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Amiodarone-induced anaphylaxis in a Chihuahua: a case report

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CASE REPORT

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ABSTRACT: Amiodarone, a class III antiarrhythmic drug, is widely used in both human and veterinary medicine to manage ventricular and supraventricular arrhythmias. While its efficacy in rhythm control is well-established, the drug is associated with significant adverse effects, affecting multiple organ systems. In humans, amiodarone-induced toxicity commonly involves the pulmonary, hepatic, thyroid, and dermatological systems, with pulmonary toxicity being one of the most severe complications. Acute hypersensitivity reactions, including anaphylaxis, are rare but have been reported, particularly in association with intravenous (IV) formulations containing polysorbate 80. In veterinary medicine, amiodarone is increasingly used to treat life-threatening arrhythmias in dogs, yet its safety profile is less extensively studied. Unlike humans, dogs appear to be more susceptible to immediate hypersensitivity reactions following IV administration, characterized by severe cutaneous signs, hypotension, and cardiovascular collapse. The present case report describes a 9-year-old Chihuahua that developed a rapid hypersensitivity reaction, including erythema, mucosal hyperemia, and facial edema, immediately after receiving IV amiodarone. The reaction resolved spontaneously within 15 minutes without requiring corticosteroid administration. Haematological and biochemical analyses showed a mildly decreased reticulocyte value, elevated neutrophil count, and increased ALT, while all other parameters were within reference ranges. A review of the literature suggests that excipients such as polysorbate 80 and benzyl alcohol may be primary contributors to amiodarone-induced anaphylaxis in dogs. Histamine-mediated responses, severe hypotension, and cardiovascular complications have been documented in both human and veterinary cases, with dogs displaying heightened sensitivity to IV administration. Additionally, while pulmonary and thyroid toxicity are well-recognized chronic effects in human patients, hepatic and gastrointestinal toxicities are more frequently observed in dogs. This case underscores the need for heightened awareness of amiodarone-induced hypersensitivity reactions in veterinary medicine, particularly in IV formulations. Pre-medication strategies, controlled infusion rates, and close monitoring are essential to mitigating the risk of life-threatening anaphylaxis in human and canine patients. Further research is needed to better understand species-specific differences in amiodarone metabolism and toxicity.

KEYWORDS: Amiodarone, anaphylaxis triggers, Chihuahua dog, hypersensitivity

INTRODUCTION

Amiodarone is a class III antiarrhythmic drug widely used in both human and veterinary medicine for managing ventricular and supraventricular arrhythmias. While its efficacy in rhythm control is well-established, amiodarone is also known for its significant adverse effects, which can affect multiple organ systems. Notably, anaphylaxis and hypersensitivity reactions have been reported in both humans and dogs, with varying presentations and severity. In human medicine, amiodarone-induced toxicity is well-documented and typically affects the pulmonary, hepatic, thyroid, and dermatological systems. Among the most significant concerns is amiodarone-induced pulmonary toxicity (AIPT), which can lead to life-threatening interstitial pneumonitis and fibrosis [1]. Additionally, thyroid dysfunction (hypothyroidism or hyperthyroidism), liver enzyme elevation, and corneal microdeposits are common long-term effects [2]. Cutaneous reactions, including blue-grey skin discoloration and photosensitivity, have been reported, but acute hypersensitivity reactions such as anaphylaxis are considered rare [2, 3]. However, severe anaphylactic reactions, including urticaria, angioedema, and respiratory distress, have been reported in isolated human cases, particularly linked to IV amiodarone administration. Tang et al. [2] documented a case of angioedema and urticaria following IV administration, suggesting that excipients in

the formulation, specifically polysorbate 80, may be responsible rather than amiodarone itself. This aligns with findings by Masini et al. [4], who demonstrated that polysorbate 80 can trigger histamine release and systemic hypotension in experimental models.

In veterinary medicine, amiodarone has been increasingly used to manage life-threatening arrhythmias, yet its safety profile is not as extensively studied as in humans. The most reported side effects in dogs include hypotension, vomiting, diarrhea, and hepatotoxicity [5]. Thyroid dysfunction is less commonly reported in dogs compared to humans; instead, hepatic toxicity and gastrointestinal symptoms are more frequently observed [6].

One of the notable adverse effects in dogs is anaphylactic reactions following IV amiodarone administration. Levy et al. [5] and Cober et al. [7] documented cases of severe hypersensitivity reactions, including hypotension, tachypnea, and severe cutaneous signs. Unlike in humans, where pulmonary toxicity is a significant concern, in dogs, immediate hypersensitivity reactions leading to cardiovascular symptoms are observed more frequently. Additionally, cutaneous symptoms such as severe skin reactions [7] and histamine-mediated responses [4] indicate that excipients in IV formulations may contribute to triggering anaphylaxis in dogs.

Therefore, this investigation highlights the need for increased awareness of amiodarone-induced hypersensitivity reactions in veterinary medicine, particularly with intravenous formulations. Pre-medication protocols, controlled infusion rates, and vigilant monitoring are critical to reducing the risk of life-threatening anaphylaxis in both human and canine patients. Further research is warranted to elucidate species-specific differences in amiodarone metabolism and toxicity.

CASE PRESENTATION

A 9-year-old male Chihuahua (6 kg) was referred for a splenectomy and castration. A routine ultrasound revealed a tumor-like lesion in the splenic parenchyma and benign polycystic prostatic hypertrophy. The owners reported no behavioral changes or clinical symptoms. Haematological and biochemical analyses showed a mildly decreased reticulocyte value (19.1 pg), elevated neutrophil count (12.69 × 10^9/L), and increased ALT (166 U/L), while all other parameters were within reference ranges (Tables 1 and 2).

Table 1. Haematology test results

Test	Result	Reference value	Unit	Notes
Red blood cell (RBC)	8.29	5.65 – 8.87	x10^{12}/L	
Haematocrit	0.555	0.373 – 0.617	L/L	
Haemoglobin	194	131 – 205	g/L	
Mean corpuscular volume (MCV):	66.9	61.6 – 73.5	fL	
Mean corpuscular hemoglobin (MCH)	23.4	21.2 – 25.9	pg	
Mean corpuscular hemoglobin concentration (MCHC)	350	320 – 379	g/L	
Red cell distribution width (RDW)	18.2	13.6 – 21.7	%	
% Reticulocytes	0.4		%	
Reticulocytes	35.6	10.0 – 110.0	K/µL	
Reticulocyte Haemoglobin	19.1	22.3 – 29.6	pg	↓ Low RETIC-HGB
White blood cell (WBC)	14.91	5.05 – 16.76	x10^9/L	
% Neutrophils	85.2		%	
% Lymphocytes	7.4		%	
% Monocytes	5.2		%	
% Eosinophils	2.1		%	
% Basophils	0.1		%	
Neutrophils	12.69	2.95 – 11.64	x10^9/L	↑ High
Lymphocytes	1.11	1.05 – 5.10	x10^9/L	
Monocytes	0.78	0.16 – 1.12	x10^9/L	
Eosinophils	0.32	0.06 – 1.23	x10^9/L	
Basophils	0.01	0.00 – 0.10	x10^9/L	
Platelets	333	148 – 484	x10^9/L	
Platelet distribution width (PDW)	12.0	9.1 – 19.4	fL	
Mean platelet volume (MPV)	11.5	8.7 – 13.2	fL	
Plateletcrit	0.38	0.14 – 0.46	%	

Table 2. Biochemical test results

Test	Result	Reference value	Unit	Notes
Glucose	5.87	3.89 – 7.95	mmol/L	
Creatinine	86	44 – 159	µmol/L	
Urea	3.7	2.5 – 9.6	mmol/L	
BUN:Creatinine ratio	11			
Phosphorus	1.34	0.81 – 2.20	mmol/L	
Calcium	2.43	1.98 – 3.00	mmol/L	
Total Protein	67	52 – 82	g/L	
Albumin	34	22 – 39	g/L	
Globulin	34	25 – 45	g/L	
Albumin:Globulin ratio	1.0			
ALT	166	10 – 125	U/L	↑ High
ALP	68	23 – 212	U/L	
GGT	11	0 – 11	U/L	Upper limit
Bilirubin - Total	<2	0 – 15	µmol/L	
Cholesterol	4.17	2.84 – 8.26	mmol/L	
Amylase	1,026	500 – 1,500	U/L	
Lipase	449	200 – 1,800	U/L	

BUN: blood urea nitrogen; ALT: alanine aminotransferase; GGT: gamma-glutamyl Transferase; ALP: alkaline phosphatase

Intraoperative anesthetic monitoring indicated stable parameters throughout the procedure. Postoperative electrocardiography revealed pronounced tachycardia and tachyarrhythmia, with a heart rate exceeding 210 bpm. Two boluses of IV lidocaine (2 mg/kg) administered at 5-minute intervals failed to stabilize the arrhythmia. Due to persistent tachyarrhythmia, a bolus of IV amiodarone (1 mg/kg) was given, resulting in a heart rate reduction to 128 bpm, a regular pulse, and pronounced tachypnea. However, an immediate allergic reaction occurred following amiodarone administration, characterized by erythema of the dog's head, pinnae, inguinal region, and trunk, mucosal hyperemia, and edema of the eyelids, lips, and tongue (Figure 1).

Oxygen therapy and IV NaCl were administered. The reaction, which appeared within seconds of amiodarone (Arytmil 50 mg/mL) administration, resolved spontaneously within 15 minutes. Dexamethasone was not required, as symptoms subsided without intervention.

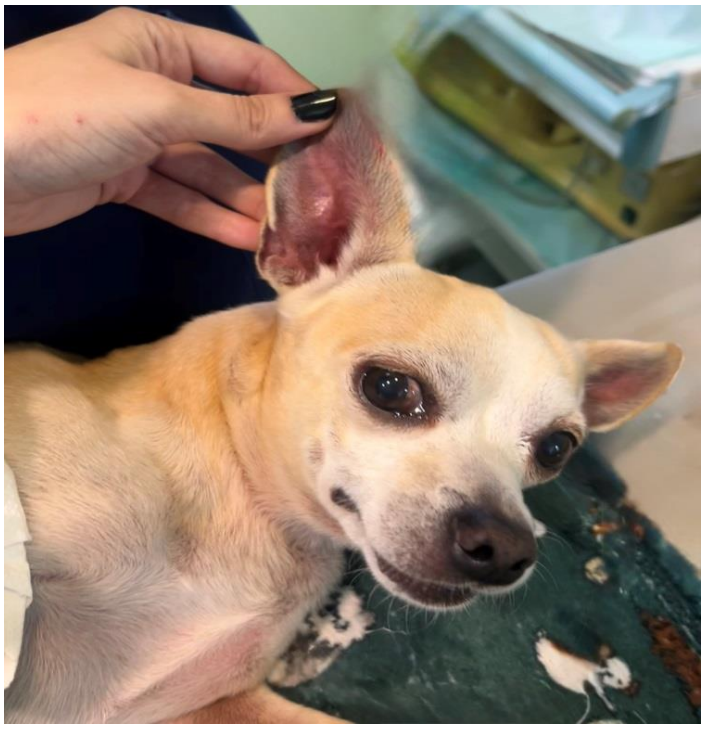

Figure 1. Erythema of the dog's head, pinnae, and trunk. Edema of the eyelids and lips.

DISCUSSION

Anaphylaxis due to IV amiodarone is rare in humans [8] but has been reported in isolated cases. Tang et al. [2] documented a case of severe anaphylaxis in a patient receiving IV amiodarone, leading to facial edema, hypotension, and cardiac arrest requiring advanced resuscitation measures. The suspected pathophysiology involved mast cell degranulation and inflammatory mediator release, which can induce Kounis syndrome, a form of acute coronary hypersensitivity reaction [2]. Additionally, Averin et al. [3] reported angioedema, urticaria, and respiratory distress in a human patient following IV amiodarone administration, emphasizing the potential role of excipients polysorbate 80 in triggering histamine-mediated reactions. In contrast, dogs appear to be more susceptible to amiodarone-induced anaphylaxis, particularly when administered IV formulations containing polysorbate 80 and benzyl alcohol. Cober et al. [7] reported five cases of anaphylaxis in dogs, characterized by severe erythema and urticaria in all cases, pruritus, facial swelling, and subcutaneous edema in three dogs, hypersalivation and agitation in multiple cases, and cardiovascular collapse requiring aggressive resuscitation in one case. Masini et al. [4] demonstrated that polysorbate 80 induces massive histamine release and profound hypotension in dogs, further confirming that excipient-mediated hypersensitivity plays a significant role in anaphylaxis observed in reported cases.

Hypotension is a common acute side effect of intravenous amiodarone in both humans and dogs. In humans, Tang et al. [2] identified polysorbate 80 and benzyl alcohol as primary contributors to acute vasodilation and hypotension, rather than the active drug itself. In certain cases, hypotension resulted in cardiogenic shock, requiring vasopressor therapy. In dogs, hypotension appears to be more severe and rapid in onset. Cober et al. [7] documented a case where a dog experienced life-threatening hypotension, with systolic blood pressure dropping from 115 to 40 mmHg within minutes of intravenous amiodarone infusion. Additionally, Masini et al. [4] established a direct correlation between polysorbate 80-induced hypotension and plasma histamine levels, indicating a histamine-mediated vasodilation mechanism.

Amiodarone-induced pulmonary toxicity is a significant side effect in humans, occurring in up to 10% of long-term users [9]. The toxicity can appear as interstitial pneumonitis, fibrosis, or pleural effusion, and its occurrence is dose-dependent. In contrast, pulmonary toxicity is rarely reported in dogs. Although tachypnea and respiratory distress have been observed after IV administration [7], there are no documented cases of chronic pulmonary fibrosis in veterinary literature. This indicates that dogs may metabolize amiodarone differently, which may reduce the risk of long-term lung complications.

In humans, elevated hepatic enzyme levels and thyroid dysfunction (either hypo- or hyperthyroidism) are well-documented chronic effects [9]. Thyroid toxicity is attributable to iodine overload, which leads to metabolic disturbances. In dogs, hepatic toxicity is more prevalent than thyroid dysfunction. Pedro et al. [6] reported increased liver enzyme levels in dogs receiving long-term oral amiodarone treatment, whereas thyroid abnormalities were rare. This indicates species-specific differences in iodine metabolism.

The route of administration significantly influences amiodarone's side effect profile in dogs. While IV amiodarone is associated with rapid-onset, life-threatening anaphylaxis and cardiovascular collapse, oral administration carries risks of chronic toxicities, primarily affecting the liver and gastrointestinal tract [6, 5]. The choice of administration should be carefully tailored to the patient's condition, considering the severity of arrhythmia, risk of hypersensitivity, and long-term organ function.

Cober et al. [7] reported that adverse effects of a wide range of amiodarone doses in dogs were not dose-dependent. In humans, the infusion rate of amiodarone impacts systemic blood pressure, requiring a controlled rate below 15 mg/min intravenously. Our rapid administration likely contributed to observed adverse effects. However, Cober et al. [7] noted that even at lower infusion rates within the recommended threshold for humans, adverse effects persisted in most dogs.

Amiodarone hypersensitivity reactions, particularly those triggered by excipients such as polysorbate 80 and benzyl alcohol, have been well-documented in both human and veterinary medicine [2, 4]. However, preventative measures to mitigate these adverse reactions in veterinary practice have not been extensively explored. One potential strategy to reduce hypersensitivity risk involves pre-medication with antihistamines and corticosteroids. In human cardiology, antihistamines (e.g., diphenhydramine) and corticosteroids (e.g., dexamethasone) are sometimes used before the administration of high-risk IV medications known to trigger anaphylaxis [3]. A similar approach could be considered in high-risk canine patients, particularly those with previous allergic reactions or a history of drug hypersensitivity. Due to the high risk of hypersensitivity reactions with IV amiodarone in dogs [7], alternative antiarrhythmic drugs are advisable. Sotalol, a class III drug, effectively manages ventricular arrhythmias with fewer acute hypersensitivity reactions [6]. Diltiazem, a calcium channel blocker, is

commonly used for rate control in supraventricular tachyarrhythmias and is well-tolerated [5]. While oral amiodarone might be suitable for long-term control, IV formulations should be used with caution due to their risks.

CONCLUSIONS AND RECOMMENDATIONS

This case report presents a rare but clinically significant instance of anaphylaxis following intravenous amiodarone administration in a Chihuahua, underscoring the potential for severe hypersensitivity reactions in canine patients. The resolution of symptoms without corticosteroid intervention suggests a transient, self-limiting response; however, the event raises important concerns regarding the acute safety profile of amiodarone in veterinary use.

While amiodarone remains a cornerstone antiarrhythmic agent in both human and veterinary medicine, this case highlights key species-specific differences in adverse effect profiles. In humans, chronic toxicities such as pulmonary fibrosis and thyroid dysfunction are more prevalent, whereas dogs appear to be more susceptible to acute, histamine-mediated reactions—including life-threatening anaphylaxis and hypotension. The role of excipients like polysorbate 80 and benzyl alcohol as potential anaphylaxis triggers should not be underestimated and warrants further investigation.

Given these risks, we recommend that the use of intravenous amiodarone in dogs be approached with caution, particularly in small breeds or patients with known sensitivities. Pre-treatment with antihistamines, slow infusion rates, and close cardiovascular monitoring may help mitigate adverse outcomes. Where possible and not contraindicated, consideration should be given to alternative antiarrhythmic drugs with a more favorable safety profile in canine patients, such as lidocaine, procainamide, or sotalol, depending on the underlying arrhythmia and clinical context.

In both veterinary and human medicine, this case reinforces the importance of pharmacovigilance, individualized risk-benefit assessment, and the need for further comparative studies on antiarrhythmic drug tolerability across species.

DECLARATIONS

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Authors' contribution

All authors contributed equally to this work.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Ethical approval

The authors complied with the ARRIVE guidelines and the Interdisciplinary Principles and Guidelines for the Use of Animals in Research, Testing, and Education by the New York Academy of Sciences, Ad Hoc Animal Research Committee. Informed owner consent was obtained for all procedures and activities described in this paper.

Competing interests

All authors declare that they have no conflict of interest.

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