PRACTICAL PHARMACOLOGY

What's New in the Management of Feline Chronic Kidney Disease

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Chronic kidney disease (CKD) is routinely diagnosed and managed in primary care veterinary practice and is a common cause of mortality in middle-aged and geriatric cats.[1] New serum biomarkers, such as symmetric dimethylarginine (SDMA), may aid in recognizing cats with CKD before traditional indicators of glomerular filtration rate (GFR), such as urea and creatinine, move out of the reference range, but it is important to realize that substantial nephron loss has occurred by the time the SDMA is persistently above the reference range.[2,3] A potentially treatable underlying cause for CKD, such as pyelonephritis, chronic partial obstruction, or exposure to nephrotoxic agents, may be identified. However, the reason for renal compromise is not apparent in more than 80% of cases, and renal histopathology simply indicates chronic interstitial nephritis and tubulointerstitial fibrosis.[4]

Irrespective of the trigger, CKD should be regarded as inevitably progressive, as the extra workload placed on surviving nephrons will shorten their longevity. In the absence of targeted treatments, clinicians must focus on managing patient wellbeing and supporting the functionality of the remaining nephrons. Fortunately, new products specifically designed for cats with CKD (**TABLE 1**) provide practitioners with additional options for these patients and should be incorporated as appropriate into truly holistic treatment plans.

Abstract

Management strategies for cats with chronic kidney disease (CKD) are focused on maintaining patient wellbeing while mitigating ongoing nephron loss. Several feline-specific products have recently been developed to address common causes of clinical compromise, such as hypertension, weight loss, dehydration, and ongoing tubular damage. Novel options for cats with CKD include telmisartan (Semintra), an angiotensin II receptor blocker, for the treatment of feline hypertension; capromorelin (Elura), a ghrelin receptor agonist, for mitigation of weight loss; nutrient-enriched water (Hydra Care) to promote adequate fluid intake; and AST-120 (Porus One), an oral adsorbent, to reduce gastrointestinal uptake of key uremic toxins. These products are useful additions to our toolbox and enable practitioners to more effectively support these vulnerable patients.

Take-Home Points

- Telmisartan (Semintra) is an effective option for the management of cats with systemic hypertension and has also been shown to mitigate proteinuria in cats with CKD.
- Capromorelin (Elura) has been shown to improve food intake and support weight gain in cats with CKD; this drug acts directly on the hypothalamus to trigger food-seeking behaviors and increase growth hormone secretion.
- Hydra Care is a highly palatable nutrient-enriched fluid; cats offered this product showed a clear preference for this compared to water, with an increased total daily fluid intake.
- AST-120 (Porus One) traps indoxyl sulfate and p-cresyl sulfate within the gastrointestinal tract; these uremic toxins are associated with ongoing nephron loss and are thought to contribute to the progression of CKD.

TELMISARTAN ORAL SOLUTION (SEMINTRA)

Approval status: U.S. Food and Drug Administration (FDA) approved (2018)

Manufacturer: Boehringer Ingelheim Animal Health (bi-animalhealth.com)

Mechanism of action: Telmisartan is an angiotensin II receptor blocker, with specificity for the type 1 receptor.[5] Activation of this receptor subtype has numerous deleterious effects on the vasculature, heart, and kidneys, such as vasoconstriction, fibrosis, and the creation of a proinflammatory state. Interestingly, activation of the angiotensin II type 2 receptor results in counterregulatory effects, such as vasodilation and inhibition of fibrosis and inflammation.[6]

Although angiotensin-converting enzyme (ACE) inhibitors, such as enalapril and benazepril, limit the conversion of angiotensin I to angiotensin II, other enzymes (called chymases) are unaffected by these agents.[6] Consequently, circulating concentrations of angiotensin II are often robust, despite complete inhibition of ACE.[6] Therapeutic agents such as telmisartan are designed to mitigate the downstream effects of angiotensin II and therefore provide significant advantages over the traditional ACE inhibitors.[5]

Indication: Semintra is labeled in the United States for the control of systemic hypertension in cats.[7] This drug has not been evaluated in cats with severe hypertension (i.e., systolic arterial blood pressure [SABP] >200 mm Hg), and practitioners should consider prescribing amlodipine in these circumstances.[8]

Administration: The starting dosage is 1.5 mg/kg PO q12h for 14 days, followed by 2 mg/kg PO q24h. The long-term dose may be decreased in 0.5 mg/kg increments if systolic blood pressure falls below 120 mm Hg. Semintra is a liquid formulation and may be given directly into the mouth or mixed with a small amount of food.

Key clinical data: In a placebo-controlled study of cats with hypertension, Semintra reduced SABP by an average of 19.2 mm Hg after 14 days, and more than 50% of treated cats had an SABP <150 mm Hg at

TABLE 1 Select Adjunctive/Supportive Treatments for Cats With Chronic Kidney Disease

TRADE NAME	AGENT NAME	MECHANISM OF ACTION	INDICATION(S)
Semintra (Boehringer Ingelheim)	Telmisartan	Angiotensin II receptor blocker	▪ Moderate hypertension (systolic blood pressure ≤200 mm Hg) ▪ Proteinuria
Elura (Elanco)	Capromorelin	Ghrelin receptor agonist	▪ Documented weight loss ▪ Suboptimal body or muscle condition score
Hydra Care (Purina)	Nutrient-enriched water	Increases total daily fluid intake	▪ Subclinical dehydration ▪ Urolithiasis, cystitis, or constipation
Porus One (Dechra)	AST-120	Oral adsorbent	▪ Renal insufficiency

day 28.[9] Another study described a cohort of cats receiving Semintra for up to 6 months and reported a long-term response rate of >60%.[10]

Most common side effects: Adverse reactions reported in a 5-month effectiveness study included weight loss, vomiting, dehydration, and anemia.[7] It is important to bear in mind that these may reflect underlying/concurrent diseases.

Clinical use: Semintra is an appropriate first choice for mild to moderate hypertension. As the introduction of any vasoactive agent can alter renal blood flow and GFR, it is important to recheck both blood pressure and serum creatinine concentration within 7 to 10 days. An increase in creatinine of more than 20% indicates a significant drop in renal perfusion/filtration and mandates a dose reduction or a switch to an alternative option.[8]

Practitioners should be very cautious when using any angiotensin II receptor blocker with an ACE inhibitor or a nonsteroidal anti-inflammatory drug, as the cumulative decrease in GFR may result in acute kidney injury.[11]

Practitioners should be very cautious when using any angiotensin II receptor blocker with an ACE inhibitor or a nonsteroidal anti-inflammatory drug, as the cumulative decrease in GFR may result in acute kidney injury.[11] In addition to its antihypertensive effects, Semintra has been shown to mitigate proteinuria in cats, and it is licensed in Europe, Canada, and the United Kingdom for this purpose at a dosage of 1 mg/kg PO q24h.[12] Blood pressure should be monitored to check for iatrogenic hypotension.

CAPROMORELIN ORAL SOLUTION (ELURA)

Approval status: FDA approved (2020)

Manufacturer: Elanco Animal Health (elanco.com)

Mechanism of action: Capromorelin is a ghrelin receptor agonist.[13] Ghrelin is often referred to as the hunger hormone, as it is released from the stomach during the interprandial interval and acts on the hypothalamus to trigger powerful food-seeking behaviors. It also supports growth hormone secretion and has prokinetic and anti-inflammatory effects. Drugs such as capromorelin have been shown to increase voluntary food intake and drive weight gain in both dogs and cats.[13,14]

Indication: Elura is labeled for the management of weight loss in cats with CKD. Based on its mechanism of action, it may be used off-label to support food intake in cats with a variety of other conditions.

Administration: The recommended dosage is 2 mg/kg PO q24h. Elura is a liquid formulation (20 mg/mL) and may be given with or without food.[15]

Key clinical data: In a field study of cats with stable CKD and >5% weight loss managed at first-opinion practices, cats in the treatment arm gained an average of >5% body weight in just 56 days; cats in the control group lost an average of 1.6% over the same time period.[16] Many of the cats receiving Elura had measurable improvement in body weight after just 2 weeks of treatment.

Most common side effects: Ptyalism was routinely noted in both efficacy and safety studies, occurring soon after administration.[15] Other side effects include vomiting, lethargy, and behavior change. In a small subset of cats, Elura does appear to cause a transient decrease in heart rate and blood pressure; telemetry studies in healthy cats indicate that these effects wear off after 1 week of daily administration.[17] On the basis of these findings, Elura should not be given to significantly compromised cats, as these effects may be clinically deleterious.

Clinical use: Elura is indicated in any cat with CKD and a suboptimal body or muscle condition score or documented weight loss. It should not be given to cats with evidence of hypersomatotropism (acromegaly) as it will cause changes in growth hormone secretion, and

it should be used with caution in cats with diabetes mellitus and those with insulin-resistant conditions such as iatrogenic hypercortisolism.[15,16] Based on long-term safety studies in healthy cats, Elura may be safely used for prolonged periods without any concerns. Based on its mechanism of action, the author feels it is more appropriate to lower the dose for long-term use rather than decrease the frequency of administration.

NUTRIENT-ENRICHED WATER (HYDRA CARE)

Approval status: Not applicable (over the counter)

Manufacturer: Purina (purina.com)

Mechanism of action: Hydra Care is a poultry-flavored opaque liquid containing amino acids from whey protein, hydrolyzed protein from poultry, and glycerol; sodium and phosphorus content are minimal.[18]

Indication: Hydra Care is designed to address the issue of suboptimal fluid intake in cats with various conditions, including CKD. One of the challenges associated with the management of cats with CKD is maintaining an adequate level of hydration. As CKD progresses and the kidneys' ability to conserve water diminishes, cats are vulnerable to chronic subclinical dehydration.[19] This condition is well recognized in elderly humans with CKD and is associated with depression, decreased mobility, and constipation; in the absence of direct evidence in cats, it is still reasonable to assume the same sequelae.[20]

Administration: Hydra Care is supplied in 85-mL pouches, with a recommended intake of 2 pouches per day.

Key clinical data: In studies in healthy cats, those offered Hydra Care along with a dry food diet consumed on average 50% more liquid each day.[18] It is noteworthy that these cats demonstrated a clear preference for Hydra Care compared with tap water, choosing to take in >90% of their daily free liquid in the form of Hydra Care when given the choice. Food intake was similar for cats in the treatment and control groups.

Most common side effects: None reported

Clinical use: Hydra Care should be recommended in any cat vulnerable to subclinical dehydration or those with conditions in which increased fluid intake is likely to be beneficial, such as urolithiasis, idiopathic cystitis, or constipation.

AST-120 (PORUS ONE)

Approval status: Not applicable (over the counter)

Manufacturer: Dechra Veterinary Products (dechra-us.com)

Mechanism of action: AST-120 is a carbon-based adsorbent. These agents are engineered particles that draw molecules deep within their physical structure using van der Waals forces and are routinely used for the removal of toxins from the blood or gastrointestinal tract.[21] Although renal function is traditionally evaluated using serum urea and creatinine concentrations, dozens of other compounds in the blood are also regarded as uremic toxins and similarly accumulate as GFR decreases.[22,23] Some of these chemicals contribute to patient morbidity and are thought to drive the progression of CKD.[22] AST-120 is given orally and specifically binds indoxyl sulfate and p-cresyl sulfate.[24] These substances are of significant interest in human nephrology as they are not effectively removed by dialysis; instead, they accumulate in renal tubular cells and cause oxidative damage.[25]

Indication: Porus One is indicated in cats with compromised renal function.

Administration: Porus One is given once daily at a dose of 0.5 g; it is tasteless and odorless and should be administered mixed with a small amount of wet food. A box of the product contains 30 single-dose pouches.

Key clinical data: AST-120 was licensed as Kremezin in Japan in 1991 for the management of human patients with CKD and is now widely used for this purpose throughout Asia. It is particularly effective at reducing circulating concentrations of indoxyl sulfate and p-cresyl sulfate in humans. Long-term use of AST-120 in humans with renal compromise is thought to delay the expected decline in renal function and postpone the initiation of hemodialysis.[26] A recent study in cats demonstrated significantly higher levels of indoxyl sulfate and p-cresyl sulfate in patients with CKD, and it is likely that these compounds are similarly deleterious to renal function in this species.[27] Although the effects of Porus One in cats with CKD have not been reported, a study in 12 healthy geriatric

cats demonstrated >60% decrease in serum indoxyl sulfate concentrations after 8 weeks.[28]

Most common side effects: None reported

Clinical use: Porus One should be considered as part of a holistic care plan for any cat with renal compromise. It should not be given within 2 hours of oral medications, as there is concern that concurrent administration may decrease the bioavailability of other therapeutic agents. TVP

References

1. O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Longevity and mortality of cats attending primary care veterinary practices in England. *J Feline Med Surg*. 2015;17(2):125-133. doi:10.1177/1098612X14536176
2. Braff J, Obare E, Yerramilli M, Elliott J. Relationship between serum symmetric dimethylarginine concentration and glomerular filtration rate in cats. *J Vet Intern Med.* 2014;28(6):1699-1701. doi:10.1111/jvim.12446
3. Hall JA, Yerramilli M, Obare E, Jewell DE. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in cats with chronic kidney disease. *J Vet Intern Med*. 2014;28(6):1676-1683. doi:10.1111/jvim.12445
4. Chakrabarti S, Syme HM, Brown CA, Elliott J. Histomorphometry of feline chronic kidney disease and correlation with markers of renal dysfunction. *Vet Pathol*. 2013;50(1):147-155. doi:10.1177/0300985812453176
5. Battershill AJ, Scott LJ. Telmisartan. *Drugs*. 2006;66(1):51-83. doi:10.2165/00003495-200666010-00004
6. Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. *J Vet Intern Med.* 2019;33(2):363-382. doi:10.1111/jvim.15454
7. Semintra. Prescribing information. Boehringer Ingleheim. 2018. Accessed August 20, 2022. https://www.semintra.com/pdf/MERL18201%20SEMINTRA%20US%201-page%20PI%20v1c.pdf
8. Acierno MJ, Brown S, Coleman AE, Jepson RE, Papich M, Stepien RL, Syme HM. ACVIM consensus statement: guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. *J Vet Intern Med*. 2018;32(6):1803-1822. doi:10.1111/jvim.15331
9. Glaus TM, Elliott J, Herberich E, Zimmering T, Albrecht B. Efficacy of long-term oral telmisartan treatment in cats with hypertension: results of a prospective European clinical trial. *J Vet Intern Med*. 2019;33(2):413-422. doi:10.1111/jvim.15394
10. Coleman AE, Brown SA, Traas AM, Bryson L, Zimmering T, Zimmerman A. Safety and efficacy of orally administered telmisartan for the treatment of systemic hypertension in cats: results of a double-blind, placebo-controlled, randomized clinical trial. *J Vet Intern Med*. 2019;33(2):478-488. doi:10.1111/jvim.15429
11. Sparkes AH, Caney S, Chalhoub S, et al. ISFM consensus guidelines on the diagnosis and management of feline chronic kidney disease. *J Feline Med Surg*. 2016;18(3):219-239. doi:10.1177/1098612X16631234
12. Sent U, Gössl R, Elliott J, Syme HM, Zimmering T. Comparison of efficacy of long-term oral treatment with telmisartan and benazepril in cats with chronic kidney disease. *J Vet Intern Med.* 2015;29(6):1479-1487. doi:10.1111/jvim.13639
13. Rhodes L, Zollers B, Wofford JA, Heinen E. Capromorelin: a ghrelin receptor agonist and novel therapy for stimulation of appetite in dogs. *Vet Med Sci*. 2018;4(1):3-16. doi:10.1002/vms3.83
14. Zollers B, Allen J, Kennedy C, Rhodes R. Capromorelin, an orally active ghrelin agonist, caused sustained increases in IGF-1, increased food intake and body weight in cats. Poster presented at: 2015 ACVIM Forum; June 2015; Indianapolis, Indiana.
15. Elura. Prescribing information. Elanco. Revised November 2020. Accessed August 20, 2022. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=be4beb9c-f39b-4b23-9c35-f72a049a3250
16. Wofford JA, Zollers B, Rhodes L, Bell M, Heinen E. Evaluation of the safety of daily administration of capromorelin in cats. *J Vet Pharmacol Ther*. 2018;41(2):324-333. doi:10.1111/jvp.12459
17. Food and Drug Administration. Freedom of information summary: Elura, capromorelin oral solution for cats. October 16, 2020. Accessed July 9, 2022. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/9908
18. Zanghi BM, Gerheart L, Gardner CL. Effects of a nutrient-enriched water on water intake and indices of hydration in healthy domestic cats fed a dry kibble diet. *Am J Vet Res*. 2018;79(7):733-744. doi:10.2460/ajvr.79.7.733
19. Taylor S. Dehydration. In: Harvey A, Tasker S, eds. *BSAVA Manual of Feline Practice: A Foundation Manual*. 1st ed. BSAVA; 2013:214-216.
20. Popkin BM, D'Anci KE, Rosenberg IH. Water, hydration, and health. *Nutr Rev*. 2010;68(8):439-458. doi:10.1111/j.1753-4887.2010.00304.x
21. Sato E, Hosomi K, Sekimoto A, et al. Effects of the oral adsorbent AST-120 on fecal p-cresol and indole levels and on the gut microbiota composition. *Biochem Biophys Res Commun*. 2020;525(3):773-779. doi:10.1016/j.bbrc.2020.02.141
22. Duranton F, Cohen G, De Smet R, et al. Normal and pathologic concentrations of uremic toxins. *J Am Soc Nephrol*. 2012;23(7):1258-1270. doi:10.1681/ASN.2011121175
23. Grams ME, Shafi T, Rhee EP. Metabolomics research in chronic kidney disease. *J Am Soc Nephrol*. 2018;29(6):1588-1590. doi:10.1681/ASN.2018030256
24. Schulman G, Agarwal R, Acharya M, Berl T, Blumenthal S, Kopyt N. A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study of AST-120 (Kremezin) in patients with moderate to severe CKD. *Am J Kidney Dis*. 2006;47(4):565-577. doi:10.1053/j.ajkd.2005.12.036
25. Liu WC, Tomino Y, Lu KC. Impacts of indoxyl sulfate and p-cresol sulfate on chronic kidney disease and mitigating effects of AST-120. *Toxins*. 2018;10(9):367. doi:10.3390/toxins10090367
26. Asai M, Kumakura S, Kikuchi M. Review of the efficacy of AST-120 (KREMEZIN®) on renal function in chronic kidney disease patients. *Ren Fail*. 2019;41(1):47-56. doi:10.1080/0886022X.2018.1561376
27. Summers SC, Quimby JM, Isaiah A, Suchodolski JS, Lunghofer PJ, Gustafson DL. The fecal microbiome and serum concentrations of indoxyl sulfate and p-cresol sulfate in cats with chronic kidney disease. *J Vet Intern Med*. 2019;33(2):662-669. doi:10.1111/jvim.15389
28. Mottet J, Kowollik N. Renaltec attenuates serum levels of indoxyl sulfate in geriatric cats [abstract]. *BSAVA Conf Proc*. 2019:424-425. doi:10.22233/9781910443699.58.2

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Disclosure

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