Journal of Veterinary Cardiology (2016) **18**, 10—14

Journal of Veterinary Cardiology
ESVC

www.elsevier.com/locate/jvc

Retrospective evaluation of intravenous premixed amiodarone use and adverse effects in dogs (17 cases: 2011—2014)

Nyssa A. Levy, DVM , Amy M. Koenigshof, DVM*, Robert A. Sanders, DVM

Michigan State University College of Veterinary Medicine, 736 Wilson Road, East Lansing, MI 48824, USA

Received 6 July 2015; received in revised form 11 September 2015; accepted 21 October 2015

KEYWORDS
Nexterone;
Arrhythmias;
Canine

Abstract *Objective:* The goal of this study was to evaluate the number and frequency of adverse effects in a population of clinical canine patients receiving Nexterone.
Animals: Seventeen canine patients receiving Nexterone (five of which were treated during cardiopulmonary arrest).
Methods: An electronic records search for canine patients receiving intravenous Nexterone at the Michigan State University Veterinary Teaching Hospital was performed and retrospectively evaluated for patient demographic information, pre- and post-treatment values for heart rate, blood pressure and rhythm diagnosis, as well as any documented adverse effects (hypotension, anaphylaxis, vomiting, phlebitis, and death). Data including the underlying cardiac or systemic disease, concurrent medications, as well as the final clinical diagnosis and treatment outcome were also recorded.
Results: No adverse effects were noted in this population of clinical canine patients receiving Nexterone. The median pre-treatment heart rate and blood pressure values were 160 bpm (range 120—300 bpm) and 105 mmHg (range 60—170 mmHg), respectively. After treatment, the median heart rate was significantly lower (120 bpm; range 68—172 bpm). The median blood pressure similar to the pre-treatment blood pressure (115 mmHg; range 100—150 mmHg).
Conclusion: In this study of 17 dogs receiving the premixed formulation of injectable Nexterone, no dogs were found to have acute adverse side effects. Nexterone appears to be a safe drug choice for in-hospital treatment of canine arrhythmias.

* Corresponding author.
E-mail address: koenig27@cvm.msu.edu (A.M. Koenigshof).

http://dx.doi.org/10.1016/j.jvc.2015.10.009
1760-2734/© 2015 Elsevier B.V. All rights reserved.

Further studies are needed to assess the efficacy and long-term effects of this medication and the ideal dosing protocol for various arrhythmias.
© 2015 Elsevier B.V. All rights reserved.

Introduction

Ventricular arrhythmias are potentially fatal and require fast-acting and safe therapies. Many different anti-arrhythmic medications exist, and are traditionally categorized into four main Vaughan-Williams classes depending on their primary mechanism of action. Amiodarone is classified as a Class III anti-arrhythmic drug, although it possesses characteristics of all four classes, with effects on blocking sodium, potassium and calcium channels, slowing conduction and prolonging the refractory period.[1,2] Amiodarone was first discovered in 1962, and gained initial Food and Drug Administration approval in 1985 for use as an antianginal and anti-arrhythmic drug.[3] However, severe side effects of the early formulations prevented the use of amiodarone from becoming widespread.

The initial formulation of injectable amiodarone was prepared in solution with polysorbate 80 (Tween 80) and benzyl alcohol, and required further dilution in 5% dextrose prior to intravenous administration.[4] These chemicals have been implicated in the development of adverse effects including hypotension and negative inotropy.[4] Severe adverse effects have been documented in human and canine patients receiving this formulation of amiodarone, including life-threatening hypotension, anaphylaxis, bradycardia and other arrhythmias (Torsades de pointes, asystole), acute hepatic necrosis and death, in addition to cutaneous drug reactions and injection site reactions.[2,3,5,6] Hypotension is the most common adverse reaction encountered in humans, with a reported frequency of 20% in patients receiving the formulation of amiodarone with polysorbate 80 and benzyl alcohol carrier solvents.[7–9] The incidence of hypotension has been attributed to the carrier, and is also reported to be related to the rate of infusion rather than to the total dose.[10]

Signs of anaphylaxis and acute allergic reactions have been reported in dogs receiving the formulation of injectable amiodarone with polysorbate 80 and benzyl alcohol carrier solvents.[2,5,6] In a 2012 study of 28 dogs receiving either oral or injectable amiodarone between 2003 and 2010, five received this intravenous formulation, two of which developed urticaria and facial angioedema, and one dog who developed erythema and pruritus.[5] These signs resolved in all dogs following both steroid and antihistamine therapy, in addition to discontinuation of injectable amiodarone and the initiation of oral treatment instead.[5] In another report of adverse effects in two canine patients, both dogs had successful conversion of atrial fibrillation, but experienced hypotension, phlebitis, and signs of hypersensitivity including hyperemia, pruritus and exhibition of agitated behavior.[6]

In 2008, a new formulation of amiodarone was approved by the Food and Drug Administration, and a premixed solution under the brand name Nexterone (Baxter Healthcare) became available for use in 2010. Nexterone is labeled for the treatment of ventricular fibrillation and ventricular tachycardia in human medicine, and is also of use in the conversion of atrial arrhythmias such as atrial fibrillation[a]. This formulation does not include the polysorbate or benzyl alcohol carriers, and has been shown to have less negative side effects and still be efficacious in treatment of ventricular tachycardia in people and rats.[4] Additionally, Nexterone has been shown to have no adverse hemodynamic effects or other acute adverse clinical signs such as hypersensitivity reactions when administered to healthy research dogs during preclinical trials.[11,12] Adverse effects of this new formulation are uncommon in humans, but reports include hypotension, and proarrhythmic effects leading to bradycardia, atrioventricular block, ventricular tachycardia, and asystole.[10] These adverse effects are most commonly treated by slowing the drug infusion.[10] Reactions which necessitated discontinuation of therapy have been reported in less than 2% of clinical human patients and include reports of severe hypotension, cardiogenic shock, asystole, cardiac arrest, and continued or worsening ventricular tachycardia.[10]

To date, there are no published data regarding the frequency of adverse effects of Nexterone administered to clinical canine patients. The primary goal of this study was to evaluate the number

[a] Nexterone (Baxter Healthcare; Deerfield, IL) Injection Insert FDA Reference ID: 3056994. 2011:1–16.

and frequency of adverse effects in a population of clinical canine patients receiving Nexterone.

Animals, materials and methods

An electronic records search for canine patients receiving intravenous amiodarone at the Michigan State University Veterinary Teaching Hospital was performed. Patients receiving amiodarone prior to 2011 (the first year this hospital carried Nexterone), patients receiving amiodarone other than the brand name Nexterone, or patients without a complete medical record were excluded. Records were retrospectively evaluated for: patient demographic information, pre- and post-treatment values for heart rate, blood pressure and rhythm diagnosis, as well as any documented adverse effects (hypotension, anaphylaxis, vomiting, phlebitis, and death). Data including the underlying cardiac or systemic disease, concurrent medications including anti-arrhythmic drugs administered before and after Nexterone treatment, as well as the final clinical diagnosis and treatment outcome were also recorded.

Owing to small sample size, non-parametric statistical analysis was used. Descriptive data are presented as median (range). A Wilcoxon signed-rank test was used to compare heart rate and blood pressure before and after Nexterone administration.

Results

Seventeen cases were identified that received Nexterone between 2011 and 2014. Fourteen dog breeds were represented, with three Golden Retrievers, two English bulldogs, and one each of Boxer, Beagle, Labrador Retriever, English Foxhound, Bichon Frise, Doberman Pinscher, Shar Pei, American Pit Bull Terrier, Wirehaired Pointing Griffon, Bullmastiff, St. Bernard and mixed breed dog. The median patient age was 7 years (2—14 years), and the median weight was 30 kg (7—65 kg). In this patient population, there were eight castrated males, four intact males, and five spayed females.

Patients were presented to the Emergency/Critical Care or Cardiology services with a variety of chief complaints. The most common were lethargy (6 of 17 cases) and/or a known arrhythmia (3 of 17 cases). Anorexia, motor vehicle trauma, syncope and lateral recumbency were the reasons for visit in 2 of 17 cases each, and only single cases presenting with the chief complaints of congestive heart failure, anemia, gastric dilatation/volvulus, gunshot wound, suspected cardiac tumor, abdominal distension, vomiting, as well as one case that was presented in cardiopulmonary arrest (CPA).

Less than half (7 of 17) of the patients had known underlying primary cardiac disease, including those with final clinical diagnoses of dilated cardiomyopathy in two cases, supraventricular tachyarrhythmia in two cases, and one case each of right atrial enlargement, pericardial effusion, arrhythmogenic right ventricular cardiomyopathy, and a presumed chemodectoma. Of the 10 cases with non-cardiac underlying disease, four had abdominal disease (gastric dilatation-volvulus [GDV] and mesenteric volvulus, splenic mass, splenic infarct, septic peritonitis), two had blunt trauma, and two were anemic. One case was hypothyroid and one case had chronic kidney disease and protein-losing nephropathy. Of the 17 cases, five patients were treated during CPA.

The five dogs receiving Nexterone during CPA were all treated with Nexterone during ventricular fibrillation and were unable to be resuscitated. Owing to the lack of data and inability to evaluate for adverse effects in these five dogs, they were not included in the overall statistical analysis. In the other 12 dogs receiving Nexterone in this study, nine of them survived to discharge, with the other three being euthanized because of the actual or perceived poor prognosis of the underlying disease process, determined to be acute renal failure, acute respiratory distress syndrome and splenic vein thrombosis in those patients.

In the patients receiving Nexterone for an arrhythmia unrelated to cardiac arrest, the most frequently encountered rhythm diagnosis was ventricular tachycardia (9 of 12), followed by supraventricular tachycardia (2 of 12) and atrial flutter (1 of 12). Successful conversion to sinus rhythm was achieved in 9 of 12 of these cases (seven with ventricular tachycardia, one with supraventricular tachycardia and one with atrial flutter). Overall, 9 of 12 (75%) of the non-arrest cases survived to discharge. Three patients were transitioned to oral amiodarone for continued out-of-hospital treatment.

The most commonly used dosing protocol in our hospital, which was administered in 10 of 12 of the non-arrest cases, was a 2 mg/kg intravenous bolus administered over 10 min, followed by a continuous rate infusion of 0.8 mg/kg/hr for 6 h, which was then decreased to 0.4 mg/kg/hr for 18 h (median 9 h, range 0—29 h). In the cases of CPA,

and in two non-arrest cases, dogs received bolus doses from 3 mg/kg up to 12 mg/kg, and a range of continuous rate infusion doses from 0.05 to 18 mg/kg/hr. A central venous catheter was used for Nexterone administration in only 3 of 17 cases; all others received all medications through a peripheral intravenous catheter.

In all cases, previous anti-arrhythmic therapy had failed prior to the start of Nexterone treatment. Most frequently, non-arrest patients were treated with one or more drugs including lidocaine (11 of 12) and procainamide (3 of 12). Other anti-arrhythmic drugs used were diltiazem (2 of 12), and sotalol (2 of 12). Epinephrine and atropine were administered in four of five of the CPA cases. Following Nexterone administration, 10 of 12 of the non-arrest patients were treated with additional anti-arrhythmics including sotalol (5 of 12), lidocaine (3 of 12), or procainamide (1 of 12), magnesium sulfate (1 of 12). Concurrent cardiac medications were administered in 5 of 12 cases, including furosemide (2 of 5), pimobendan (2 of 5), enalapril (2 of 5), sildenafil (1 of 5) and dobutamine (1 of 5).

Patient medical records were inspected for any documentation of adverse events, specifically hypotension, anaphylaxis, vomiting, phlebitis and death. Blood pressure measurements taken prior to and after the initiation of Nexterone treatment as well as heart rate before and after treatment were evaluated for the patients who received Nexterone in the non-arrest situation. Pre- and post-heart rate measurements were available for all 12 dogs and pre- and post-blood pressure measurements were available for 10 of 12 dogs. The median pre-treatment heart rate was 160 bpm (range 120—300 bpm), which was significantly higher ($p = 0.005$) than the post-treatment heart rate (median 120, range 68—172). There was no significant difference ($p = 0.23$) between blood pressure pre- and post-Nexterone administration (median pre 105 mmHg [range 60—170 mmHg], median post 115 [range 100—150]). No patients receiving Nexterone in the non-arrest situation developed hypotension following Nexterone administration.

Records were evaluated for a description of or treatment for signs of anaphylaxis including cutaneous signs of redness, itching, urticaria and facial angioedema, and gastrointestinal signs of vomiting and diarrhea. Records were also evaluated for any description of phlebitis including visual intravenous catheter inspection, or recorded pain on injection. No adverse events were noted during or after Nexterone administration in any of our study population.

Discussion

The results of this study show that Nexterone is a safe injectable drug to be used in dogs, as no evidence of adverse effects during or immediately after Nexterone administration was found.

A variety of dosing schemes was used in the patient population reported here, with ranges from 0.05 mg/kg to 18 mg/kg. The most common prescription was based on the human dose recommendations and adjusted to a weight-based dose, assuming an average human patient size of 75 kg. The manufacturer's recommendation for human dosing is as follows: a rapid loading infusion of 150 mg over 10 min, followed by a slow infusion of 360 mg over 6 h, and then 540 mg over the remaining 18 h.[a] Based on this, dogs commonly received an initial bolus dose of 2 mg/kg over 10 min, followed by a slow infusion of 0.8 mg/kg/hr for 6 h, followed by 0.4 mg/kg/hr for the remainder. Unfortunately, the dose administered was not recorded in all instances of CPA and resuscitation, and in the three cases with data available, they received bolus doses ranging from 3 to 13 mg/kg during resuscitation.

This study was limited by its retrospective nature. It is possible that subtle side effects such as erythema and/or pruritus could have been present but either not witnessed or not recorded. However, given the lack of objective data to support severe hypotension or worsening arrhythmias, we believe our reported instance of zero adverse events to be accurate. Median blood pressure readings were in fact higher after treatment with amiodarone, and median heart rates were similar. The lack of recorded data in the CPA cases also presented a challenge. Amiodarone was chosen as a first-line drug in only one case, which was a traumatic pneumothorax which developed ventricular fibrillation and arrested during the initial triage examination. None of the CPA cases were successfully resuscitated; however the direct effect of amiodarone in these cases could not be determined. We did not assess the development of long-term or chronic effects of oral amiodarone administration, as that was not the purpose of this study.

Conclusions

In this study, no dogs receiving the premixed formulation of injectable Nexterone were found to have acute adverse side effects. For this reason, Nexterone appears to be a safe drug choice when administered as a 2 mg/kg bolus dose over

10 min followed by an initial CRI dose of 0.8 mg/kg/hr for 6 h, and 0.5 mg/kg/hr thereafter. Further studies are needed to assess the efficacy and long-term effects of this medication as well as the ideal dosing protocol for various arrhythmias.

Conflict of interest statement

The authors do not have any conflict of interest to disclose.

References

1. Desai AD, Chun S, Sung RJ. The role of intravenous amiodarone in the management of cardiac arrhythmias. Ann Intern Med 1997;127:294—303.
2. Cober RE, Schober KE, Hildebrandt N, Sikorska E, Riesen SC. Adverse effects of intravenous amiodarone in 5 dogs. J Vet Intern Med 2009;23:657—661.
3. Mizzi A, Tran T, Mangar D, Camporesi EM. Amiodarone supplants lidocaine in ACLS and CPR protocols. Anesthesiol Clin 2011;29:535—545.
4. Somberg JC, Bailin SJ, Haffajee CI, Paladino WP, Kerin NZ, Bridges D, Timar S, Molnar J. Intravenous amiodarone (in a new aqueous formulation) for incessant ventricular tachycardia. Am J Cardiol 2002;9149:853—859.
5. Pedro B, López-Alvarez J, Fonfara S, Stephenson H, Dukes-McEwan J. Retrospective evaluation of the use of amiodarone in dogs with arrhythmias (from 2003 to 2010). J Small Anim Pract 2012;53:19—26.
6. Oyama MA, Prosek R. Acute conversion of atrial fibrillation in two dogs by intravenous amiodarone administration. J Vet Intern Med 2006;20:1224—1227.
7. Levine JH, Massumi A, Scheinman MM, Winkle RA, Platia EV, Chilson DA, Gomes A, Woosley RL. Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias. J Am Coll Cardiol 1996;27:67—75.
8. Scheinman MM, Levine JH, Cannom DS, Friehling T, Kopelman HA, Chilson DA, Platia EV, Wilber DJ, Kowey PR. Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. Circulation 1995;92:3264—3272.
9. Kowey PR, Levine JH, Herre JM, Pacifico A, Lindsay BD, Plumb VJ, Janosik DL, Kopelman HA, Scheinman MM. Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. Circulation 1995;92:3255—3263.
10. Somberg JC, Timar S, Bailin SJ, Lakatos F, Haffajee CI, Tarjan J, Paladino WP, Sarosi I, Kerin NZ, Borbola J, Bridges DE, Molnar J. Lack of a hypotensive effect with rapid administration of a new aqueous formulation of intravenous amiodarone. Am J Cardiol 2004;93:576—581.
11. Cushing DJ, Kowey PR, Cooper WD, Massey BW, Gralinski MR, Lipicky RJ. PM101: a cyclodextrin-based intravenous formulation of amiodarone devoid of adverse hemodynamic effects. Eur J Pharmacol 2009;607:167—172.
12. Cushing DJ, Cooper WD, Gralinski MR, Lipicky RJ, Kudenchuk PJ, Kowey PR. Comparison of the cardiac electrophysiology and general toxicology of two formulations of intravenous amiodarone in dogs. Cardiovasc Toxicol 2009;9:126—133.

Available online at www.sciencedirect.com

ScienceDirect