



CASE REPORT

Anaphylaxis associated with intravenous administration of alphaxalone in a dog

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Case report We describe the clinical signs and management of a case of anaphylaxis in a dog after intravenous administration of alphaxalone (Alfaxan®, Jurox, NSW, Aust), which has not been previously published. A female spayed cattle dog undergoing routine imaging for forelimb lameness was induced with Alfaxan after receiving sedation with acepromazine and methadone 70 min prior. Immediately after intravenous administration of Alfaxan, the dog exhibited vomiting and diarrhoea associated with acute hypotension. Gallbladder wall oedema was visualised consistent with anaphylaxis. The dog responded to rapid volume expansion. Adrenaline was not required. The dog made a full recovery within 6 h of the reaction and was re-anaesthetised 3 days later without incident, using propofol as the induction agent.

Conclusion To our knowledge, this is the first published case of anaphylaxis associated with intravenous Alfaxan in the dog. The APVMA reporting of reactions in small animals from 2003 to 2013 of Alfaxan is consistent with this case report's finding involving the respiratory, circulatory and gastrointestinal systems.

Keywords alphaxalone; anaesthesia; anaphylaxis; dogs

Abbreviations A:a, alveolar–arterial (gradient); ACP, acepromazine; APVMA, Australian Pesticides and Veterinary Medicines Authority; CRT, capillary refill time; HPCD, 2-hydroxypropyl-beta-cyclodextrin; MAP, mean arterial pressure

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Anaphylaxis has been defined as 'a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance'.¹ The term anaphylaxis is reserved for IgE-mediated reactions and IgE-independent events are defined as anaphylactoid reactions.² The World Allergy Organisation has proposed that the term 'anaphylaxis' be used as an overarching description for severe, life-threatening hypersensitivity reactions regardless of the immunological mechanism.³ The terms anaphylactoid and anaphylaxis are often used interchangeably because they are clinically indistinguishable and treatment for both is identical. Therefore, we refer to the reaction described in this dog as an anaphylactic reaction.

Alphaxalone (3 α -hydroxy-5 α -pregnane-11,20-dione) is an injectable general anaesthetic agent used commonly in small animal anaesthesia. Alphaxalone is a neuroactive steroid molecule.⁴ The mechanism of action is related to modulation of γ -aminobutyric acid (GABA) type A receptors and the subsequent hyperpolarising effects on neuronal cell membranes in the central nervous system are a result of chloride ion transport intracellularly.⁴ Initially introduced as CT1341 in the 1970s, 0.9% alphaxalone was used in the veterinary and human setting as a preparation combined with another neuroactive steroid, 0.3% alphadolone (21-acetoxy-3 α -hydroxy-5 α -pregnane-11,20-dione) and suspended in 20% cremophor, 0.25% sodium chloride and water for injection.⁵ That preparation was known as either Althesin or Saffan and marketed for human and animal use, respectively. More recently, 1% alphaxalone has been released as Alfaxan® (Jurox, NSW, Aust) dissolved in 2-hydroxypropyl-beta-cyclodextrin (HPCD) for use in small animals.⁶

The worldwide adoption of Alfaxan into the veterinary community was slow after it was first released in Australia in 2001, the UK in 2007, Europe in 2008 and Canada in 2011; it was FDA approved in the USA in 2012.⁷ This was likely because of reactions seen with previous formulations such as Saffan (alphaxalone–alphadolone). Saffan was manufactured with a non-ionic polyoxyethylated emulsifying vehicle, cremophor,⁵ which was linked to histamine release in many species, including the cat and dog.^{8,9} The alphaxalone–alphadolone cremophor combination was reported to cause skin erythema, oedema and postoperative vomiting in 69% of cats in one study.¹⁰ Other studies reported fluctuations in blood pressure in dogs and pigs.^{8,9,11} As a result, Saffan was contraindicated in dogs but its use continued in cats.⁶ During the late 1970s, anaphylaxis was reported in people administered Althesin (alfaxalone–alphadolone) which also contained cremophor. Of the intravenous anaesthetic agents in use at that time, Althesin was reported to have the highest frequency of adverse reactions in people, a frequency of between 1 in 11,000 and 1 in 19,000 in one study¹² and 1 in 1000 in another, 15-fold higher than thiopentone.¹³ A further study in pigs reported reactions using an alphaxalone–alphadolone combination in the absence of cremophor and concluded that the alphaxalone–alphadolone steroid molecules may themselves directly contribute to some of the observed reactions.⁸ Because of the relatively high rate of adverse reactions, Althesin was withdrawn from the market in 1984.^{6,14–16}

Given Saffan's high frequency of reactions in cats and dogs, its availability ceased in 2002.⁶ A cremophor-free alphaxalone and cyclodextrin formulation was first released in Australia in 2001 under the trade name Alfaxan. The cyclodextrin vehicle is a ring-shaped molecule with a hydrophilic surface and an inner hydrophobic core that

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allows a hydrophobic guest molecule to reside in a dissolved state and be delivered to target cells.¹⁷ This newer formulation has been demonstrated to have a high therapeutic index, high total body clearance, rapid onset and rapid recovery.^{18–20}

There are currently no published reports of anaphylaxis associated with the use of Alfaxan in small animals to the authors' knowledge. The Australian Pesticides and Veterinary Medicines Authority (APVMA) allows for voluntary reporting of adverse experiences with veterinary medicines through the Adverse Experience Reporting Program. Annual reports are available for Alfaxan between 2003 and 2013.²¹ During this period, various reactions were reported in 54 dogs and 111 cats (Table 1). Reports are also available for Saffan between 1995 and 2003,²¹ coinciding with its release and withdrawal in Australia (Table 1). Only three dogs are linked to a reaction during 1995–2003, which is likely related to Saffan's reported contraindication in dogs.⁶ There were no reports available beyond 2013 at the time of writing. The APVMA classifies the relationship between the adverse event and a drug as probable, possible, probable or possible off-label, unlikely or unknown. Only probable and possible reactions have been reported for Alfaxan and the criteria for these are described in Table 2.

Table 1. Summary of the Australian Pesticides and Veterinary Medicines Authority adverse reports for dogs and cats on Saffan and Alfaxan® between 1995–2003 and 2003–2013, respectively

Reactions	1995–2003 (Saffan)		2003–2013 (Alfaxan®)	
	Dogs (%)	Cats (%)	Dogs (%)	Cats (%)
Total	3 (100)	75 (100)	54 (100)	111 (100)
Probable	2 (66)	30 (40)	6 (11)	17 (15)
Possible	1 (33)	45 (60)	48 (89)	94 (85)
Hypotension			1 (2)	2 (2)
Bradycardia			5 (9)	3 (3)
Wheals/skin swelling		2 (3)	7 (13)	24 (22)
Erythema			2 (4)	3 (3)
HGE			1 (2)	0
Hyperexcitement			1	4 (4)
Seizure		2 (3)	4 (7)	2 (2)
Cyanosis	1 (33)	3 (4)	5 (9)	5 (5)
Respiratory	2 (66)	8 (11)	6 (11)	31 (28)
Apnoea				8 (7)
Vomiting			2 (4)	1 (1)
Diarrhoea			1 (2)	1 (1)
Cardiac arrest	2 (66)	5 (7)	4 (7)	14 (13)
Oedema		2 (3)	3 (6)	4 (4)
Vasodilation			1 (2)	0
Poor induction/ recovery			7	9 (8)
Tremors			2 (4)	4 (4)
Death	3 (100)	15 (20)	7 (13)	23 (21)

HGE, haemorrhagic gastroenteritis.

A search of the United States Food and Drug Administration Adverse Drug Experience reports²² revealed no reporting on alphaxalone, though Alfaxan was only available from 2012 in the USA. The USFDA website advises at the time of writing that the Adverse Drug Experience report is to be released in 2018. Searches of the Canadian and United Kingdom's pharmacovigilance programs^{23,24} did not yield any adverse events specifically for alphaxalone. However, the UK website only makes annual reviews available for 2014–2016.

The primary objective of this report was to describe an anaphylactic reaction in a dog attributable to intravenous administration of Alfaxan.

Case report

A 25.7-kg 2.5-year-old female spayed cattle dog was referred to the University of Queensland Veterinary Medical Centre with a 3-month history of left forelimb lameness and had received treatment with meloxicam, which was discontinued 4 days prior to arrival. Initial physical examination was unremarkable except for bilateral elbow pain and the dog was admitted for imaging and possible elbow arthroscopy the following day. The dog was fed at 20:00 hours and then fasted overnight prior to the procedure. Omeprazole (1 mg/kg PO) was commenced 1 h after feeding as per hospital protocol. Access to water was permitted until the following morning. A pre-anaesthetic physical examination on the morning prior to the procedure revealed a heart rate of 110 beats/min, respiratory rate of 28 breaths/min, pink oral mucous membranes with a capillary refill time (CRT) < 2 s and mildly anxious behaviour. Packed cell volume (41%), total protein (71 g/L) and creatinine (114 mol/L; reference range 20–177) were measured and the dog was assigned an American Society of Anaesthesiologists score of 1 by the attending anaesthetist. The dog was then premedicated with 0.03 mg/kg acepromazine (ACP) and 0.3 mg/kg methadone intramuscularly.

Table 2. Australian Pesticides and Veterinary Medicines Authority classification of adverse experiences

Probable	All of the following criteria are met:
	1. There is a reasonable association between exposure to or the use of a product and the onset and duration of the reported adverse experience 2. The description of the presenting signs is consistent with, or at least plausible, given the known pharmacology and toxicology of the product 3. There are no other equally plausible explanations (or contributing factors) for the adverse experience
Possible	When any of these criteria cannot be satisfied (due to lack of sufficient information or conflicting data) the APVMA cannot classify the relationship as probable A possible classification is given when the way the suspect product was used is one of other possible and equally plausible explanations (or contributing factors) for the adverse experience (e.g. a pre-existing condition)

Table 3. Sequential arterial electrolyte and blood gas results post reaction

Time post reaction (h)	FiO ₂ (assumed)	PaO ₂ (mmHg)	A:a gradient (reference < 15)	Lactate (mmol/L)	pH (reference 7.35–7.46)	PaCO ₂ (mmHg) (reference 30.8–42.8)	HCO ₃ ⁻ (mmol/L) (reference 18.8–25.6)	Base excess (mmol/L) (reference –0.2–3.4)
0.5	100%	460	-	3.8	7.3	39	19.9	-6.5
1	21%	80	32	3.3	7.41	33	22.6	-3.0
6	21%	93	15	0.8	7.42	37	24.9	-0.1

A:a, alveolar–arterial; HCO₃⁻, bicarbonate; FiO₂, fractional inspired O₂; PaO₂, partial pressure oxygen; PaCO₂, partial pressure CO₂.

Examination of the dog immediately prior to induction demonstrated good sedation with normal perfusion parameters. A rebreathing circuit with an out-of-circle vapouriser was used for pre-oxygenation by face mask. Inspired oxygen was not measured at any time; however, the fractional inspired O₂ (FiO₂) was presumed to be 100% based on fresh gas flow of 3 L/min. At 70 min post premedication, 3 min of pre-oxygenation by mask was administered prior to induction of anaesthesia. Induction of anaesthesia was achieved with intravenous Alfaxan titrated to effect, to a total dose of 2 mg/kg, administered at the rate of 0.25 mg/kg every 30 s. Immediately following Alfaxan administration the dog vomited a copious amount of clear fluid. The dog was intubated with a 10-mm endotracheal tube, the cuff inflated and 100% oxygen commenced at 1.5 L/min. This flow rate was increased to 3 L/min at 15 min following intubation and continued until extubation. Profuse watery diarrhoea was noted at the time of intubation, as well as pale/grey oral mucous membranes, CRT of 2 s and poor dorsal pedal and femoral pulses. Anaesthesia monitoring (Datex AS5, Helsinki, Finland) commenced immediately following intubation and consisted of pulse oximetry (SpO₂), capnography (ETCO₂), rectal temperature, electrocardiogram (ECG) and oscillometric blood pressure. The initial systolic arterial blood pressure recorded post induction was 55 mmHg, diastolic arterial blood pressure was 36 mmHg, mean arterial pressure (MAP) 43 mmHg, and a heart rate of 123 beats/min. The SpO₂ was 98% with an ETCO₂ of 21 mmHg and a respiratory rate of 24 breaths/min. A bolus of balanced isotonic crystalloid (compound sodium lactate) was administered at 40 mL/kg/h for a dose of 10 mL/kg IV and the oxygen supply was increased initially to 2 and subsequently 3 L/min. After initial fluid resuscitation the MAP increased to 72 mmHg and the heart rate was 125 beats/min with a normal sinus rhythm. The SpO₂ remained at or above 96% (FiO₂ 100%) and ETCO₂ increased to 31 mmHg. By 30 min post induction the MAP had increased to 92 mmHg with a heart rate of 155 beats/min. A dorsal pedal arterial line was placed and arterial blood gas measurement was performed (FiO₂ 100%): PaO₂ 460 mmHg; PaCO₂ 39 mmHg; lactate 3.8 mmol/L; pH 7.30; HCO₃⁻ 19.9 mmol/L; and base excess -6.5 mmol/L. The procedure was abandoned and the dog recovered from anaesthesia and was extubated. No inhalational anaesthetic had been delivered at any time. Esomeprazole at 1 mg/kg was administered IV following extubation. A moderate degree of dysphoria was noted at emergence and as a result, 0.005 mg/kg ACP was administered IV.

The dog was transferred to the intensive care unit for recovery 45 min post induction. The heart rate at admission was

220 beats/min, respiratory rate 60 breaths/min, oral mucous membranes were pale and the rectal temperature was 37°C. A sinus tachycardia was noted on ECG. A 1.5-L bolus of balanced isotonic crystalloid (compound sodium lactate) was administered via a pressure bag to treat suspected anaphylactic shock. An abdominal focussed assessment with sonography of trauma/triage was performed and gallbladder wall oedema was noted (5.5 mm; reference 2–3 mm). Scant, free, anechoic abdominal fluid was seen but was not able to be aspirated. After 2 L of isotonic crystalloid the dog's heart rate reduced to 80 beats/min with a MAP of 82 mmHg (invasive blood pressure). Chlorpheniramine was administered (12.5 mg SC), together with 10 mg metoclopramide IV and 25 mg maropitant SC. A subsequent blood gas (FiO₂ 21%) was performed: PaO₂ 80 mmHg; PaCO₂ 33 mmHg; pH 7.41; HCO₃⁻ 22.6 mmol/L; base excess -3.0 mmol/L; and lactate of 3.3 mmol/L (alveolar–arterial (A:a) gradient 32 (reference < 15); R = 0.9). The dog had been lying in lateral recumbency prior to sample collection for approximately 30 min. Oxygen support was continued by nasal oxygen line at 2 L/min. Diarrhoea was noted throughout the afternoon and evening and intravenous isotonic crystalloids (compound sodium lactate) were continued at 120 mL/h. A subsequent blood gas analysis was performed 6 h following the reaction (FiO₂ 21%): PaO₂ 93 mmHg; PaCO₂ 37 mmHg; pH 7.42; HCO₃⁻ 24.9; base excess -0.1; and lactate of 0.8 mmol/L (A:a gradient 15 (reference < 15); R = 0.9) (Table 3). Fluids were weaned to 60 mL/h overnight as there were no further gastrointestinal fluid losses and the dog's vitals remained within normal limits with a normal lactate. The dog was offered food but did not eat until the following day. Intravenous fluids were discontinued at this time.

The dog was successfully anaesthetised 3 days later without incident and without the use of alphaxalone. No drug used in the previous procedure was administered at this time.

Discussion

This is the first report of anaphylaxis following the use of Alfaxan in a dog. The APVMA reporting of reactions in small animals from 2003 to 2013 of Alfaxan is consistent with this case report's finding involving the respiratory, circulatory and gastrointestinal systems (Table 1).

This dog displayed acute signs of hypotension, gastrointestinal insult and hypoxaemia immediately after exposure to Alfaxan. Hypotension is frequently associated with vasodilation in anaphylaxis.

Despite this, clinical signs consistent with vasoconstrictive shock, including pale mucous membranes, prolonged CRT and poor pulse quality, were observed in this dog and have been associated with anaphylaxis in dogs.²⁵ The clinical manifestations of immunological anaphylaxis are a result of release of preformed mediators such as histamine from mast cells by binding of an allergen to cell surface IgE receptors.²⁵ Rapid release of vasoactive mediators leads to vasodilation and vascular permeability.²⁵ Increased vascular permeability is a characteristic feature, with redistribution of fluids leading to decreased effective circulating volume, hypovolaemia and vasoconstrictive shock.²⁵ Fulminant fluid shifts of as much as 35% of the vascular volume to the extravascular space have been reported within 10 min of an insult.^{1,2} This would explain the presence of vasoconstrictive shock in this dog.

The heart rate did not elevate from baseline immediately after the reaction, as would be expected with decreased effective circulating volume. Elevated vagal tone has been reported to accompany some instances of anaphylaxis and is thought to be a protective mechanism allowing ventricular filling during severe volume deficit and may have been responsible for this observation.²⁵ However, the heart rate increased immediately prior to admission to the intensive care unit and any increase in vagal tone may have abated. It is also possible any negative effect on the baroreceptor reflex by alphaxalone may have waned, as the plasma half-life of alphaxalone in dogs at this dose is 24 min.¹⁹ Following approximately an entire blood volume of isotonic crystalloids, the heart rate, lactate concentration and blood pressure normalised. Given the improvement in blood pressure following isotonic crystalloids, and the vasoconstrictive nature of the shock observed with only minor respiratory compromise, adrenaline was not considered necessary and therefore was not administered. Although myocardial dysfunction may have contributed to vasoconstrictive shock this is considered less likely. There was immediate evidence of substantial fluid redistribution to the gastrointestinal space and this was considered the primary cause of hypotension.

The gastrointestinal signs observed are characteristic of anaphylaxis in the dog, which is unsurprising given the gastrointestinal tract is considered the shock organ of the dog. A study investigating anaphylaxis in dogs found 56 of 61 (92%) dogs presented with gastrointestinal signs including vomiting, diarrhoea and nausea.²⁶ These signs were only observed in this case immediately after administration of Alfaxan. Diarrhoea persisted for 24 h, but the severity attenuated subsequent to the initial resuscitation period.

Gallbladder wall oedema was also demonstrated in this dog by ultrasound, with wall thickness approximately twice the reference range.²⁷ Gallbladder wall oedema was documented in 57 of 61 (93%) dogs diagnosed with anaphylaxis in one study, which defined gallbladder wall changes caused by anaphylaxis as diffuse thickening and striation (halo effect).²⁶ These changes are the result of hepatic artery vasodilation in conjunction with sinusoidal outlet sphincter vasoconstriction secondary to histamine.²⁸ Resulting portal hypertension impairs gallbladder venous drainage, which occurs via the portal system.²⁸ An elevation in alanine aminotransferase in dogs with anaphylaxis has also been reported, but this was not measured in this dog at the time nor was a baseline value available.²⁶ The fulminant nature of the symptoms observed, together with the gallbladder wall

oedema, were consistent with a diagnosis of anaphylaxis, although no universally accepted criteria exist for dogs.²⁵ Other clinical signs that are commonly associated with anaphylaxis are skin and/or mucosal tissue lesions,²⁵ although not detected in this case. Involvement of the skin, mucosal tissue or both is a major clinical criterion for diagnosing anaphylaxis in people.²⁵ A study in dogs reported cutaneous signs in only 35 of 61 (57%) dogs with anaphylaxis.²⁴ Therefore, the absence of cutaneous signs in this dog does not rule out the presumptive diagnosis of anaphylaxis.

Respiratory compromise was briefly noted, as evidenced by transient hypoxaemia, PaO₂ 80 mmHg (FiO₂ 0.21) with an A:a gradient of 32 and an increased respiratory rate. This may indicate respiratory compromise caused by bronchorrhea and/or bronchospasm associated with anaphylaxis or atelectasis resultant from recumbency.²⁹ Although the dog was not intubated at the time of vomiting, aspiration was not considered likely because the hypoxaemia was transient as evidenced by a normal A:a gradient 6 h following the reaction (Table 3). The dog appeared to maintain normal ventilation and this was not thought to be the cause of the decreased PaO₂. The dog did not clinically exhibit any further respiratory compromise and no further investigation was required.

The dog in this case study also received ACP, methadone and omeprazole prior to the procedure. ACP and methadone were administered as a premedication to anaesthesia. However, the likelihood of these premedications contributing to the signs witnessed in this dog is low. The onset of anaphylaxis is usually rapid after exposure to allergens²⁵ and these drugs were administered more than 1 h prior to the onset of clinical signs. ACP was also administered at the time of recovery in the intensive care unit because of the dysphoria. Given its potential vasodilatory effects, a low dose was trialled to good effect once the blood pressure and perfusion parameters had normalised. Chlorpheniramine was also administered in the post-reaction phase. It is recognised by the authors that an antihistamine given after the fact is likely to have little therapeutic effect. A systematic review in people suffering anaphylaxis was unable to identify any high-quality evidence for or against the use of H1 antihistamines.³⁰ Effectiveness in dogs for the treatment of anaphylaxis has also been shown to be lacking.³¹ At the commencement of anaphylaxis, histamine levels peak and rapidly normalise.²⁶ The release of a range of vasoactive mediators during anaphylaxis implies that downstream effects of inflammation are unlikely to be attenuated or reversed by the use of an antihistamine. Omeprazole was also administered 18 h prior to the procedure and esomeprazole immediately post reaction to reduce the risk of reflux oesophagitis. Given this timeline, these proton pump inhibitors are considered less likely as a causative agent.

Alphaxalone itself cannot be conclusively demonstrated to be the inciting cause of the clinical signs described here because HPCD as the vehicle may be responsible. There are no published reports of β -cyclodextrins causing anaphylaxis. A study examining beagle dogs sensitised to HPCD could not induce anaphylactic reactions.³² Previously, the alphaxalone–alphadolone combination was suggested to be responsible for immunological reactions when administered in the absence of either cremophor or HPCD vehicle in pigs.⁸ Regardless, this report does not aim to isolate the actual trigger of

anaphylaxis in this dog associated with the use of Alfaxan. Rather it describes the clinical signs of anaphylaxis seen following the use of Alfaxan in a dog, which may assist clinicians in identifying allergic and anaphylactic reactions associated with this drug. The dog had had one previous anaesthetic for ovariohysterectomy, but the anaesthetic details for that procedure were unable to be obtained by the authors. Additionally, the Alfaxan used in this case was within date, stored appropriately as per the manufacturer's guidelines and had been used without incident in other patients. Contaminants within the breathing system, such as residual isoflurane and cleaning agents, cannot be completely excluded as the inciting cause for the reaction described. However, the breathing circuits are thoroughly cleaned using medizyme (Whitely, NSW, Aust), rinsed and allowed to air dry. Further, the dog was anaesthetised without incident 3 days later using a cleaned hospital breathing system with isoflurane. A literature search has failed to reveal any report of anaphylaxis associated with enzymatic detergents. The breathing circuit used was washed as per hospital protocol. Therefore, these agents were unlikely to have caused this reaction.

In conclusion, this report describes clinical signs consistent with anaphylaxis in a dog after intravenous Alfaxan. The frequency of reactions to Alfaxan in dogs appears to be low.

Although only 54 dogs over a 10-year period were reported to the APVMA, with 6 probable and 48 possible reactions to Alfaxan, it is likely more have gone unreported. The authors have been using Alfaxan since its release in Australia in 2001 and have not encountered signs consistent with an anaphylactic reaction previously. Therefore, Alfaxan continues to be a popular choice of intravenous induction agent for small animal anaesthetic induction at our institution.

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