



Advances in Appetite Stimulants in Pets with Chronic Kidney Disease

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Dysrexia in CKD

Clinical signs of nausea, vomiting and dysrexia are common in patients with chronic kidney disease (CKD). In a recent survey of owners of cats with CKD, 43% of respondents reported abnormal appetite in their cats, necessitating 77% of those owners to coax the pet to eat more than 50% of the time.¹ Adequate caloric support is crucial for chronically ill patients and there is evidence that CKD results in an increased metabolic state, making adequate nutrition even more of a challenge.² In humans CKD protein energy wasting and poor body condition is associated with decreased survival even in patients on dialysis.³ Poor body condition score is also associated with a poorer prognosis in dogs and cats with CKD.^{4,5} In a recent study cats were demonstrated to have lost weight before CKD diagnosis as well as to continue to lose

weight during the disease process.⁵ A recent study assessing quality of life parameters in CKD cats revealed that CKD cats scored significantly lower than healthy young or geriatric cats in the categories of "appetite" and "liking food."⁶ Additionally, poor appetite is perceived as a significant quality of life concern and can cause significant emotional distress to owners.⁷

Uremic toxins are sensed by the chemoreceptor trigger zone of the area postrema in the brain, which subsequently stimulates emesis by the vomiting center. Experimental ablation of the area postrema inhibits uremic vomiting in dogs with total nephrectomy, illustrating the involvement of this structure in the pathophysiology of the disease.⁸ It has long been thought that uremia has effects on the intestinal tract, such as hyperacidity, uremic

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gastritis and ulceration that lead to further unwillingness to eat, but our understanding of the relevance of this pathophysiology to cats and dogs is incomplete. Cats with CKD have been shown to have elevated concentrations of gastrin that increase with the severity of renal failure,⁹ but the relationship between gastrin, gastric acid secretion, and gastric pathology has not been fully described. Gastrin is excreted by the kidneys, and it is hypothesized that as renal function declines, hypergastrinemia develops, resulting in gastric hyperacidity.⁹ However, cats that have gastrin-secreting tumors with levels of hypergastrinemia similar to those found in cats with CKD have significant gastric pathology; but this has not been demonstrated in cats with CKD.^{10,11} In human CKD the development of gastric hyperacidity appears to be inconsistent, and may be related to the presence of *Helicobacter* spp. infection.¹² In a recent study evaluating the type and prevalence of histopathologic lesions in the stomachs of cats with CKD, gastric fibrosis and mineralization were found to be prominent alterations rather than the uremic gastropathy lesions previously described in dogs and humans (uremic gastritis, ulceration, vascular injury, edema).¹¹ Additionally, uremic gastropathy has been reported to be less severe in dogs compared to that described in humans. Gastrointestinal hemorrhage in cats and dogs with CKD may be more attributable to factors such as uremic thrombocytopenia rather than overt ulcerative lesions, which appear to be relatively rare.¹³ Therefore, the administration of gastric protectants such as sucralfate

may not be justified, unless obvious clinical evidence of gastrointestinal hemorrhage such as melena is appreciated.

In addition to buildup of uremic toxins and alterations in the gastrointestinal tract, the basic pathophysiology of appetite regulation may be significantly abnormal in animals with CKD. Appetite regulation is quite complex and involves a multitude of signaling compounds, but a refined summary is that regulation involves orexigenic substances that activate the hunger center (i.e., ghrelin) and anorexigenic substances that activate the satiety center of the brain (i.e., leptin, cholecystokinin, obestatin, des-acyl ghrelin).¹⁴ In humans, CKD is associated with an increased accumulation of anorexigenic substances secondary to decreased glomerular filtration rate without a concomitant increase in orexigenic substances such as ghrelin. Additionally anorexigenic substances have been demonstrated to be significantly higher in CKD patients with poor body condition than those with normal body condition.¹⁴

Appetite Stimulants – Cyproheptadine and Mirtazapine

Once metabolic complications of CKD such as dehydration, hypertension, anemia, hypokalemia, and nausea and vomiting have been addressed, appetite stimulants may be used to encourage food intake, particularly in late-stage patients and in patients in which a feeding tube is not desirable to the owner. Cyproheptadine has been used for some time as an appetite stimulant and has anecdotal efficacy in many patients; however, its efficacy has never been scientifically

evaluated. Owners should be aware mirtazapine and cyproheptadine cannot not be administered concurrently; cyproheptadine is used as an antidote for serotonin effects of mirtazapine overdose and thus negates efficacy of the latter.

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Mirtazapine has become more commonly used and recent exploration of its pharmacodynamics and pharmacokinetics has provided information for more effective use in animals.¹⁵⁻¹⁷ Pharmacodynamic studies in cats have illustrated that it can be a potent appetite stimulant, but higher doses are more commonly associated with side effects (hyperexcitability, vocalization, tremors).¹⁸ Smaller, more frequent doses are recommended. Pharmacokinetic studies have demonstrated that the half-life is short enough that it could be administered daily in normal cats. Dose recommendations are 1.88 mg every 24 hours in cats without liver or kidney disease and 0.6-1 mg/kg once to twice daily in dogs without liver or kidney disease.

Mirtazapine has been less well studied in dogs, but in one study in research dogs was found to have a relatively

short half-life.¹⁵ Therefore twice-daily administration may be more effective than daily administration. Anecdotally the efficacy of mirtazapine in dogs for appetite stimulation seems variable. No studies have looked at its efficacy in canine CKD patients. Additional studies are needed to determine if this drug can be used more effectively in this species.

Mirtazapine in CKD

A study was performed to determine the pharmacokinetics of mirtazapine in cats with CKD and in age-matched controls to investigate the effects of renal impairment in this species and the potential for dose modification.¹⁶ Six CKD cats and 6 age-matched controls (AMC) were enrolled. Two CKD cats each from International Renal Interest Society (IRIS) stage II, III and IV were included. Blood samples were collected over 48 hours after a single oral dose of 1.88 mg of mirtazapine. CKD cats had significantly longer clearance and higher area under the curve (AUC) than geriatric controls. In comparison to a 9.2 hour half-life in normal cats, elderly cats had a half-life of 12.1 hours and CKD cats had a half-life of 15.2 hours. Calculated accumulation factor for q48-hour dosing of 1.88 mg in CKD cats was 1.15. It was concluded CKD appears to delay the clearance of mirtazapine. A single low dose of mirtazapine resulted in a half-life compatible with a 48-hour dosing interval in CKD cats unlike young normal cats, in which daily dosing would be appropriate.

The use of mirtazapine in cats with CKD has also been explored in a placebo-controlled, double-masked crossover clinical trial.¹⁹ Cats with CKD often experience hyporexia and vomiting, and may benefit from administration of mirtazapine due to its appetite stimulant and anti-nausea properties. In this study eleven cats with stable CKD were randomized to receive 1.88 mg mirtazapine or placebo orally every other day for three weeks, then, after a 4-day washout period, crossed over to the alternate three-week treatment. Physical examination and serum biochemistry profile were performed before and after each treatment period, and owners kept daily logs of appetite, activity, behavior, and vomiting episodes. In comparison to placebo, mirtazapine administration to CKD cats resulted in a statistically significant increase in appetite ($P = 0.02$) and activity ($P = 0.02$) and a statistically significant decrease in vomiting ($P = 0.047$).¹⁹ Mirtazapine administration resulted in a statistically significant increase in weight ($P = 0.002$). Median weight gain during mirtazapine administration was 0.18 kg (range, 0-0.45 kg) and 91% of cats gained weight during mirtazapine administration. Median weight loss during placebo administration was 0.07 kg (range, 0-0.34 kg) and 82% of cats lost weight during the placebo period. Forty-five percent of cats experienced an increase in BCS during mirtazapine administration, all of which had a suboptimal BCS. Cats

who already had optimal BCS did not have any change. Mirtazapine is an effective appetite stimulant in cats with CKD and resulted in significantly increased appetite and weight. Mirtazapine also appears to have anti-emetic properties and resulted in significantly decreased vomiting in cats with CKD. It was concluded that this drug could be a useful adjunct to the nutritional management of cats with CKD.

Mirtazapine also is amenable to transdermal administration and has been demonstrated to achieve both appropriate serum levels and appetite stimulation in healthy cats.²⁰

Transdermal Mirtazapine

Mirtazapine also is amenable to transdermal administration and has been demonstrated to achieve both appropriate serum levels and appetite stimulation in healthy cats.²⁰ Transdermal administration is an extremely attractive method for administering medications. However, not all drugs are amenable to transdermal application and each requires testing for appropriate drug exposure and clinical efficacy. A study was performed assessing the use of transdermal mirtazapine (TMZ) compounded into Lipoderm® gel.²⁰ It was concluded that transdermal mirtazapine is an effective route of administration. A daily dose of 7.5 mg TMZ achieves measureable serum concentrations and significant appetite stimulation despite variance in compounded gel concentrations,

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but side effects denote a lower dose is indicated. Doses ranging from 1.88-3.75 mg are currently being studied in CKD cats in a placebo-controlled clinical trial.

Appetite Stimulants – Ghrelin Agonist Capromorelin

Availability of the ghrelin agonist capromorelin may also provide additional opportunities to address appetite in dogs and cats with CKD by targeting the dysregulation of appetite that occurs with disease. In both human and rodent studies,

administration of ghrelin has resulted in increased appetite and energy intake in patients with CKD.¹⁴ In recent veterinary abstracts, administration of capromorelin resulted in increased appetite, food intake and weight in normal and inappetent dogs and increased food intake and weight in laboratory cats.^{21,22,23}

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