Journal of Veterinary Cardiology (2018) ■, ■–■

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Journal of Veterinary Cardiology
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Evaluation of the inhibitory effects of telmisartan on drug-induced renin-angiotensin-aldosterone system activation in normal dogs☆

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Received 10 November 2017; received in revised form 20 July 2018; accepted 23 July 2018

KEYWORDS
Canine;
Plasma renin activity;
Aldosterone breakthrough

Abstract *Introduction:* This study examined whether the angiotensin II receptor blocker telmisartan had inhibitory effects on drug-induced renin-angiotensin-aldosterone system (RAAS) activation in normal dogs.
Animals: Five healthy laboratory beagles were used in this study.
Methods: Each dog received amlodipine (0.5 mg/kg, q12h, PO) alone for 14 days. Starting on the next day, animals received both amlodipine and telmisartan (1.0 mg/kg, q24h, PO) for 84 days. Systolic blood pressure, heart rate, plasma biochemical variables (blood urea nitrogen, creatinine, and electrolytes), plasma renin activity, and 24-h urinary aldosterone elimination (U-Aldo) were measured before amlodipine administration; at day 0; and at days 1, 7, 14, 28, 56, and 84 of telmisartan treatment.
Results: Telmisartan was associated with significant decreases in systolic blood pressure on day 56 (p=0.046), whereas heart rate did not significantly change during this treatment (p=0.061). Plasma renin activity was significantly increased on

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https://doi.org/10.1016/j.jvc.2018.07.009

Please cite this article in press as: Konta M, et al., Evaluation of the inhibitory effects of telmisartan on drug-induced renin-angiotensin-aldosterone system activation in normal dogs, Journal of Veterinary Cardiology (2018), https://doi.org/10.1016/j.jvc.2018.07.009

days 1, 7, 28, 56, and 84 during telmisartan administration (all $p=0.04$). No change in median U-Aldo was detected following telmisartan administration ($p=0.241$). When U-Aldo was evaluated in individual animals, two dogs displayed evidence of aldosterone breakthrough.

Conclusions: Telmisartan administration did not suppress RAAS activation. The appearance of aldosterone breakthrough supports the incomplete blockade of RAAS activation.

Abbreviations

ABT	aldosterone breakthrough
ACEI	angiotensin-converting enzyme inhibitor
Ang II	angiotensin II
ARB	angiotensin II receptor blocker
HR	heart rate
MMVD	myxomatous mitral valve disease
MRA	mineralocorticoid receptor antagonist
PRA	plasma renin activity
pre-amlo	before amlodipine administration
RAAS	renin-angiotensin-aldosterone system
SBP	systolic blood pressure
U-Aldo	24-h urinary aldosterone elimination

Introduction

The renin-angiotensin-aldosterone system (RAAS) is one of the compensatory mechanisms activated in response to a decrease in cardiac output, which may occur during heart failure. However, chronic RAAS activation exacerbates heart failure, in part through the effects of excess angiotensin II (Ang II) and aldosterone, resulting in increases in the cardiac preload and afterload and further fibrosis of the myocardium and vascular endothelium [1,2]. Therefore, RAAS suppression therapy using angiotensin-converting enzyme inhibitors (ACEIs) [3,4] and mineralocorticoid receptor antagonists (MRAs) [5,6] is the standard therapy for cardiac diseases, as it improves outcome in dogs with heart failure.

In clinical trials of ACEIs and Ang II receptor blockers (ARBs) in human patients with heart failure, the phenomenon in which the blood aldosterone concentration declines due to RAAS suppression therapy in the early period of therapy but subsequently rebounds with continued treatment, termed aldosterone breakthrough (ABT), has been reported [7]. Although the existence of ABT has been accepted, many unclear points remain, and there is no consensus regarding its definition. In human patients, ABT is defined on the basis of a single blood aldosterone concentration relative to a baseline value (i.e. increases in aldosterone secretion despite RAAS suppression therapy) or a cutoff value (i.e. aldosterone secretion exceeds the mean or upper reference range of a normal population despite RAAS suppression therapy) [7]; on the other hand, the detection of ABT in dog is based on a urinary aldosterone creatinine ratio which has been validated as an estimate of 24-h urinary aldosterone elimination (U-Aldo) [8]. Moreover, in dogs, ABT is defined as either urinary aldosterone:creatinine ratio greater than a baseline number (i.e. individual's value before initiation of therapy for RAAS suppression) or greater than a population-derived cut-off value (1.0 μg/g) [8,9]. It has been suggested that the increase in aldosterone levels due to ABT may attenuate the organ-protective effects of RAAS suppression therapy in human patients [10]. Aldosterone breakthrough has been observed after the administration of ACEIs in dogs with drug-induced RAAS activation and naturally occurring mitral valve disease [8,9,11–13]. However, whether ABT occurs after treatment with ARBs in dogs is unknown.

The ARB telmisartan has been used recently to treat proteinuria in veterinary medicine [14,15]. Telmisartan stimulates Ang II type 2 receptors in addition to its inhibitory effects on Ang II type 1 receptors. The activation of Ang II type 1 receptor by Ang II induces vasoconstriction, cardiac endothelial cell proliferation, and aldosterone secretion. By contrast, Ang II type 2 receptor stimulation by Ang II exhibits vasodilation, inhibition of cell proliferation and hypertrophy, and nitric oxide production. The ARBs act directly on the Ang II receptor rather than preventing Ang II production and so block Ang II independent of the pathway by which it is produced. For this reason, telmisartan can potentially suppress the effects of Ang II more effectively than ACEIs, as Ang II can be produced by non–ACE-dependent mechanisms.

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