

Adverse Effects of Intravenous Amiodarone in 5 Dogs

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Dog 1

A 74.0-kg, 1.5-year-old, castrated male Newfoundland was presented for pharmacological cardioversion of atrial fibrillation. Three months before presentation, the dog was diagnosed with “lone” atrial fibrillation (ie, atrial fibrillation in the absence of detectable structural heart disease), underwent successful transthoracic electrical direct current (DC) cardioversion, and was treated with sotalol^a (2.0 mg/kg PO q12h). Reversion to atrial fibrillation was confirmed 2½ months later by ECG.

At presentation, the dog was asymptomatic and receiving sotalol^a (2.0 mg/kg PO q12h). Physical examination was normal except for an irregular heart rhythm, variable pulse quality, and pulse deficits. The biochemical profile was within reference intervals for the laboratory. Echocardiography was normal. An ECG confirmed atrial fibrillation with a ventricular response rate of 130–160 bpm. The dog was admitted to the hospital Intensive Care Unit for pharmacologic cardioversion.

On the 1st day, the dog received 3 doses of lidocaine^b (2 mg/kg IV q10min) with no change in rate or rhythm. Dofetilide^c (6.76 µg/kg PO q12h) then was administered and the dosage subsequently increased to 6.76 µg/kg PO q8h on day 2. After 5 doses, the dog remained stable without a change in heart rate or underlying rhythm, but ventricular premature complexes (VPC) were noted including couplets and triplets. Dofetilide was discontinued on day 3 for presumed lack of efficacy and possible induction of ventricular ectopy, which resolved with discontinuation. The owner then elected pharmacologic conversion with IV amiodarone over other treatment options. On day 4, the dog was sedated with acepromazine^d (0.02 mg/kg IM) and butorphanol^e (0.2 mg/kg IM) for venous catheter placement. Amiodarone^f was adminis-

Abbreviations:

CHF	congestive heart failure
CRI	constant rate infusion
DC	direct current
VPC	ventricular premature contraction

tered IV as a constant rate infusion (CRI) at 300 µg/kg/min. Before beginning the CRI, the dog's systolic blood pressure was 115 mmHg. Two minutes after administration, injection site pain was noted and the CRI was decreased (150 µg/kg/min). After a total of 175 mg had been administered, the dog began salivating and pawing at its face. Its head and trunk became diffusely and severely erythematous, the muzzle and periorbital region became swollen, and severe weakness developed. Amiodarone was discontinued. The dog's systolic blood pressure, measured by Doppler, was 40–45 mmHg and atrial fibrillation remained with a ventricular response rate of 180–260 bpm. Because of a suspected anaphylactic reaction, IV Plasma Lyte 148^g and Hetastarch^h fluids (total dose: 4 and 1 L, respectively), diphenhydramineⁱ (1 mg/kg IV), and dexamethasone sodium phosphate^j (0.8 mg/kg IV) were administered. A CRI of norepinephrine (0.3 µg/kg/min) was also begun. Over the next 2 hours, the dog's systolic blood pressure increased from 90 to 110 mmHg and the ventricular rate decreased from 120 to 150 bpm. The dog was discharged without antiarrhythmic therapy the next day and was started on digoxin and diltiazem administered orally for ventricular rate control 2 weeks later.

Dog 2

A 41-kg, 10-year-old, spayed female Doberman Pinscher was presented for reevaluation of previously diagnosed dilated cardiomyopathy. On presentation, the dog was receiving enalapril (0.5 mg/kg PO q12h), sotalol^a (2 mg/kg PO q12h), mexiletine^k (7.3 mg/kg PO q8h), L-thyroxine (10 µg/kg PO q12h), and furosemide^l (1 mg/kg PO q24h). Physical examination showed a fast heart rate with a regular rhythm, which based on ECG was diagnosed as a monomorphic left ventricular tachycardia with a rate of 270 bpm. An IV catheter was placed and 4 lidocaine^b boluses (2 mg/kg IV q5min) were administered with no change in the rhythm. An initial procainamide^m bolus (4 mg/kg IV) then was administered followed by four 2 mg/kg boluses every 5–8 minutes without a change in the rhythm. Intravenous administration of 0.45% NaCl (2.5 mL/kg/h) with potassium (0.49 mEq/kg/d) and MgSO₄ (1 mEq/kg/d) was begun. Serum electrolyte concentrations were within reference ranges. Amiodarone HCl^f 50 mg/mL diluted in 50 mL of

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5% dextrose in water was started (170 µg/kg/min CRI). Five minutes after administration, the dog became extremely agitated and began hypersalivating. The CRI was discontinued and restarted 5 minutes later at a decreased rate (85 µg/kg/min). Diffuse erythema and hives developed over the body and head several minutes later. The amiodarone was discontinued, and the erythema and hives resolved within 30 minutes. The fast monomorphic ventricular tachycardia continued, and the dog was placed under general anesthesia for synchronized transthoracic DC electrical cardioversion. Torsade de Pointes developed and deteriorated into ventricular fibrillation and death.

Dog 3

A 33-kg, 2-year-old, intact male Labrador Retriever was presented for chronic coughing, anorexia, and ascites. Congestive heart failure (CHF) was diagnosed the previous day by the primary care veterinarian. The dog was started on furosemideⁿ (1.2 mg/kg PO q8h), pimobendan^o (0.3 mg/kg PO q12h), benazepril^p (0.15 mg/kg PO q24h), and verapamil^q (2.4 mg/kg PO q8h). On presentation, coughing, labored breathing, and tachypnea were observed. Harsh lung sounds and a grade V/VI left basilar continuous heart murmur were auscultated. The heart rhythm was irregular with a rate of 140 bpm, variable pulse quality, and pulse deficits. A CBC and biochemical profile were within reference ranges for the laboratory except for serum concentrations of creatinine (118 µmol/L; reference range, 35–106 µmol/L), potassium (3.4 mmol/L; reference range, 3.6–5.4 mmol/L), and magnesium (0.44 mmol/L; reference range, 0.47–0.63 mmol/L). Thoracic radiographs indicated left-sided CHF. An ECG confirmed atrial fibrillation with a ventricular response rate of 140 bpm. Echocardiography showed a left-to-right shunting patent ductus arteriosus (PDA), left ventricular eccentric hypertrophy, severe mitral regurgitation, and normal left ventricular systolic function. The dog was hospitalized and treated with furosemideⁿ (1.2 mg/kg PO q8h), pimobendan^o (0.22 mg/kg PO q12h), benazepril^p (0.3 mg/kg PO q24h), diltiazem^r (0.9 mg/kg PO q8h), methyl digoxin^s (0.022 mg/kg PO q12h), potassium chloride^t (1.8 mg/kg PO q12h), and magnesium chloride^u (0.9 mg/kg PO q24h). Six days later, the dog underwent general anesthesia for cardiac catheterization and transvenous PDA coil embolization. Amiodarone^v (9 mg/kg PO q12h) was started 2 days before the procedure. Normal sinus rhythm was achieved by transthoracic electrical DC cardioversion before cardiac catheterization. After successful PDA closure, amiodarone^v (14 µg/kg/min IV CRI) was initiated for prevention of recurrence of atrial fibrillation. Frequent monomorphic ventricular premature contractions (VPCs) were treated with mexiletine^w (30 µg/kg/min CRI). Twenty hours after starting the amiodarone CRI, the dog developed severe generalized erythema. The amiodarone was discontinued, and the erythema resolved overnight. The dog was started on orally administered amiodarone (4.5 mg/kg PO q12h) without complications and discharged 4 days later in normal sinus rhythm.

Dog 4

A 30-kg, 6-year-old, intact female German Shepherd Dog was presented for reevaluation of a cardiac pacemaker generator site infection. A pacemaker with a dual chamber paced, dual chamber sensed, dual chamber responsive, and rate adaptive (DDDR) setting had been implanted 17 months earlier for persistent atrial standstill. Four weeks after implantation, an infection of the generator pocket was detected and treated with several antibiotics without resolution. The owner declined pacemaker replacement. The condition deteriorated until the infected pulse generator pocket opened spontaneously and mechanical trauma caused pacemaker malfunction. On presentation, physical examination was unremarkable, except for the infected generator site and a slow irregular heart rhythm. A CBC indicated mild leukocytosis ($22.4 \times 10^9/L$; reference range, $6.0\text{--}17 \times 10^9/L$), mature neutrophilia ($19.07 \times 10^9/L$, reference range, $3.0\text{--}11.5 \times 10^9/L$), and monocytosis ($1.62 \times 10^9/L$, reference range, $0.04\text{--}1.35 \times 10^9/L$). The biochemical profile was unremarkable. Thoracic radiography showed cardiomegaly with left atrial enlargement and proper pacemaker lead positioning in the right heart. An ECG indicated atrial flutter with a ventricular response rate between 60 and 140 bpm. On echocardiography, mild left-sided volume overload, mitral valve insufficiency, and normal left ventricular systolic function were found. Surgery was scheduled the next day to replace the pulse generator. Twenty-four hours before surgery, amiodarone^v (13.3 µg/kg/min CRI) was instituted to terminate the atrial flutter. Ten to 15 minutes after starting the infusion, restlessness, tachypnea, tachycardia, severely pruritus, urticaria, and severe, generalized erythema developed (Fig 1). The CRI was discontinued, prednisolone^x (2 mg/kg IV) was given, and the erythema resolved. Surgery was performed the next day. After induction of anesthesia, amiodarone (13.3 µg/kg/min CRI) again was started. The dog developed diffuse erythema, leading to discontinuation of the amiodarone and the administration of prednisolone^x (2 mg/kg IV). A new pulse generator was placed continuously capturing the heart,

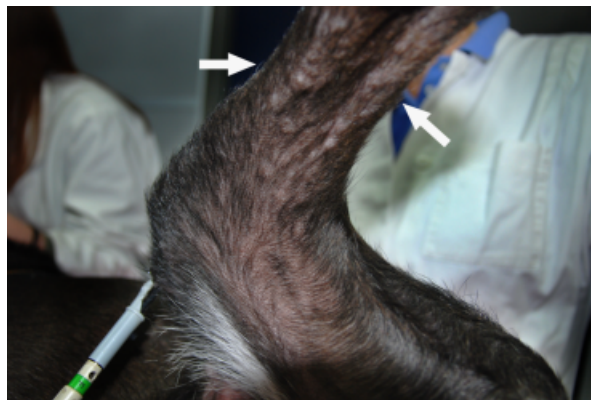


Fig 1. Image of the left hindlimb of Dog 4, 15 minutes after a continuous rate infusion of amiodarone was started. Note the severe urticaria and erythema on the lateral aspect of the hindlimb (arrows).

and the atrial rhythm converted to atrial standstill by the end of the intervention. The erythema resolved within 36 hours and the dog was discharged.

Dog 5

A 21-kg, 2-year-old, intact female mixed breed dog was presented for exercise intolerance and an arrhythmia. Physical examination showed regular tachycardia with a heart rate of 184 bpm. A CBC and biochemical profile were unremarkable except for mild hypokalemia (3.5 mmol/L, reference range, 3.6–5.4 mmol/L). Thoracic radiography indicated generalized cardiomegaly with moderate left atrial enlargement. A regular, narrow complex tachycardia, suspected to be of supraventricular origin, with a heart rate of 190 bpm was found on ECG. Echocardiography detected mild tricuspid, aortic, and mitral insufficiency, mild left atrial enlargement, and normal left ventricular systolic function. The dog was sedated with buprenorphine^v (0.0075 mg/kg IV) and acepromazine^z (0.05 mg/kg IV). Multiple antiarrhythmic medications were administered in an attempt to convert the arrhythmia, including 2 boluses of diltiazem^r (0.25 mg/kg IV q2min), lidocaine^{aa} (2 mg/kg IV), and 3 boluses of propafenone^{bb} (1 mg/kg IV q1min). Normal sinus rhythm was achieved with propafenone for 15 minutes before reverting back to the arrhythmia. Forty minutes after propafenone, the dog was given 3 boluses of amiodarone^v (1 mg/kg IV q2min) with no effect on the cardiac rhythm. Five minutes after the last dose, the dog's pinnae, shoulders, inguinal region, and vulva developed severe erythema. Vulvar edema was also noted. The dog was given prednisolone^x (1 mg/kg IV), and 30 minutes later the erythema and swelling started to resolve. The dog was discharged on propafenone (1 mg/kg PO q8h).

Discussion

Amiodarone is a benzofuran-derivative Vaughan Williams class III antiarrhythmic agent with ancillary electrophysiologic characteristics. Amiodarone leads to prolongation of action potential duration, delayed repolarization, and increased effective refractory period in supraventricular and ventricular tissues, particularly the sinus node, atrioventricular (AV) node, and His-Purkinje system. Amiodarone slows intraventricular conduction by blocking sodium channels, and impedes AV nodal conduction by blocking β -adrenergic receptors and calcium channels.¹ It is used in people for the acute and chronic treatment and prevention of supraventricular and ventricular arrhythmias.^{2,3} It is being used with increasing frequency for similar indications in veterinary medicine.^{4–6}

Intravenous use of amiodarone has been associated with both cardiovascular and noncardiovascular adverse effects in people including hypotension, bradycardia, AV block, hepatocellular injury, proarrhythmia, hyper and hypothyroidism, pulmonary toxicity, acute respiratory distress, pulmonary fibrosis, and optic neuropathies.^{3,7} Adverse effects of chronic, oral administration in dogs

have been reported and include bradycardia, thyroid dysfunction, ocular abnormalities, neutropenia, anemia, gastrointestinal upset, and hepatopathies.^{6,8,9} Few reports document adverse effects of IV administration of amiodarone in veterinary medicine.⁵

This report documents acute adverse reactions to IV administration of commercially available amiodarone. All dogs acutely developed severe skin reactions. Three dogs had pruritus and subcutaneous edema. Two dogs showed agitation and pawing at the face. One dog developed tachypnea and tachycardia, and another dog an injection site reaction. Similar signs were described previously in 2 dogs treated with amiodarone IV for cardioversion of postoperative atrial fibrillation.⁵ These adverse signs resolved with discontinuation of amiodarone and corticosteroid administration. In our study, 1 dog also developed severe, life-threatening hypotension that occurred only a few minutes after initiation of amiodarone administration and required immediate intensive care.

Amiodarone intrinsically has negative inotropic and chronotropic effects and can lower blood pressure due to its β - and calcium channel blocking properties. However, in a structurally normal canine heart, the hypotensive effects are minimal.^{10,11} The degree of hypotension seen in Dog 1 was greater than can be attributed solely to the pharmacologic properties of amiodarone given the dog's unremarkable echocardiographic findings.

In people, hypotension requiring intervention is the most common adverse effect of IV amiodarone, observed in approximately 20% of patients in controlled clinical trials.^{12–14} The hypotensive crisis after IV amiodarone is thought to be caused by solvents added to the liquid drug formulation. The commercially available formulation of amiodarone^{cc} and its generic preparations contain polysorbate 80 and benzyl alcohol to keep poorly water soluble amiodarone HCl in solution. In studies of dogs^{15–20} comparing the cardiovascular effects of IV amiodarone with polysorbate 80, amiodarone without polysorbate 80, and polysorbate 80 alone caused direct myocardial depression, vasodilatation, and severe hypotension. Only mild cardiac depression without hypotension occurred with amiodarone alone.^{15–20} These studies concluded that polysorbate 80 given IV had a marked cardiodepressive effect causing hemodynamic compromise. Only 1 dog in our study had severe hypotension, but blood pressure was not measured in any of the other dogs. The other dogs also may have experienced some degree of hypotension that was not detected.

Polysorbate 80 has been shown to cause anaphylactic reactions in people and histamine release in dogs.^{21–23} In 1 study,²² IV administration of a medication containing polysorbate 80 led to a severe anaphylactic response. Based upon skin prick and basophil activation tests, IgE immunoblotting, and direct and indirect IgE-specific ELISA it was documented that only the solvent induced the adverse reaction. The authors²² also concluded that the adverse effects probably were caused by nonimmunologic anaphylactic mechanisms associated with basophil degranulation and release of proinflammatory mediators causing a non-IgE-mediated type of hyper-

sensitivity.²² A study in healthy experimental dogs²³ evaluating the systemic effects of polysorbate 80 reported severe systemic hypotension within 10 minutes of IV administration. Increased blood histamine concentrations, pruritus, erythema, tachycardia, and bronchospasm occurred and were positively correlated with circulating histamine concentrations. Premedication with H1 and H2 blockers attenuated the reactions without altering histamine release. Polysorbate 80 added ex vivo to purified mast cells of rats also induced histamine release.²³ The latter studies confirmed polysorbate 80's adverse effects on arterial blood pressure and skin in dogs. The IV formulations administered in this study all contained the solvents polysorbate 80 and benzyl alcohol and all dogs developed skin reactions with IV amiodarone. These abnormalities may have been induced, at least in part, by the solvent. The latter conclusion is supported by studies evaluating the IV use of a formulation of amiodarone not containing polysorbate 80, which failed to document vasodilatation or adverse skin reactions.^{10,11}

The adverse reactions described in this case series may not have been solely due to the solvent polysorbate 80. All dogs reported, received multiple medications before administration of amiodarone. Amiodarone used in combination with other antiarrhythmics such as digoxin and procainamide may increase blood concentrations and potentiate the effects of concurrent medications.² However, to the authors' knowledge, there are no reports specifically focusing on drug interactions of amiodarone in dogs with cardiac disease. The only medication common in all of these dogs was amiodarone, adverse effects did not develop until amiodarone was administered, and with 1 exception clinical signs developed immediately after amiodarone was given. The fact that a wide dose range of amiodarone was used in the dogs suggests that the adverse effects observed were not dose dependent.

In people, the rate of amiodarone administration influences systemic blood pressure, and therefore it is administered no faster than 15 mg/min/patient IV. Administration of amiodarone in our dogs may have been too rapid, contributing to the adverse effects. However, with 1 exception, amiodarone administration was below the recommended rate used in people, and the adverse effects also occurred after the rate was decreased.

A new aqueous formulation of amiodarone^{dd} for IV use recently has been developed (currently in Phase III human clinical trials) and does not contain polysorbate 80. This formulation has been shown in animals and people to lack hypotensive adverse effects and has not caused any adverse skin effects.^{17,18,20,24} It has electrophysiological properties comparable with Cordarone IV^{cc} and is as efficacious for the treatment of ventricular arrhythmias as lidocaine in people and experimental dogs.^{24,25} It may become a safe alternative to the currently available formulations of amiodarone.

The 5 dogs described here developed acute adverse reactions to IV amiodarone including pruritus, erythema, subcutaneous edema, hives, agitation, tachypnea, and hypotension. These effects may be related to the solvent polysorbate 80 found in the different drug formulations used. Therefore, such formulations should be used with

caution in veterinary practice with close monitoring of blood pressure and observation for development of skin reactions. An aqueous formulation lacking polysorbate 80 but displaying similar clinical efficacy currently is undergoing clinical trials and may soon become commercially available.

Footnotes

- ^a Sotalol, Par Pharmaceutical Inc, Spring Valley, NY
 - ^b Lidocaine, Butler Animal Health, Dublin, OH
 - ^c Dofetilide, Pfizer, New York, NY
 - ^d Acepromazine, Vedco Inc, St Joseph, MO
 - ^e Butorphanol, Fort Dodge Animal Health, Fort Dodge, IA
 - ^f Amiodarone HCL, Bedford Laboratories, Bedford, OH
 - ^g Plasmalyte 148, Baxter Health Corporation, Deerfield, IL
 - ^h Hetastarch, Abbot Pharmaceuticals, Abbot Park, IL
 - ⁱ Diphenhydramine, Baxter Healthcare Corporation
 - ^j Dexamethasone SP, Vedco Inc
 - ^k Mexiletine, Teva Pharmaceuticals, Sellersville, PA
 - ^l Salix, Intervet Inc, Millsboro, DE
 - ^m Procainamide, Hospira Inc, Lake Forest, IL
 - ⁿ Dimazon, Intervet, Unterschleissheim, Germany
 - ^o Vetmedin, Boehringer Ingelheim, Ingelheim, Germany
 - ^p Fortekor, Novartis, Pharma AG, München, Germany
 - ^q Isoptin, Abbott, Wiesbaden, Germany
 - ^r Dilzem, Gödecke, Karlsruhe, Germany
 - ^s Lanitop, Roche Pharmaceuticals, Mannheim, Germany
 - ^t Rekawan, Riemser Serum AG, Greifswald-Insel Riems, Germany
 - ^u Magnesium Verla, Verla-Pharm, Tutzing, Germany
 - ^v Cordarex, Sanofi Aventis, Gentilly, France
 - ^w Mexitil, Boehringer Ingelheim
 - ^x Solu-Decortin, Merck, Darmstadt, Germany
 - ^y Temgesic, Essex Pharma, Muenchen, Germany
 - ^z Vetranquil, CEVA, Tiergesundheits Düsseldorf, Germany
 - ^{aa} Xylocain 2%, Astra Zeneca, Wedel, Germany
 - ^{bb} Rytmonorm, Abbot
 - ^{cc} Cordarone IV, Wyeth Pharmaceuticals, Philadelphia, PA
 - ^{dd} Amio-Aqueous, Academic Pharmaceuticals, Lake Bluff, IL
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