Case Report
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Telmisartan Treatment of Refractory Proteinuria in a Dog

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A 6-year-old female spayed Beagle with a 19-month history of refractory proteinuria was presented for examination. Previous urine protein-to-creatinine ratio (UPC) measurements had revealed progressive proteinuria, with values ranging from 0.6 at initial evaluation to 5.16 at highest (reference interval, <0.2), despite medical intervention with increasing doses of benazepril HCl[a] (0.6–1.02 mg/kg PO q12h) and control of systemic hypertension. The only clinicopathologic abnormalities identified on a total of 6 automated complete blood counts[b] (CBC) and 12 serum chemistry analyses[c] were persistent hypercholesterolemia (295–491 mg/dL; reference interval, 119–254 mg/dL) and intermittent hypophosphatemia, the latter noted on 6 occasions (1.2–2.8 mg/dL; reference interval, 2.9–5.1 mg/dL). The dog was not azotemic during this time. Urine samples, collected via cystocentesis, were repeatedly positive for the presence of protein on dipstick[d] analysis, with urine specific gravities (USG) of 1.010–1.048 (laboratory reported reference interval, 1.030–1.050) and inactive sediments. Four aerobic bacterial cultures were performed at various time points, with no bacterial growth documented. The dog had an inactive urine sediment and negative bacterial urine culture 1 month before the current evaluation. Serum antibody titers[e] and PCR analysis[f] were negative for tick-borne/rickettsial diseases. In addition, multiple radiographic and abdominal ultrasonographic examinations failed to identify upper or lower urinary tract abnormalities. Clinical systemic arterial hypertension was documented with retinal lesions and indirect methods on repeated examinations before the development of proteinuria, with systolic values of 200–290 mmHg identified. Normotension was initially achieved using amlodipine[g] (0.15 mg/kg PO q12h), and the dog was noted to be normotensive (systolic blood pressure, 120 mmHg) at the time proteinuria was first observed. The proteinuria persisted despite maintenance of normotension, including 14 months while the dog was given a combination treatment of benazepril (0.6 mg/kg q12h) and amlodipine (0.15 mg/kg q12h). Concurrent medical conditions included atypical hypoadrenocorticism, nonspecific hepatopathy, atopy, and endoscopically confirmed chronic gastritis.

Abbreviations:

ACEi	angiotensin-converting enzyme inhibitor
Ang	angiotensin
ARB	angiotensin II subtype 1 receptor blocker
BP	blood pressure
CKD	chronic kidney disease
GFR	glomerular filtration rate
RAAS	renin-angiotensin-aldosterone system
UPC	urine protein-to-creatinine ratio
USG	urine specific gravity

At the time of the present evaluation, the dog was being treated with benazepril (1.02 mg/kg PO q12h, increased from 0.76 mg/kg q12h 1 month earlier), omega-3 fatty acids[h] (66 mg/kg PO q12h, started 12 months earlier), and a moderately protein-restricted and omega-3 fatty acid supplemented diet[i] (started 2 months earlier), as well as amlodipine (0.33 mg/kg AM and 0.22 mg/kg PM, doses she had been receiving for 8 months), dexamethasone[j] (0.025 mg/kg PO every 48 hours), ursodiol (15 mg/kg PO q24h), diphenhydramine (1 mg/kg PO q12h), omeprazole (1 mg/kg PO q24h as needed), and sucralfate (500 mg as needed).

On presentation, abnormalities were not detected on physical examination of the dog, except for a body condition score of 5 of 9. Indirect systolic blood pressure was 150 mmHg. Repeat CBC, serum chemistry analysis, and urinalysis revealed continued mild hypophosphatemia (1.6 mg/dL), hypercholesterolemia (428 mg/dL), and persistent urine dipstick proteinuria (4+) with a USG of 1.023. The hypophosphatemia appeared secondary to intermittent owner-administered sucralfate for perceived gastritis while the dog was fed a protein-restricted diet; the owner was therefore initially instructed to discontinue sucralfate. The only new finding was mild hyperglycemia (131 mg/dL; reference interval, 66–109 mg/dL), deemed attributable to stress. The UPC was 3.39, a value not considered clinically significantly different[1] from that obtained 1 month prior (4.99). Because of the canine lack of response to antiproteinuric therapies, telmisartan[k] was prescribed at a dosage of 5 mg (0.43 mg/kg) PO once daily for 7 days to assess tolerance of the medication, with instructions to the client to increase to 5 mg (0.43 mg/kg) PO every 12 hours thereafter. In an attempt to reduce the number of medications, the dog received daily, the frequency of benazepril

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administration was arbitrarily reduced to once daily because of lack of historic response and to minimize risk of medication adverse effects. Treatment with all other medications was continued as previously prescribed.

Repeat UPC, performed when the dog had been receiving twice-daily telmisartan for 1 week, was 1.02, reflecting a 70% reduction. Serum chemistry analysis revealed persistent hypophosphatemia (1.6 mg/dL), hypercholesterolemia (386 mg/dL), and hyperglycemia (129 mg/dL). Assessment of thyroid hormone and antibody concentrations[l] did not support hypothyroidism as a contributor to the canine chronic hypercholesterolemia, and while fasted samples were analyzed, an association with the high-fat diet could not be discounted. Skim milk supplementation was added to the regimen to aid in correcting hypophosphatemia and other medications were continued at previously prescribed doses.

Three weeks later, the canine's UPC was 2.49, however no medication adjustments were made. After an additional 5 weeks of treatment, the UPC declined to 0.33 and the systolic blood pressure was 110 mmHg. At that time, the dose of telmisartan was increased to 10 mg (0.79 mg/kg) in the morning and 5 mg (0.38 mg/kg) in the evening in an attempt to completely normalize the canine proteinuria. Because of the telmisartan dose escalation, the dose of benazepril was further reduced to 0.39 mg/kg every 24 hours. One month later, the UPC further declined to 0.14 with the systolic blood pressure at 130 mmHg and benazepril treatment was discontinued. At most recent recheck, 31 weeks after the discontinuation of benazepril and on 10 mg (0.9 mg/kg) of telmisartan once daily, UPC remains reduced (0.33).

Discussion

This report details the successful management of canine nephrotic-range proteinuria using the angiotensin II subtype 1 (AT_1) receptor antagonist, telmisartan. The dog of this report had a maximal reduction in UPC of 50% within 2 months of angiotensin-converting enzyme inhibitor (ACEi) administration; however, even at the time of maximal reduction, the magnitude of proteinuria remained clinically significant (UPC, 1.99). In contrast, UPC reductions of 70% and 95.9% were noted within 2 weeks and 3 months of first administration of telmisartan, respectively, with eventual and persistent reduction in UPC even in the face of ACEi discontinuation and with once daily dosing of the angiotensin receptor blocker (ARB). The borderline proteinuria noted at the canine's last recheck examination could reflect a continued primary renal disease process, however a minor contribution from the subtherapeutic dose of glucocorticoid cannot be ruled out.

Both pre- and postrenal causes of proteinuria were repeatedly excluded in the present case. Remaining potential causative factors include alterations in glomerular hemodynamics, filtration permselectivity, or tubular handling of urine protein as a result of any one of a number of initial renal insults.[2] Because renal biopsy was not performed in the present case, it is not possible to further characterize a potential underlying cause of the canine's proteinuria or definitively determine if additional targeted medications would have been beneficial at resolving the proteinuria. Similarly, it is not clear whether the systemic hypertension identified on initial presentation was a causal factor in the observed proteinuria (a correlation that has been previously described in dogs[3,4]), a result of chronic renal pathology, or a combination of both. Persistence and progression of urinary protein loss despite BP normalization suggests primary underlying renal pathology, although in one study of dogs with naturally occurring renal disease of various etiologies, increased magnitude of proteinuria was only weakly associated with significant reductions in renal excretory function.[3]

Treatment with ACEi decreases proteinuria in naturally occurring models of CKD in dogs.[5,6] However, despite an overall effect of lowering proteinuria within populations, ACEi are not universally successful, with the degree of antiproteinuric effect varying considerably on a patient-to-patient basis. For example, in a veterinary clinical trial designed to evaluate the efficacy of enalapril as a treatment for naturally occurring proteinuria, a clinically significant (ie, 50%) reduction in proteinuria was noted in only 9/14 (64%) of subjects, with 3/14 (22%) experiencing an increase in proteinuria despite treatment with up-titrated doses of enalapril.[5] In the dog of the present report, proteinuria persisted despite BP normalization in response to antihypertensive treatment with the calcium channel blocker, amlodipine, and in the face of treatment with a relatively high dose of benazepril.[7] Lack of complete response could represent continued influence of the RAAS because of incomplete blockade and is consistent with previous studies in which the magnitude of observed reductions in blood pressure and proteinuria after treatment with an ACEi were not proportional.[5,8]

When proteinuria persisted in the dog of this report despite incremental ACEi dose escalation, alternative options were sought to address the possibility of persistent Ang II production despite treatment with an ACEi—the so-called "angiotensin escape"—a phenomenon ascribed primarily to non–ACE-dependent pathways of Ang I-to-Ang II conversion.[9] In this situation, a drug that directly antagonizes Ang II independent of its origin would provide particular theoretical benefit. In the dog of the present report, the ARB telmisartan was chosen for this purpose. The decision to initiate treatment with this particular ARB was based on the finding that the ARB telmisartan is superior to enalapril and losartan in attenuating the blood pressure response to exogenous Ang I administration.[m] When given PO at 1 mg/kg once daily for 1 week to 6 normal dogs, telmisartan was able to completely abolish (ie, affect a 100% reduction of) the systolic pressor response to 100 ng of intravenous Ang I/kg at 90 minutes postdose in all subjects. On the contrary, enalapril (0.5 mg/kg PO twice daily for 1 week)

reduced the pressor response to the same dose of Ang I by only 67 ± 16% (mean ± SD) when the latter was given 90 minutes postenalapril in the same dogs ($P < .05$).

Telmisartan, as all ARBs, selectively antagonizes the AT_1 receptor bypassing intermediary activation steps within the RAAS cascade. Telmisartan administration PO to healthy dogs at 1.0 mg/kg/day significantly increases urine volume and sodium excretion.[10,11] These findings are similar to previous investigations of the prototype ARB, losartan, which was documented to increase renal blood flow, GFR, and sodium excretion while reducing renal vascular resistance without significantly impacting systemic hemodynamics when given IV.[11,12] Physiologically, these outcomes are consistent with the prevention of Ang-induced vasoconstriction of pre- and postglomerular arterioles and inhibition of tubular sodium absorption. Independent of vascular resistance modulation, multiple reports and human-based meta-analyses have documented the antiproteinuric, anti-inflammatory, and renoprotective effects of telmisartan across several disease conditions including HIV infection, essential hypertension, and diabetic nephropathy.[13–15] Telmisartan's BP-independent anti-inflammatory and antioxidant properties are thought to stem from partial agonism of the peroxisome proliferator-activated receptor-gamma, which is involved in carbohydrate and lipid metabolism.[16] While there is a wealth of information describing the clinical benefit of telmisartan in human medicine, little evidence exists to document the clinical benefit of telmisartan in the management of veterinary cardiovascular or proteinuric renal disease.

This report describes the role of telmisartan in the clinical resolution of canine proteinuria following failure of complete response to ACEi treatment. While conclusions are difficult to draw from the response of a single dog, the ability of the dog of the present report to be weaned off additional antiproteinuria therapies and the lack of observed adverse reactions are encouraging. Further prospective clinical trials are needed to fully assess treatment success, determine an appropriate dose range, and identify potential adverse effects before telmisartan can be routinely recommended for the treatment of canine proteinuria.

Footnotes

[a] Benazepril HCl; Amneal Pharmaceuticals Inc, Glasgow, KY
[b] Advia 120 Hematology system; Siemens Healthcare Diagnostics Inc, Deerfield, IL
[c] Modular Analytics P-module; Roche Diagnostics Corporation, Indianapolis, IN
[d] Multistix 10 SG reagent strips; Siemens Medical Solutions USA, Malvern, PA
[e] Tick-borne Diseases Panel; Infectious Diseases Laboratory, University of Georgia, Athens, GA
[f] Canine FastPanel PCR; Antech Diagnostics, Irvine, CA
[g] Amlodipine besylate; Ascend Laboratories LLC, Montvale, NJ
[h] Nature's Bounty Inc, Bohemia, NY
[i] K/D Canine renal health diet; Hill's Pet Nutrition Inc, Topeka, KS
[j] Dexamethasone USP; Roxane Laboratories, Columbus, OH.
[k] Telmisartan; Glenmark Pharmaceuticals Ltd, Mumbai, India
[l] Thyroid Panel 3; Antech Diagnostics, Irvine, CA
[m] Coleman AE, Schmiedt CW, Handsford CG, Reno LR, Garber ED, Brown SA. Attenuation of the pressor response to exogenous angiotensin by angiotensin receptor blockers in normal dogs. Data to be presented at the American College of Veterinary Internal Medicine Forum, Nashville, TN, June 2014

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Conflict of Interest Declaration: The authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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