Study on occurrence of aldosterone breakthrough in dogs

Summary of Doctoral Thesis

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Chronic renin-angiotensin-aldosterone system (RAAS) activation causes cardiac, vascular and kidney remodeling, which are associated with the progression of cardiac and kidney disease. Therefore, RAAS suppression therapy using angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) is the standard therapy for treating these diseases. However, aldosterone breakthrough (ABT), a phenomenon in which the blood or urinary aldosterone concentration declines due to RAAS suppression therapy in the early period of therapy but subsequently rebounds with long-term therapy, has been reported. ABT has been observed after the administration of ACEI in dogs with drug-induced RAAS activation and naturally occurring myxomatous mitral valve disease. However, whether ABT occurs during RAAS suppression therapy in dogs with chronic kidney disease (CKD) remains unknown. ABT has reportedly been associated with worsening disease in human patients. Therefore, in human patients, a mineralocorticoid receptor antagonist (MRA) has been used in combination with an ACEI or ARB to prevent the adverse effects caused by excess aldosterone, and the effectiveness of the drug has been reported. However, there are few study that investigate the usefulness of MRA in dogs.

Therefore, the objectives of the present study were to (1) determine if alacepril has a long duration of suppressive effects on drug-induced RAAS activation in dogs, (2) investigate whether telmisartan has suppressive effects on drug-induced RAAS activation in dogs, (3) investigate whether MRA has organ-protecting actions on drug-induced RAAS activation in dogs, and (4) investigate whether ABT occurs in dogs with proteinuric kidney disease during telmisartan therapy.

1. Evaluation of the inhibitory effects of alacepril on drug-induced RAAS activation in normal dogs (Chapter 2)

It has been reported that ACEI (e.g., benazepril and enalapril) have inhibitory effect on drug-induced RAAS activation in dogs. However, the duration of the RAAS suppression effect 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.

Five clinically healthy beagle dogs bred in our laboratory were used. Each dog received amlodipine (0.5 mg/kg, q12 h, PO) for 14 days and then alacepril (1.5 mg/kg, q12 h, PO)

administration was initiated along with the continuation of amlodipine (0.5 mg/kg, q12 h, PO). To measure the time course of the RAAS response to amlodipine and alacepril administration, urinary aldosterone-to-creatinine ratio (U-Aldo:C) was measured on days −14, 0 (baseline, BL), 1, 7, 14, 28, and 56.

U-Aldo:C significantly increased after amlodipine administration. In addition, U-Aldo:C significantly decreased after alacepril administration on days 14 and 28 relative to the BL level but increased on day 56 such that the difference in level between day 56 and BL was no longer significant . Concentrations of U-Aldo:C ≥ BL were observed after alacepril administration on day 56 in two dogs.

Based on these data, alacepril temporarily suppressed drug-induced RAAS activation in healthy dogs but its clinical application may be limited by its duration of action. In light of this decrease in RAAS inhibitory activity with time, it is possible that ABT occurred.

2. Evaluation of the inhibitory effects of telmisartan on drug-induced RAAS activation in normal dogs (Chapter 3)

In human patients with chronic heart failure and CKD, ABT has been reported during RAAS suppression therapy ACEI and/or ARB. However, whether ABT occurs after treatment with ARB in dogs is unknown. Therefore, this study investigated whether telmisartan has suppressive effects on drug-induced RAAS activation in dogs.

Five clinically healthy beagle dogs bred in our laboratory were used. Each dog received amlodipine (0.5 mg/kg, q12 h, PO) for 14 days (amlodipine run-in period, designated days −14 to BL), after which telmisartan (1.0 mg/kg, q24 h, PO) was added and treatment was continued for an additional 84 days (designated days 1 to 84). 24-h urinary aldosterone elimination (U-Aldo) was measured on days −14, BL, 1, 7, 14, 28, 56 and 84.

U-Aldo significantly increased after amlodipine administration. No change in median U-Aldo was detected following telmisartan administration. When U-Aldo was evaluated in individual dogs, two animals exhibited evidence of ABT.

Based on these data, Administration of the ARB, telmisartan, did not prevent (or possibly contributed to) a further rise in U-Aldo in 2 of 5 dogs. This suggested that telmisartan dose not fully

suppress drug-induced RAAS activation in dogs. Therefore, it is necessary to consider the existence of ABT during the ARB therapy in dogs.

3. Evaluation of the effects of MRA combined with alacepril on drug-induced RAAS activation in normal dogs (Chapter 4)

In human patients, MRA has been used in combination with an ACEI or ARB to prevent the adverse effects caused by excess aldosterone, and the effectiveness of the drug has been reported. However, there are few study that investigate the usefulness of MRA in dogs. The objective of this study was to investigate whether MRA has organ-protecting actions on drug-induced RAAS activation in dogs.

Five clinically healthy beagle dogs bred in our laboratory were used. A prospective cross-over study was designed. Each dog received amlodipine (0.5 mg/kg, q12 h, PO) for 14 days and then combination therapy using alacepril (1.5 mg/kg, q12 h, PO) and MRA was initiated along with the continuation of amlodipine (0.5 mg/kg, q12 h, PO). The types of MRA, spironolactone (2 mg/kg, at either q24 h or q12 h, PO) or eplerenone (at either 5 mg/kg or 10 mg/kg, q24 h, PO) was administered. To assess the organ-protecting actions of MRA, serum galectin-3 (Gal-3) concentration as a biomarker for tissue fibrosis was measured on days −14, BL, 1, 7, 14, 28, and 56.

Serum Gal-3 concentration significantly decreased after spironolactone administration (days 1 and 28, q24 h group; days 14 and 28, q12 h group) relative to the BL level. On the other hand, serum Gal-3 concentration did not differ significantly versus BL on any evaluation day after the administration of eplerenone.

Based on these data, spironolactone (2 mg/kg, at either q24 h or q12 h, PO) temporarily decreased serum Gal-3 concentration in dogs with drug-induced RAAS activation. Therefore, administration of spironolactone at this dosage could be useful for the organ-protecting actions.

4. ABT during RAAS suppression therapy in dogs with proteinuric kidney disease (Chapter 5)

ABT has reportedly been associated with worsening disease in human patients. On the other hand, whether ABT occurs during RAAS suppression therapy in dogs with CKD remains unknown.

Therefore, this study investigated whether ABT occurs in dogs with proteinuric kidney disease during telmisartan therapy.

The medical records of dogs diagnosed with proteinuric kidney disease were reviewed retrospectively. The diagnostic criterion for proteinuric kidney disease was urine protein-to-creatinine ratio (UPC) ≥ 1.0, when the urine sample had been collected by cystocentesis or using bladder catheters. In this study, ABT was defined as U-Aldo:C > 1.0 μg/g at after telmisartan administration.

In total, 10 dogs were included in this study. In 7/10 dogs (70%), U-Aldo:C was > 1.0 μg/g at after telmisartan administration.

Based on these data, ABT occurred in dogs with proteinuric kidney disease during RAAS suppression therapy.

In conclusion, this study confirmed that ACEI or ARB dose not fully suppress drug-induced RAAS activation in dogs. Moreover, it becomes clear that ABT is associated with these results. In addition, this study indicated that administration of spironolactone could be useful for the organ-protecting actions in dogs with drug-induced RAAS activation. Finally, the present study revealed that ABT occurred in dogs with proteinuric kidney disease during RAAS suppression therapy. Therefore, further prospective studies are warranted to evaluate whether ABT influences the clinical outcomes in dogs with chronic heart failure and CKD.