MIRTAZAPINE—HOW MUCH IS TOO MUCH?
We look at ideal dosing practices for this appetite stimulant in cats to avoid adverse side effects.

FOCUS ON

Mirtazapine: Addressing Appetite in Cats

***Jessica Quimby**, DVM, PhD, DACVIM, Associate Professor*
The Ohio State University, Columbus, Ohio

Both oral and transdermal mirtazapine are now commonly used in clinical practice. This article reviews studies of oral mirtazapine and current recommendations for cats, including normal cats, geriatric cats, and cats with kidney or liver disease. It also summarizes recent literature on transdermal mirtazapine in cats and briefly discusses mirtazapine use in dogs.

MECHANISM OF ACTION

The mechanism of action by which mirtazapine stimulates appetite is not fully described, but it likely involves antagonism of the $5HT_{2c}$ receptor. This receptor is known for its appetite inhibition activity, as well as antagonism of the H_1 receptor, which also helps regulate appetite.[1,2] Mirtazapine also has antiemetic effects in humans and cats. This is likely a result of antagonism of the $5\text{-}HT_3$ receptor, which is important in the physiology of emesis.[3,4]

ORAL MIRTAZAPINE

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic studies in cats have shown that the median half-life of oral mirtazapine is 9.2 hours for the 1.88-mg dose and 15.9 hours for the 3.75-mg dose in normal young animals; this is much shorter than originally postulated.[5] When a 1.88-mg dose was given to young normal cats daily, no significant drug accumulation occurred.[5] Mirtazapine does not display linear pharmacokinetics in cats: In other words, metabolism appears slowed at higher doses, possibly because of overburdened enzyme systems.

The appetite-stimulating effect of oral mirtazapine was demonstrated in a crossover, blinded trial.[5] Cats receiving oral mirtazapine at 1.88 mg q24h and 3.75 mg q24h ingested significantly more food than did cats given placebo. However, significantly more side effects (increased vocalization, activity, and socialization) were seen with the higher dose, and the amount of food ingested did not differ between the dose groups. On the basis of this research, 1.88 mg is recommended as the initial starting dose for oral mirtazapine and can be given as frequently as daily in young normal cats.

Side Effects

The most common adverse effects reported to the ASPCA Animal Poison Control Center in 84 cats intentionally or accidently exposed to oral mirtazapine included vocalization, agitation, vomiting, abnormal gait/ataxia, restlessness, tremors/trembling,

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hypersalivation, tachypnea, tachycardia, and lethargy.[6] Onset of clinical signs ranged from 15 minutes to 3 hours after ingestion, and clinical signs resolved in 12 to 48 hours. The most common doses associated with signs of toxicity were 15 mg (40 cats) and 3.75 mg (25 cats); only 1 call was received for the 1.88-mg dose. These data highlight the benefit of dispensing exact doses of mirtazapine, given the frequency of accidental oral administration of a full 15-mg tablet. The greater number of adverse effects at 3.75 mg than at 1.88 mg supports the recommendation that 1.88 mg is a more appropriate starting dose for stimulating appetite while limiting side effects.

Use in Kidney Disease

The half-life of oral mirtazapine is prolonged in humans with chronic kidney disease (CKD) because of its renal excretion. A study in cats has yielded similar results.[7] Compared with age-matched geriatric control cats, cats with CKD had significantly longer half-life and higher drug exposure. Specifically, when 6 cats with IRIS (International Renal Interest Society) stage 2 and 3 CKD were administered a single oral 1.88-mg dose of mirtazapine, it had a half-life of 15.2 hours; in comparison, its half-life was 12.1 hours when administered to geriatric cats and 9.2 hours when given to young normal cats.[5,7] On the basis of accumulation factor calculations, the researchers concluded that CKD delays the clearance of oral mirtazapine and that a single low dose of mirtazapine resulted in a half-life compatible with a 48-hour dosing interval in cats with CKD; in contrast, daily dosing is appropriate in young cats.

A placebo-controlled, double-masked crossover clinical trial randomly assigned 11 cats with stable IRIS stage 2 and 3 CKD to receive 1.88 mg of mirtazapine or placebo orally q48h for 3 weeks.[4] In the cats with CKD that received mirtazapine, appetite and weight increased significantly and vomiting decreased significantly compared with the placebo group.[4] Median weight gain during mirtazapine administration was 0.18 kg (range, 0 to 0.45 kg), and 91% of cats gained weight during therapy. Median weight loss during placebo administration was 0.07 kg (range, 0 to 0.34 kg), and 82% of cats lost weight. The authors concluded that this drug was a useful adjunct to the nutritional management of cats with CKD.

Use in Liver Disease

In humans, liver disease delays the clearance of oral mirtazapine because of its hepatic metabolism, and a study in cats had similar results.[8] When administered to cats with liver disease (alanine aminotransferase [ALT] > 200 U/L or total bilirubin > 1 mg/dL), a single oral 1.88-mg dose had a median half-life of 13.8 hours (range, 7.9 to 61.4 hours) compared with 7.4 hours (range, 6.7 to 9.1 hours) in age-matched control cats.[8] Although mirtazapine half-life was correlated with alkaline phosphatase, ALT, and total bilirubin, the alterations in metabolism varied; it was challenging to predict which cats would be the most affected. However, on the basis of this study, the clinical recommendation would be to give oral mirtazapine q48h to q72h to cats with significant liver disease.

Single and repeat doses of mirtazapine transdermal ointment achieve measurable and clinically relevant plasma concentrations in cats.[10]

TRANSDERMAL MIRTAZAPINE

Transdermal administration of medications is an extremely attractive method. However, not all drugs are amenable to this application, and each requires testing for appropriate drug exposure and clinical efficacy. Several studies have demonstrated that mirtazapine is suitable for transdermal administration.[9-11] Early pilot studies showed that in young, healthy cats, compounded transdermal mirtazapine achieved clinically relevant serum concentrations, without the need for higher doses.[9] The drug was effective and resulted in a significant increase in appetite, rate of food ingestion, activity, begging behavior, and vocalization. However, concerns about compounded transdermal mirtazapine include inaccuracy of commercially available gel preparations and the risk of contamination of ingredients used to manufacture compounded gels.[9]

The Food and Drug Administration recently approved transdermal mirtazapine ointment to manage unintended weight loss in cats, and pharmacokinetic and pharmacodynamics studies have documented its

efficacy.[10,11] Single and repeat doses of mirtazapine transdermal ointment achieve measurable and clinically relevant plasma concentrations in cats.[10]

In a large multicenter, double-blind, randomized, placebo-controlled, pharmacodynamic study, 2 mg of this ointment was applied daily, for 14 days, to the inner ear pinnae of cats with greater than 5% unintended weight loss.[11] Cats in the mirtazapine group gained significantly more weight compared with baseline (mean gain, 3.94% ± 5.37%) than did those in the placebo group (mean gain, 0.41% ± 3.33%). Transdermal administration appeared well tolerated locally and systemically. The pharmacokinetics of mirtazapine transdermal ointment have not been studied in feline patients with CKD; however, analysis of a subset of such patients enrolled in this pharmacodynamic study showed that incidence of behavioral adverse events (vocalization and hyperactivity) did not significantly differ between cats with and without CKD.[11]

ORAL MIRTAZAPINE IN DOGS

Fewer studies have evaluated use of mirtazapine in dogs. Anecdotally, it does not seem to be as effective in stimulating appetite as it is in cats. A pharmacokinetic study performed in beagle dogs demonstrated that the mean half-life of oral mirtazapine administered at approximately 1.1 to 1.3 mg/kg was only 6.2 hours.[12] On the basis of the significantly shorter half-life in dogs compared with other species, twice-daily administration may be more effective for appetite stimulation. However, studies to confirm this have not been performed. Mirtazapine may also have prokinetic properties in dogs, but additional study is needed.[13]

SUMMARY

Mirtazapine is an effective appetite stimulant in cats. The weight gain it causes is likely due to increased caloric intake. A starting dose of 1.88 mg orally q24h is recommended in nongeriatric, physiologically normal cats, and administration of 1.88 mg orally q48h is recommended in elderly cats, cats with CKD, and cats with liver disease. Side effects are dose related and are less likely to occur at this low dose. Mirtazapine is amenable to transdermal administration; in this form it can achieve clinically relevant serum levels and result in weight gain. It is approved for cats at a labeled dose of 2 mg q24h. Mirtazapine has not been well studied in dogs. TVP

Jessica M. Quimby

After receiving her veterinary degree from the University of Wisconsin-Madison and completing a small animal rotating internship in Sacramento, California, Jessica Quimby spent 2 years in feline practice in Grand Rapids, Michigan, and then moved to Colorado State University for a combined small animal internal medicine residency and PhD program. She completed a PhD focusing on feline CKD in 2012 and was a faculty member at Colorado State until 2017. Dr. Quimby is now on the faculty at the Ohio State University. Her research continues to focus on chronic kidney disease in cats. Current research areas include the study of renal aging, telomere length and cellular senescence, novel treatment strategies, and evidence-based supportive care strategies. She has an interest in clinical trials and feline clinical pharmacology that is aimed at improving supportive care and quality of life in cats with CKD.

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