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Mirtazapine as an appetite stimulant and anti-emetic in cats with chronic kidney disease: A masked placebo-controlled crossover clinical trial

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ABSTRACT

Cats with chronic kidney disease (CKD) often experience inappetence and vomiting and might benefit from the administration of mirtazapine, a medication with appetite stimulant and anti-nausea properties. The aim of this placebo-controlled, double-masked crossover clinical trial was to evaluate the effects of mirtazapine on bodyweight, appetite and vomiting in cats with CKD. Eleven cats with stable CKD were randomized to receive 1.88 mg mirtazapine or placebo orally every other day for 3 weeks. After a 4 day washout period, each cat crossed over to the alternate treatment for 3 weeks. Physical examinations and serum biochemistry profiles were performed before and after each treatment period and owners kept daily logs of appetite, activity, behavior, and vomiting episodes.

Compared to placebo, mirtazapine administration resulted in a statistically significant increase in appetite ($P = 0.02$) and activity ($P = 0.02$) and a statistically significant decrease in vomiting ($P = 0.047$), as determined by Wilcoxon matched pairs analysis. Cats treated with mirtazapine also gained significant bodyweight compared with placebo-treated cats ($P = 0.002$) as determined by linear mixed model analysis. Median weight gain during mirtazapine administration was 0.18 kg (range 0–0.45 kg). Median weight loss during placebo administration was 0.07 kg (range 0–0.34 kg). Mirtazapine is an effective appetite stimulant and anti-emetic for cats with CKD and could be a useful adjunct to the nutritional management of these cases.

Introduction

Chronic kidney disease (CKD) is a common condition in elderly cats, with at least 30% of the population affected by 15 years of age (Boyd et al., 2008). Currently no treatment other than renal transplantation has been shown to reverse or halt declining renal function for any significant period of time (Polzin, 2011). Therefore, medical management is the mainstay of treatment and can help cats live with the metabolic complications of the disease and improve their quality of life (Roudebush et al., 2009; Polzin, 2011). The clinical signs of feline CKD include polyuria, polydipsia, decreased appetite, weight loss and vomiting. Treatments that directly target nausea and appetite, in addition to medical therapies for metabolic complications, are beneficial, as nutrition affects long-term prognosis. In chronically ill cats, and specifically in CKD, poor body condition has been correlated with decreased survival (Kopple, 1994; Sanderson, 2000; Parker and Freeman, 2011). In addition, several studies have documented the therapeutic value of specially formulated diets in the management of CKD (Elliott et al., 2000; Plantinga et al., 2005; Ross et al., 2006). These diets contain restricted amounts of high quality protein, adequate non-protein calories, and are restricted in phosphorus (Ross et al., 2006). However, some cats refuse to eat specially formulated diets, making the maintenance of appetite and food intake for these cats a key therapeutic target. Additionally, poor appetite is perceived by owners as a significant quality of life concern and anorexia in companion animals can cause emotional distress to owners (Reynolds et al., 2010).

Mirtazapine, a tetracyclic antidepressant, has utility in veterinary patients because of several beneficial side effects, namely its significant anti-nausea, anti-emetic, and appetite stimulating properties. These effects are mainly mediated through antagonism of the 5-HT_3 receptor, which is important in the physiology of emesis (Kast and Foley, 2007). Recent pharmacodynamic and pharmacokinetic studies in cats have demonstrated the appetite stimulating properties of mirtazapine, and have also determined appropriate dose rates and intervals for healthy cats and cats with CKD (Quimby et al., 2011a,b). The purpose of this clinical trial was

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to assess the efficacy of mirtazapine as an appetite stimulant and an anti-emetic in cats with CKD, thus providing evidence for the value of this medication in the nutritional management of cats with CKD.

Materials and methods

Cats

Cats with stable CKD (a priori determination of serum creatinine of 177–442 μmol/L [2.0–5.0 mg/dL]) and a history of decreased appetite or poor body condition were enrolled. Diagnostic tests required within 1 month of enrollment included a serum biochemistry profile, complete blood count, urinalysis, urine culture, blood pressure, and serum total thyroxine measurement. Exclusion criteria included a normal appetite, other systemic illnesses, complications associated with CKD such as pyelonephritis or ureteral obstruction, or history of uremic crisis requiring hospitalization and IV fluid therapy within the month prior to study enrollment. Other concurrent therapies such as dietary management, famotidine, potassium supplementation, anti-hypertensive medications and subcutaneous fluids were allowed if they had started more than 2 weeks before the beginning of the trial and given consistently throughout the study period. No treatment changes were allowed during the study period; if treatment changes were deemed medically necessary, the cat was removed from the study.

The study was approved by the Institutional Animal Care and Use Committee at Colorado State University (#10-2036A), and all owners reviewed and signed consent forms prior to participation in the study.

Study design

This was a double-masked placebo-controlled prospective study. Generic mirtazapine (Aurobindo Pharma) was compounded into a 1.88 mg (1/8 of the commercially available 15 mg tablet) capsule by the Colorado State University (CSU) Veterinary Medical Center pharmacy according to Professional Compounding Centers of America protocol. The method used is guaranteed to produce accurate compounding to within 10% of the target dose. An identical placebo capsule was manufactured containing lactose. The lots were coded A and B and the pharmacy staff kept the key to the code. A preset randomization for order of distribution (AB or BA) was determined using an online random number generator and as cats were enrolled they were assigned consecutively to a treatment regimen. The clinician and cat owner were masked as to the treatment order.

A physical examination, bodyweight measurement, body condition score (Purina Body Condition System; Laflamme, 1997), and serum biochemistry profile were performed at the beginning of the study. The first treatment was given every 48 h for 3 weeks followed by a 4 day (equivalent to 5 half-lives of mirtazapine) washout period before the second treatment was given using the same dosing schedule. Owners were asked to fill out a daily log sheet giving details of their cats' appetite, vomiting episodes, activity level, quality of life, and any occurrences of unusual behavior (Appendix A).

At the end of each treatment period, the log sheets were collected and a physical examination, bodyweight measurement, body condition score, and serum biochemistry profile were performed. For each cat enrolled, physical examinations and body condition scores were performed by the same clinician. The occurrence of adverse effects was determined using incidence of unusual behaviors recorded in the daily owner log, and the results of serum biochemistry performed before and after each phase of the study. All serum biochemistry profiles were performed at the CSU Diagnostic Laboratories.

Statistical analysis

To determine sample size for the study, an initial power calculation was performed based on the assumption that a 10% change in bodyweight would be considered clinically significant. Assuming an average cat weight of 5 kg, a standard deviation of 1.0, and $\alpha = 0.05$, a sample size of 33 cats was calculated to give a power of 0.80 to detect a change in weight of 0.5 kg.

Appetite and activity data were converted to the following clinical scores: −1, decreased appetite or activity; 0, unchanged appetite or activity, and 1, increased appetite or activity. Scores were summed over the 3 week treatment period. The number of vomiting episodes over 21 days and the summed clinical scores for appetite and activity were compared between placebo and mirtazapine treatment phases using a Wilcoxon matched pairs test. Non-parametric statistical analyses were used as the sample size was small and the data were not normally distributed.

Bodyweight, body condition score, serum creatinine, BUN, potassium, and phosphorus were compared individually using linear mixed model analysis (SAS 9.3, SAS Institute). Specifically, a two-period crossover model was used which included period, randomization (AB or BA) and treatment as fixed effects, and cat within randomization as a random effect. Residuals were plotted to assess normality; because serum phosphorus had a large residual for one reading, a rank transformation was performed, but overall results were the same. For all analyses, a P value of <0.05 was considered to be statistically significant.

Results

Cats

A flow chart describing study enrollment, allocation, outcome and analysis is presented in Fig. 1. As recruitment of cats proved to be difficult, statistical analysis was performed when approximately 50% of the cats had been enrolled. A total of 16 cats with CKD were enrolled in the clinical trial, and 11 cats successfully completed the trial. The 11 cats that completed the trial included five domestic short hairs, three Siamese mixes, one Tonkinese, one Persian and one domestic long hair. The median age was 15 years (range 10–17) with six spayed females and five castrated males. Seven cats were classified as International Renal Interest Society (IRIS) stage 2, and four cats were IRIS stage 3 (Polzin, 2011). One of the four cats with stage 3 CKD progressed to stage 4 between study enrollment and study initiation.

Effect of mirtazapine in cats with CKD

Weight gain occurred in 91% of the cats with CKD during the mirtazapine administration phase, and in contrast 82% of cats lost weight during the placebo phase. Median weight gain during mirtazapine administration was 0.18 kg (range 0–0.45 kg). Median weight loss during placebo administration was 0.07 kg (range 0–0.34 kg). Forty-five percent of cats receiving mirtazapine demonstrated an increase in body condition score. All of the cats that experienced increased body condition score had a suboptimal body score at the beginning of the treatment period, whereas 85% of those that had no change already had an optimal body condition score. No owners reported adverse behavioral changes associated with mirtazapine administration.

Appetite score (Fig. 2) and activity score (Fig. 3) were significantly increased when cats received mirtazapine, in comparison to placebo ($P = 0.02$ for both parameters). Appetite score was increased in 91% of cats during the mirtazapine phase and activity score was increased in 55%. Additionally, there was a statistically significant decrease in vomiting ($P = 0.047$; Fig. 4) during the mirtazapine phase.

The administration of mirtazapine for 3 weeks to cats with CKD resulted in a statistically significant increase in weight based on linear mixed model analysis (coefficient = 0.11, CI = 0.06–0.18, $P = 0.002$; Table 1). Statistically significant differences in body condition score or relevant renal biochemistry values were not detected during either treatment period. A summary of relevant renal biochemistry values, performed before the study, between treatment phases and at the end of the study, is presented in Table 1. No period or randomization effects were detected by the linear mixed model analysis, indicating that progression of disease did not affect study results.

One cat experienced a marked increase in alanine aminotransferase (ALT) activity of 744 U/L (reference interval 25–120 U/L) with a normal alkaline phosphatase, presumptively attributed to the 3 weeks of mirtazapine administration, with no associated clinical abnormalities. The increase in ALT activity resolved within 3 weeks, once mirtazapine was discontinued. After the end of the study, the owner elected to administer the mirtazapine therapy again as the cat had responded so well clinically. ALT increase (731 U/L) with no associated clinical signs was once again noted and once again resolved within 3 weeks after the discontinuation of mirtazapine.

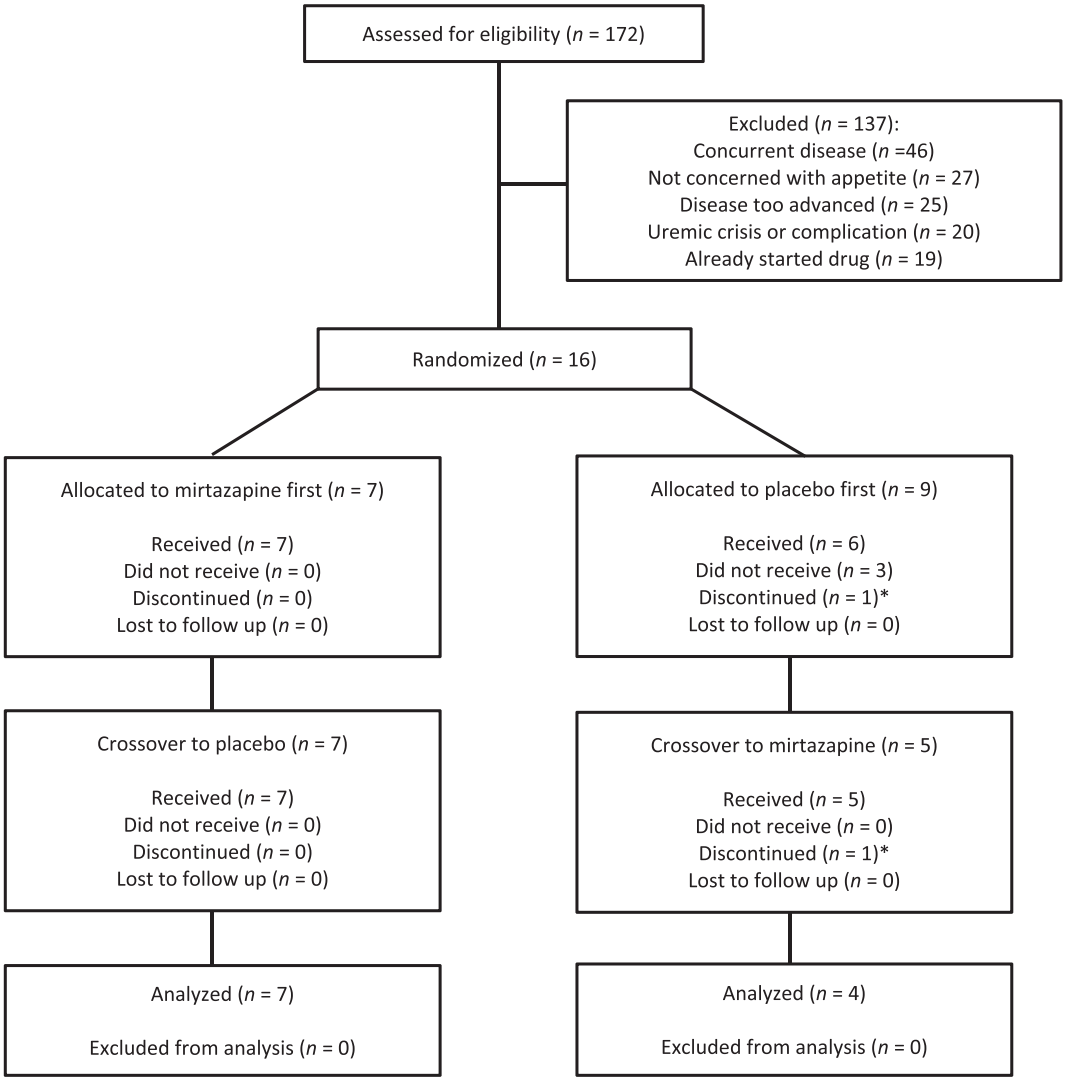

Fig. 1. Flow chart describing assessment for eligibility, enrollment, allocation, outcome and analysis of cats with CKD for the mirtazapine study; a placebo-controlled, masked crossover clinical trial. Three cats that were randomized failed to start the trial. *Denotes uremic crisis resulting in disqualification of the cat from the study.

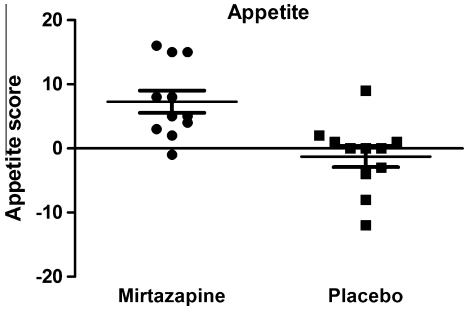

Fig. 2. Effect of 3 weeks of mirtazapine administration on appetite of cats with CKD. In comparison to placebo, a statistically significant increase in appetite score was seen in cats with CKD ($n = 11$) administered 1.88 mg mirtazapine every other day for 3 weeks ($P = 0.02$).

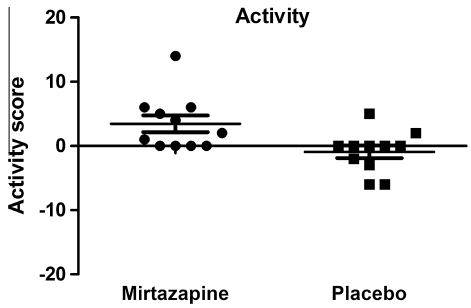

Fig. 3. Effect of 3 weeks of mirtazapine administration on activity level of cats with CKD. In comparison to placebo, a statistically significant increase in activity was seen in cats with CKD ($n = 11$) administered 1.88 mg mirtazapine every other day for 3 weeks ($P = 0.02$).

Discussion

In this placebo-controlled, masked crossover clinical trial, repeated administration of 1.88 mg of mirtazapine to cats with CKD every 48 h for 3 weeks resulted in statistically significant increases in appetite and bodyweight. A statistically significant increase in activity and a statistically significant decrease in vomiting were also detected. As poor body condition has been correlated with decreased survival in CKD (Kopple, 1994; Sanderson, 2000; Parker and Freeman, 2011), these results have potentially significant implications for the management of cats with CKD, although the current study did not evaluate long-term

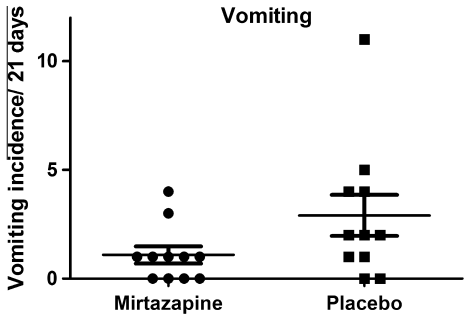

Fig. 4. Effect of 3 weeks of mirtazapine administration on vomiting in cats with CKD. In comparison to placebo, a statistically significant decrease in vomiting was seen in cats with CKD ($n = 11$) administered 1.88 mg mirtazapine every other day for 3 weeks ($P = 0.047$).

administration or survival. Loss of appetite is a significant quality of life concern to owners, and mirtazapine could be a valuable tool for veterinary practitioners to use to help alleviate the emotional distress experienced by owners managing hyporexic or anorexic cats with CKD.

The efficacy of mirtazapine in increasing appetite and promoting weight gain has previously been explored in several species. A Phase 2 clinical trial in humans experiencing cancer-related anorexia and cachexia demonstrated increased appetite and weight as a result of mirtazapine administration (Riechelmann et al., 2010). Additionally, a recent study in mice with pancreatic carcinoma and gemcitabine-induced cachexia demonstrated a significant increase in appetite and weight when mirtazapine was administered (Jiang et al., 2012). In the veterinary field, the original publication reporting mirtazapine use in dogs and cats was an uncontrolled clinical trial in which 24 dogs and 17 cats with varying medical conditions were treated with doses extrapolated from human medicine (Cahill, 2006). Mirtazapine therapy led to an excellent response in 12 cases, a better response than standard therapy in 16 cases, and an equivocal response in 13 cases. It was suggested that the best responses were seen in animals with kidney disease or undergoing chemotherapy (Cahill, 2006).

Previously, in a placebo-controlled study, we described the efficacy of a single dose of mirtazapine for stimulating appetite in young healthy cats (Quimby et al., 2011b), but the current study is the first placebo-controlled trial to describe its efficacy in increasing appetite and weight in feline patients with inappetence and poor body condition score secondary to a chronic illness. Cats with appetites that were considered to be normal by their owners were not included in the present study. This strengthens the results of this study as it can be concluded that mirtazapine is of clinical benefit to cats with poor appetites; however the results cannot be extrapolated to cats with CKD with a normal appetite.

Cats with concurrent diseases and those experiencing uremic crises or advanced CKD were not included in this clinical trial, leading to the exclusion of a large number of potential participants. It was the authors' decision that the efficacy of the drug could not be adequately assessed when appetite could potentially be confounded by other factors. It is acknowledged that this is not necessarily representative of the population for which this medication would be prescribed. However, it could be argued that it would be medically unethical for those cats to receive 3 weeks of placebo therapy, and thus the evaluation of mirtazapine in those cats was not addressed in the present study. The resultant difficulties with case recruitment lead to lower than desired numbers for study power based on our a priori power calculation. While this reduced the chances of finding statistically significant effects, the lower than expected sample size does not reduce the strength of the significant findings of the study.

The results of this study are consistent with descriptions of the anti-emetic and appetite stimulating properties of mirtazapine in humans (Pae, 2006; Kast and Foley, 2007; Chen et al., 2008; Kim et al., 2008; Chang et al., 2010; Riechelmann et al., 2010). Several studies have described successful palliation of nausea and vomiting in human patients; particularly cancer patients undergoing chemotherapy (Pae, 2006; Kast and Foley, 2007; Kim et al., 2008). Mirtazapine has also been used to decrease nausea and vomiting associated with intrathecal morphine injections and in a recent study, patients undergoing gynecological surgery who were pre-medicated with mirtazapine had significantly reduced pre-operative anxiety and post-operative nausea and vomiting (Chen et al., 2008; Chang et al., 2010). To the best of the authors' knowledge, the current clinical trial provides the first published information about the anti-nausea and anti-emetic effects of mirtazapine in cats.

The side effects of mirtazapine in cats include increased activity, vocalization, and anecdotal reports of dysphoria or excitability that occur in a dose-dependent manner (Quimby et al., 2011b). In the original uncontrolled clinical trial, higher doses in cats were associated with muscle tremors, but otherwise the medication was well tolerated (Cahill, 2006). No significant behavioral side effects were noted with the dosing regimen used in our study. However, given the small number of cats that completed the study, side effects might be uncommon enough to preclude detection in this sampling frame. One cat did experience subclinically elevated ALT, which resolved with discontinuation of mirtazapine. A similar case was reported in humans, in which an individual experienced a dose-dependent asymptomatic increase in liver enzyme activity that resolved after mirtazapine was discontinued (Adetunji et al., 2007). The mechanism underlying this finding is unclear, but it is recommended that liver enzymes are monitored in cats receiving mirtazapine, and it would be prudent to avoid mirtazapine administration in cats that experience this side effect.

Table 1
Pre-treatment and post-treatment comparison of weight and serum biochemistry parameters relevant to renal function. Results are displayed as median (range).

	Bodyweight (kg)	Creatinine (μmol/L)	Creatinine (mg/dL)	BUN (μmol/L)	BUN (mg/dL)	Phosphorus (μmol/L)	Phosphorus (mg/dL)	Potassium (mEq/L)
Pre-mirtazapine	3.6 (2.7–4.7)	248 (169–504)	2.8 (1.9–5.7)	17.5 (11.4–30)	49 (32–84)	1.5 (1.0–2.1)	4.6 (3.1–6.4)	4.2 (3.5–5.4)
Post-mirtazapine	3.8* (2.8–4.9)	230 (186–451)	2.6 (2.1–5.1)	19.3 (15–35.3)	54 (42–99)	1.7 (1.4–2.7)	5.3 (4.2–8.4)	4.4 (3.1–5.4)
Pre-placebo	3.8 (2.8–4.9)	230 (169–451)	2.6 (1.9–5.1)	19.3 (15–28.6)	54 (42–80)	1.6 (1.0–2.7)	5.0 (3.2–8.4)	4.3 (3.1–4.9)
Post-placebo	3.6* (2.8–4.7)	239 (177–557)	2.7 (2.0–6.3)	17.1 (12.1–30)	48 (34–84)	1.5 (1.0–4.0)	4.8 (3.2–12.4)	4.3 (3.3–5.6)

* Indicates a statistically significant difference between treatment phases when compared using linear mixed model analysis ($P = <0.05$).

Conclusions

This placebo-controlled, masked crossover clinical trial demonstrated that the oral administration of 1.88 mg of mirtazapine every other day for 3 weeks to cats with CKD resulted in significantly increased appetite. Additionally, significant weight gain, increased activity and decreased vomiting were demonstrated. Mirtazapine could be a useful adjunctive therapy in the management of inappetence, nausea and poor body condition associated with CKD in cats.

Conflict of interest statement

The authors disclose a pending patent application on the intellectual data described in this study.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tvjl.2013.05.048.

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