RESEARCH PAPER

Effects of orally administered enalapril on blood pressure and hemodynamic response to vasopressors during isoflurane anesthesia in healthy dogs

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Abstract

Objective To examine whether preanesthetic administration of enalapril, compared with placebo, results in a greater decline in blood pressure (BP) or decreased responsiveness of BP to isotonic fluids or vasopressors in healthy dogs during isoflurane anesthesia.

Study design Randomized, experimental, placebo-controlled, blinded, crossover study.

Animals Twelve healthy, female, purpose-bred beagles.

Methods Dogs underwent the following week-long treatment protocols, each preceded by a 1 week washout period: oral placebo twice daily (PLA); oral enalapril, 0.5 mg kg\(^{-1}\) twice daily, with the 15th dose withheld on the day of anesthesia (ENA-W), and oral enalapril, 0.5 mg kg\(^{-1}\) twice daily, with the 15th dose administered 90 minutes prior to anesthetic induction (ENA). On day 8 of each treatment period, dogs were anesthetized in random order utilizing a standard protocol. Following stabilization at an end-tidal isoflurane concentration (F\(_{\text{E}}\)\(_{\text{Iso}}\)) of 1.3%, invasively measured systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressure were continuously recorded via telemetry. Hypotension (SAP < 85 mmHg) was treated with the following sequential interventions: lactated Ringer’s solution (LRS) bolus (10 mL kg\(^{-1}\)); repeated LRS bolus; dopamine (7 µg kg\(^{-1}\) min\(^{-1}\)); and dopamine (10 µg kg\(^{-1}\) min\(^{-1}\)) first without and then with vasopressin (1 mU kg\(^{-1}\) hour\(^{-1}\)).

Results Compared with the PLA but not the ENA-W group, the ENA group had significantly lower average SAP, DAP and MAP at an F\(_{\text{E}}\)\(_{\text{Iso}}\) of 1.3%, spent more minutes in hypotension, and required a greater number of interventions to correct moderate-to-severe mean arterial hypotension.

Conclusions In healthy dogs, enalapril administered 90 minutes prior to isoflurane anesthesia increases the degree of intra-anesthetic hypotension and the number of interventions required to correct moderate-to-severe hypotension.

Clinical relevance Dogs receiving angiotensin-converting enzyme inhibitors on the day of anesthesia may exhibit clinically significant intra-anesthetic hypotension.

Keywords angiotensin-converting enzyme inhibitor, dog, enalapril, intraoperative hypotension, renin–angiotensin–aldosterone system.

Introduction

The renin–angiotensin–aldosterone system (RAAS) plays an important role in regulating body sodium...
and water content, and vascular tone, thereby helping to maintain blood pressure (BP) and venous return during periods of hemodynamic stress, such as those experienced during general anesthesia (Laragh et al. 1972). Angiotensin-converting enzyme inhibitors (ACEi), which block the RAAS by preventing conversion of angiotensin I to angiotensin II, are commonly prescribed in veterinary clinical practice for the treatment of various cardiovascular and renal diseases. By reducing the amount of circulating angiotensin II, ACEi mitigate the potentially harmful chronic vasoconstrictive and volume-retaining effects of this peptide. Because patients receiving an ACEi prior to anesthetic events may be at greater risk for intra-anesthetic hypotension, there is debate about whether these agents should be discontinued in the perioperative period.

In people, intraoperative hypotension (Colson et al. 1999; Bertrand et al. 2001; Comfere et al. 2005; Miceli et al. 2009; Auron et al. 2011) and functional acute kidney injury (Coca et al. 2013) are more common in patients receiving RAAS antagonists on the day of surgery and these individuals may be refractory to standard interventions for hypotension during the anesthetic period (Licker et al. 1996; Brabant et al. 1999a,b; Meerschaert et al. 2002). However, there are currently no consensus guidelines in human medicine that support the continuation or withdrawal of these drugs in the perioperative period. In general, most authors recommend the withdrawal of these medications on the day of anesthesia, but there are conflicting reports regarding the relative risks and benefits. For example, one prospective, randomized trial of human patients undergoing cardiac surgery showed that although those in whom an ACEi was withheld on the morning of anesthesia exhibited significantly greater BP values following induction than did those in whom an ACEi was administered, the former group also experienced significant postoperative hypertension, leading to unease regarding the possible risk for unintended ‘rebound’ hypertension in certain patients (Pigott et al. 1999).

In veterinary patients, little information is available on the effects of preanesthetic administration of RAAS-blocking agents. One prospective study of healthy cats showed greater reductions in post-induction systolic BP among young cats in which enalapril was administered 3 hours prior to induction in comparison with those treated with placebo (Ishikawa et al. 2007). A study in healthy dogs and dogs with mitral insufficiency reported similar findings; however, to date, these data have been presented only in abstract form (Uechi et al. 2007).

The purpose of this experimental, placebo-controlled crossover study was to evaluate the effects of enalapril on BP and BP responses to intravenous (IV) fluid or vasopressors in dogs anesthetized with isoflurane. We hypothesized that healthy dogs receiving enalapril for 7 days prior to isoflurane anesthesia would demonstrate reduced intra-anesthetic BP and less intra-anesthetic responsiveness to IV fluid and pressors compared with dogs administered placebo, and that these effects would be mitigated by the withholding of enalapril on the morning of anesthesia.

**Materials and methods**

**Animals**

Eight intact and four spayed adult, female, purpose-bred beagles were used for this experimental, placebo-controlled, blinded, crossover study. Prior to their inclusion in the study, the dogs’ general health was confirmed by the findings of physical examination, packed cell volume, serum chemistry profile and echocardiography. Dogs were excluded from the study if there was evidence of congenital heart disease, cardiomyopathy, hemodynamically significant valvular heart disease, or pulmonary hypertension on echocardiography. Mitral or aortic valve insufficiency was considered hemodynamically insignificant if the degree of valvular insufficiency was trace or mild, and if all indices of left ventricular and left atrial size and left ventricular systolic function were within normal reference ranges.

All dogs were vaccinated against common viral diseases. Dogs were housed in pairs, had access to water at all times, and were fed a commercially available adult canine ration (Purina Veterinary Diets EN Gastroenteric Canine Dry Formula; Nestlé Purina Petcare Company, PA, USA) once daily. The Institutional Animal Care Committee of the University of Georgia approved all activities.

**Instrumentation**

At least 2 weeks prior to the start of the study, a pressure-sensing telemetry device (Model TA11PA-D70; Data Sciences International, MN, USA) was surgically inserted into the femoral artery of each dog, as previously described (Miller et al. 2000; Coleman et al. 2013). This device was part of a