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

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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.

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Further studies are needed to assess the efficacy and long-term effects of this medication and the ideal dosing protocol for various arrhythmias.

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.