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Evaluation of the effect of an angiotensin-converting enzyme inhibitor, alacepril, on drug-induced renin—angiotensin—aldosterone system activation in normal dogs

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Abstract *Introduction:* To determine if alacepril, an angiotensin-converting enzyme inhibitor, has a long duration of action for inhibition of drug-induced renin—angiotensin—aldosterone system (RAAS) activation in normal dogs.
Animals: Five healthy laboratory dogs were used in this study.
Materials and Methods: Each dog received amlodipine (0.5 mg/kg, q12h, p.o.) for 14 days, followed by amlodipine (0.5 mg/kg, q12h, p.o.) and alacepril (1.5 mg/kg, q12h, p.o.) for 56 days. Blood pressure (systolic blood pressure [SBP]; mean blood pressure; and diastolic blood pressure), heart rate, and urinary aldosterone-to-creatinine ratio (UAld:Cre), as an indicator of RAAS activation, were measured on days −14, 0 (baseline [BL]), 1, 7, 14, 28, and 56.
Results: SBP decreased by 10% (p=0.08), and UAld:Cre increased significantly (p=0.04) relative to the BL level after administration of amlodipine. SBP increased after 14 days of alacepril administration relative to BL (p=0.97), and statistically significant increase was first observed on day 28 (p=0.02). Heart rate significantly decreased after alacepril administration on days 14, 28, and 56 (p=0.02). UAld:Cre significantly decreased after alacepril administration on days 14 and 28 ($p \leq 0.03$) relative to the BL level but increased on day 56 such that the difference was no longer significant (p=0.32).

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Discussion: These incomplete and temporary pharmacological blockade of RAAS activation by alacepril suggest that aldosterone breakthrough may have occurred.
Conclusions: Alacepril inhibited activation of RAAS in the short term but is not expected to have a long duration of action.

Abbreviations

ACE	angiotensin-converting enzyme
BL	baseline
DBP	diastolic blood pressure
HR	heart rate
MBP	mean blood pressure
RAAS	renin—angiotensin—aldosterone system
SBP	systolic blood pressure
UAld:Cre	urinary aldosterone-to-creatinine ratio

Introduction

Activation of the renin—angiotensin—aldosterone system (RAAS) in the early stage of heart disease is a useful compensatory mechanism and significantly contributes to hemodynamic improvement. However, activation of RAAS causes cardiac and vascular remodeling, which are associated with the progression of cardiac disease [1,2]. Therapies for the treatment of chronic heart failure have been aimed at relieving symptoms and delaying disease progression because heart failure is typically an irreversibly progressive condition.

Myxomatous mitral valve disease commonly occurs in dogs, and angiotensin-converting enzyme (ACE) inhibitors have been regarded as a first-line therapy. The benefits of ACE inhibitors have been demonstrated in multiple clinical trials in dogs with chronic heart disease [3—6]. Alacepril is an ACE inhibitor that can be deacetylated to form desacetylalacepril with sulfhydryls and then converted to captopril in the body after administration. Captopril, an active metabolite, causes vasodilation of arteries and veins by inhibiting ACE. Desacetylalacepril has a vasodilating effect by inhibiting peripheral sympathetic nervous activation after mobilization into the arterial wall [7,8]. In addition, desacetylalacepril and captopril have direct eliminative effects of active oxygen because of the action of sulfhydryls [9]. ACE inhibitors with sulfhydryls (e.g. zofenopril) cause increased vascular endothelial nitric oxide production and decreased oxidant stress [9], which may help to prevent and improve vascular endothelial dysfunction and vascular remodeling. It has been reported that ACE inhibitors (e.g. benazepril and enalapril) have a long-term inhibitory effect on ACE activity [10] and have been shown to improve clinical signs in dogs with chronic heart failure [3,6]. However, the duration of the ACE inhibitory action of alacepril is unknown.

The objective of this study was to determine if alacepril has a long duration of action for inhibition of drug-induced RAAS activation in normal dogs.

Animals, materials, and methods

Dogs

Five clinically healthy beagle dogs bred in our laboratory were used (Table 1). This study was approved by the Animal Experiments Committee of Nippon Veterinary and Life Science University (acceptance no: 25continued-13).

Study protocol

After 1 week of allowing the dogs to acclimate, a telemetry system (PowerLab; ADInstruments, Nagoya, Japan) was implanted in each animal. The dogs were housed in individual metal cages. Fresh drinking water was freely accessible, and the dogs were fed commercial dry food twice a day (at 8:00 AM and 8:00 PM) under a 12:12-hour light/dark cycle (lights on at 8:00 AM; lights off at 8:00 PM).

Table 1 Baseline characteristics of dogs.

No	Age (years)	Body weight (kg)	Sex
1	0.8	9.2	Intact female
2	4.1	11.4	Spayed female
3	4.7	11.5	Spayed female
4	7.0	8.3	Intact female
5	1.2	9.2	Intact female