l	163	166		144–160
K ⁺	mmol/l	4.3	3.8		3.5–5.8
Cl ⁻	mmol/l	117	131		109–122
Serum chemistry					
Glucose	mmol/l	7.6	8.4	7.4	4.2–6.9
ALT	U/l		95	17	8–80
ALP	U/l		1351	805	30–400
Urea	mmol/l		16.1	16.4	2.5–9.6
Creatinine	umol/l		241	205	44–159
Total protein	g/l		64	57	
Albumin	g/l		24	18	27–38
PCV	%		48		

*IDEXX Laboratories.

renal perfusion (mean arterial pressures above 60 mm Hg and systolic pressures above 90 mm Hg). By carefully monitoring lung sounds and blood pressure and adjusting fluid rates accordingly, the MAP was maintained above 90 mm Hg and urine output was 2.6 ml/kg/h.

On day 2, the patient remained comatose and responsive only to deep pain. Atipamizole was continued every 5 hours. Owing to the presence of a fever throughout the day (39.4–40.6 °C), Metronidazole (Flagyl, Fresenius Kabi) at 20 mg/kg i/v bid was added to the existing antibiotic cover. Blood was taken for serum chemistry and electrolytes (Table 1). The patient had a haematocrit of 48 %, normal potassium levels and mild hyperglycaemia. Blood urea nitrogen and creatinine concentration and ALP activity were raised.

The elevated haematocrit suggested mild dehydration. However, perfusion seemed to be well maintained with intravenous fluids and colloids as the heart rate stayed between 108–140, the systolic blood pressure between 112–124 mm Hg, the diastolic blood pressure between 51–59 mm Hg and the MAP at 75 mm Hg. Colloid administration was changed on the second day from bolus therapy to pulse therapy at 2 ml/kg every 2 hours.

Oxygen saturation was maintained above 95 % without oxygen supplementation. Urine production was measured at an average of 2.0 ml/kg/h over 24 hours. Furosemide (2 mg/kg s/c) was given once to improve urine production. The patient vomited for the first time and developed a bloody diarrhoea. Metoclopramide was continued at 0.5 mg/kg s/c tid, but Cimetidine (Lenamet, Fresenius Kabi) at 10 mg/kg i/v tid, Sucralfate (Ulsanic, Aspen Pharmacare Ltd, Gallo Manor) at 10 ml p/o tid and Buprenorphine (Temgesic, Schering Plough, Isando) were added to the therapy. A naso-oesophageal tube was inserted in the oesophagus to

the level of the 7th intercostal space (confirmed by radiography) to facilitate nutritional support with an enteral feed (Survimed, Fresenius Kabi).

On day 3, the patient regained consciousness, showed interest in her environment, was ambulatory and could eat and drink on her own. Rectal temperature was normal throughout the day (38.7 °C). Tube feeding was changed to hand feeding every 4 hours. Fluids were continued but the rate was lowered to 38 ml/h and the colloids were discontinued. Medication continued unchanged except for the discontinuation of atipamizole.

The faeces were soft and brown without evidence of diarrhoea or fresh blood and there was no vomiting throughout the day. The patient pulled out her urinary catheter, which was not replaced owing to her clinical improvement and urine production was not measured. However, the patient was taken outside regularly and normal urination was observed 5 times throughout the 24-hour period. It was thought at this stage that the patient would make a full recovery so no blood samples were taken for serum chemistry analysis.

On day 4, the patient vomited 3 times. In addition to metoclopramide, which had been part of the treatment protocol for 2 days, prochlorperazine (Stemetil, Aventis, Midrand) was added at 0.5 mg/kg i/m tid and the patient was put back on naso-gastric tube feeding. The fluid rate was increased slightly (50 ml/h) to compensate for losses incurred by vomiting. The antibiotics, analgesic and cytoprotective medications were continued. Serum chemistry (Table 1) revealed low albumin (18g/l), normal ALT but slightly raised ALP activity (805 U/l). Blood urea nitrogen and creatinine concentrations were elevated, 16.4 mmol/l and 205 µmol/l respectively, but were not significantly changed from previous days. The patient

was still producing urine. An ultrasound examination of the abdomen showed a small amount of free abdominal fluid between the liver lobes. This was not aspirated. The echogenicity of the liver parenchyma appeared normal as did renal architecture.

The dog acutely decompensated and went into cardiac arrest on the morning of day 5. Ventricular fibrillation was diagnosed on an electrocardiogram. Cardiopulmonary resuscitation was immediately instituted. Blood taken during resuscitation for electrolyte determination revealed severe hyperkalaemia (11.4 mmol/l). The hyperkalaemia was considered the cause of the cardiac arrhythmia. Cardiopulmonary resuscitation was terminated after 10 min as the pupils had remained fixed and dilated and no return of spontaneous circulation had occurred. Permission was granted by the owner for a *post mortem* examination.

Macroscopic pathology revealed severe, ventral, subcutaneous oedema and moderate serosanguinous ascites. The left kidney was friable with severe peri-renal and diffuse renal haemorrhage. Half of the right kidney was similarly affected. Other abnormalities noted were severe diffuse hepatomegaly, friable adrenal glands, 2 gastric ulcers of 1 cm diameter each and severe pulmonary congestion in the caudo-dorsal lung lobes with multifocal areas of atelectasis.

Histopathological examination of the kidneys revealed severe, diffuse renal cortical haemorrhage, which resulted in obliteration of the interstitial tissue. Severe, acute, multifocal, glomerular and tubular necrosis was evident. The cells revealed increased eosinophilia, dissociation from the basement membrane, karyolysis and pycnotic nuclei. A few tubular epithelial cells contained golden yellow intracytoplasmic pigment (haemosiderin). About 50 % of the glomeruli revealed a homoge-

neous eosinophilic appearance with loss of cellular detail and few scattered nuclei of mesangial and endothelial cells still visible (glomerular necrosis). Moderate numbers of neutrophils infiltrated the interstitial tissue as a result of the necrosis. Mild, multifocal areas of fibrin deposition in the glomerular interstitium were evident with a few tubular lumens containing protein casts. Severe congestion of blood vessels was evident in the cortex with moderate congestion visible in the medulla.

The liver revealed severe, diffuse congestion with severe dilatation of the sinusoids with blood and resultant severe pressure atrophy of the hepatocytes. Mild, multifocal areas of fatty hepatosis and necrosis were also evident. The lungs showed moderate, diffuse congestion with severe accumulation of alveolar macrophages in the alveolar lumens. There was also a moderate fibrinous oedema in the lungs. Moderate congestion of brain blood vessels was observed. Histology of the thyroid gland, parathyroid gland, stomach, pancreas, gastro-intestinal tract and bone marrow were normal.

An incidental finding in this case was the presence of three 0.75 cm growths on the cranio-ventral urinary bladder mucosa, which were histologically diagnosed as papillary non-infiltrating transitional cell carcinomas.

DISCUSSION

The acute median oral lethal dose (LD₅₀) of amitraz in the rat is 800 mg/kg¹³. The LD₅₀ for amitraz in dogs is 100 mg/kg while the toxic effect dose is 10 mg/kg⁶. This case study presents a dog that ingested an estimated 78 mg/kg of amitraz. Signs of amitraz toxicity usually appear 1 hour after oral administration and serum concentrations peak approximately 6 hours later¹². This patient was dosed with amitraz more than 6 hours before arrival at the veterinary hospital. It was assumed, therefore, that the toxin had been fully absorbed.

Amitraz stimulates both alpha₁ and alpha₂-adrenoreceptors but most of the clinical effects observed are a result of its alpha₂-adrenergic agonistic activity^{4,10,13}. In the rat, amitraz is a potent inhibitor of monoamine oxidase and prostaglandin E₂ synthesis but the role of this in amitraz poisoning in dogs is unknown¹⁴. The alpha₂-adrenoreceptor effect produces central nervous system and respiratory depression, bradycardia, gastrointestinal stasis, diarrhoea, vomiting and hypothermia⁹. Hypotension is seen in humans and guinea pigs but peripheral vasoconstriction results in hypertension in dogs^{2,3,10,14}. Hypertension and vasoconstriction is followed by a decrease in heart rate and

cardiac output². The decrease in heart rate and cardiac output are not solely the result of a baroreceptor reflex from hypertension because amitraz inhibits the baroreceptor reflex and yohimbine restores it¹⁶. Reduced baroreceptor function could lead to cardiovascular collapse¹⁶. This was seen in our patient, which required intravascular volume support to maintain blood pressure.

As an antidote, atropine is not recommended to counteract bradycardia caused by amitraz toxicity because it does not reverse all alpha₂-agonist effects on the cardiovascular system⁹⁻¹⁰. While increasing heart rate it may potentiate hypertension⁹. The resulting increase in myocardial oxygen consumption may predispose to cardiac arrhythmias⁹. Atropine also aggravates gastrointestinal hypomotility⁹.

Amitraz effects on ventilation include a decrease in respiratory rate, tidal volume and minute ventilation². The hypoxaemia in this patient was most likely the result of pulmonary oedema. Respiratory rate remained high and therefore it seems unlikely that amitraz caused respiratory depression. Miosis occurs in man but mydriasis dominates in dogs¹⁴. Besides species differences, clinical signs are also dose-dependent. Bradycardia and respiratory depression are replaced by tachycardia and hyperventilation in severe intoxication². Bradycardia was not noted in this patient. This was either a result of the high dose of amitraz administered or a consequence of systemic shock (hypotension, acidosis) and circulatory compromise.

Alpha₂-adrenergic stimulation inhibits insulin release from the pancreas and increases glucagon which causes hyperglycaemia^{5,13,17}. A mild persistent hyperglycaemia was seen in this case. Hyperglycaemia has been reported in humans exposed to amitraz and following experimental administration of amitraz^{5,12,14}. Topical application and intravenous administration of amitraz has been shown to increase baseline plasma glucose levels and blunt insulin response following a glucose challenge^{11,17}. Caution should therefore be exercised when amitraz is used in diabetic dogs. Yohimbine can reverse the effects of amitraz on insulin¹⁷. Insulin levels increase rapidly and glucose decreases after administration of an alpha₂-antagonist and this can be used to assist in the diagnosis of amitraz toxicity¹². Amitraz also decreases antidiuretic hormone (ADH) and renin secretion, which leads to an increase in urine production⁵. In human patients, an increase in urine production has been noted following intoxication⁵.

Yohimbine is an alpha₂-adrenergic antagonist and will competitively displace amitraz from the alpha₂-receptors thus reversing central nervous system depression, bradycardia, hypertension and gastrointestinal effects¹⁰. It may cause tachycardia and tachypnoea. Atipamizole, another specific alpha₂-adrenergic antagonist, may be superior to yohimbine as an amitraz antagonist because it has less cardiorespiratory effects. This patient was given 6 treatments of atipamizole at 0.06 mg/kg i/m at 5-h intervals. A dose of 0.05–0.2 mg/kg i/m is recommended although the lower dose is usually sufficient¹². As the half-life of atipamizole is short (<2 hours) and the elimination half-life of amitraz dose dependant (1.5–2 hours for doses of 1 mg/kg and 23.6 hours for doses of 100 mg/kg), atipamizole may be repeated at 2- to 4-hour intervals if necessary to control symptoms^{6,12}.

Amitraz produces neurological depression¹². The neurological depression in this patient lasted 2 days. This would support the longer half-life of amitraz following higher doses.

Amitraz is metabolised in the liver and will cause dose-dependant hydropic and fatty changes in hepatocytes⁸. Hepatic injury was evident at necropsy in this patient.

Acute renal failure in this patient was most likely the result of both toxic and anoxic insults following poisoning. At presentation marked shock was evident, which would cause renal hypoxia/anoxia. The patient responded positively to therapy, showing adequate urine production, normal serum K⁺, and stable urea and creatinine concentrations. This led to an erroneous clinical underestimation of the renal damage. It is interesting to note that clinical improvement occurred despite more than 75% of the renal cortex having been injured or necrotic. Ultimately the patient died due to the inability of the kidneys to excrete potassium.

In a retrospective case study of hospital acquired renal failure, histopathology was the only definitive evidence of acute renal failure in 5 of 29 dogs¹. In another 5 cases, acute renal failure, diagnosed on serum urea and creatinine concentrations, appeared to resolve based on serum chemistry yet acute tubular injury was still present on histopathology¹. The above 2 scenarios indicate the difficulties in diagnosing acute renal failure by serum chemistry in some individuals. This case mimicked the second scenario whereby a clinical diagnosis of renal injury was made but the extent of this damage was underestimated due to clinical improvement of the patient after therapy. The

authors therefore suggest intensive monitoring of renal function in cases of amitraz toxicity. In addition to continued monitoring of urine production and BUN and creatinine concentrations, urine sediment should be examined daily for casts and urine solute excretion measured.

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