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

P A Oglesby, K E Joubert and T Meiring

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.


INTRODUCTION

Amitraz (N[6,9,12]-[2,4-dimethylphenyl]-N-(2,4-dimethylphenyl)iminomethyl-N-methylmethanimidamide) is a topical acaricide used in veterinary medicine for dogs and livestock. 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. The most common form of amitraz toxicity in dogs is ingestion of amitraz-impregnated collars. Amitraz toxicity is seldom fatal following ingestion if treated with an alpha2 antagonist. Most of the clinical signs of toxicity are related to amitraz’s stimulation of alpha2-adrenergic receptors. 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. Death from amitraz in animals is usually the result of respiratory failure from profound central nervous system depression.

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 miosis. Tachycardia (198 beats per minute), hyperventilation (168 breaths per minute) 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, menence 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 out. Anti-emetic therapy was started using metoclopramide (Clopamor, Fresenius Kabi) at 0.5 mg/kg 4-hourly. Atipamizole (Antisedan, Kabi) was given at 20 mg/kg bid iv.

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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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 concentrations were elevated, 16.4 mmol/l and 205 µmol/l, respectively, but were not significantly different from the reference values (144–160 and 3.5–5.8 mmol/l). 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 caused by the presence 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 pyknotic nuclei. A few tubular epithelial cells contained golden yellow intracytoplasmic pigment (haemosiderin). About 50 % of the glomeruli revealed a homoge-

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**Table 1: Serum chemistry and electrolyte values.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Reference values*</th>
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<tbody>
<tr>
<td><strong>Electrolytes</strong></td>
<td></td>
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<tr>
<td>Na⁺ mmol/l</td>
<td>163</td>
<td>166</td>
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<td>144–160</td>
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<tr>
<td>K⁺ mmol/l</td>
<td>4.3</td>
<td>3.8</td>
<td></td>
<td></td>
<td>3.5–5.8</td>
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<tr>
<td>Cl⁻ mmol/l</td>
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<td>131</td>
<td></td>
<td></td>
<td>109–122</td>
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<tr>
<td><strong>Glucose mmol/l</strong></td>
<td>7.6</td>
<td>8.4</td>
<td>7.4</td>
<td></td>
<td>4.2–6.9</td>
</tr>
<tr>
<td>ALT U/l</td>
<td>95</td>
<td>17</td>
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<td>8–80</td>
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<tr>
<td>ALP U/l</td>
<td>1351</td>
<td>805</td>
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<td>30–400</td>
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<td>Urea mmol/l</td>
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<td>16.4</td>
<td></td>
<td></td>
<td>2.5–9.6</td>
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<tr>
<td>Creatinine umol/l</td>
<td>241</td>
<td>205</td>
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<td></td>
<td>44–159</td>
</tr>
<tr>
<td>Total protein g/l</td>
<td>64</td>
<td>57</td>
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<tr>
<td>Albumin g/l</td>
<td>24</td>
<td>18</td>
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<td>27–38</td>
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<tr>
<td>PCV %</td>
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<td>48</td>
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*IDEXX Laboratories.
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, gastrointestinal tract and bone marrow were normal.

An incidental finding in this case was the presence of three 0.75 cm growths on the crano-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/kg⁴. The LD₅₀ for amitraz in dogs is 100 mg/kg while the toxic effect dose is 10 mg/kg². 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-adrenergic receptors but most of the clinical effects observed are a result of its alpha₂-adrenergic agonistic activity⁴,⁵,¹³. 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 unknown⁵. The alpha₂-adrenergic receptor effect produces central nervous system and respiratory depression, bradycardia, gastrointestinal stasis, diarrhoea, vomiting and hypothermia¹. Hypotension is seen in humans and guinea pigs but peripheral vasoconstriction results in hypertension in dogs²,³,⁴,¹³. 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 this⁶. Reduced baroreceptor function could lead to cardiovascular collapse⁶. 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 alpha₁-agonist effects on the cardiovascular system⁶,¹⁰. While increasing heart rate it may potentiate hypertension¹. The resulting increase in myocardial oxygen consumption may predispose to cardiac arrhythmias⁶. Atropine also aggravates gastrointestinal hypomotility¹.

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 dogs¹¹. 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.

Alpha₁-adrenergic stimulation inhibits insulin release from the pancreas and increases glucagon which causes hyperglycaemia⁵,¹⁷. A mild persistent hyperglycaemia was seen in this case. Hyperglycaemia has been reported in humans exposed to amitraz and following experimental administration of amitraz⁵,¹²,¹⁴. Topical application and intravenous administration of amitraz has been shown to increase baseline plasma glucose levels and blunt insulin response following a glucose challenge⁵,¹⁷. Caution should therefore be exercised when amitraz is used in diabetic dogs. Yohimbine can reverse the effects of amitraz on insulin⁵. 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 toxicity⁵. Amitraz also decreases antidiuretic hormone (ADH) and renin secretion, which leads to an increase in urine production⁴. In human patients, an increase in urine production has been noted following intoxication⁴.

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 effects⁵. 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 sufficient⁴. As the half-life of atipamizole is short (<2 hours) and the elimination half-life of amitraz dose dependent (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 symptoms⁵,¹². Amitraz produces neurological depression⁴. 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-dependent hydroptic and fatty changes in hepatocytes⁴. 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 noted following intoxication. Reduced kidney function and cardiac output may mimic the second scenario whereby a clinical diagnosis of renal injury was still present on histopathology. In a retrospective case study of hospital acquired renal failure, histopathology was the only definitive evidence of acute renal failure in 5 of 29 dogs⁴. 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 histopathology⁴. 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.

REFERENCES
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