

INTRODUCTION

Management of Weight Loss in Cats

Weight loss and anorexia in cats are common problems secondary to numerous underlying diseases. Prolonged anorexia and weight loss can lead to serious sequelae such as hepatic lipidosis [1], reduced immunity [1], delayed wound healing [2], decreased survival times [3], and indirectly influence an owner's decision to euthanize cats with chronic disease [4].

Regardless of the underlying disease, appetite modulation via pharmacotherapy can play a valuable role to improve a patient's nutritional status and ability to recover from the underlying illness or injury [2]. There are no approved veterinary products to manage weight loss in cats.

Mirtazapine

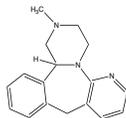
Mirtazapine is a noradrenergic and specific serotonergic antidepressant with antiemetic and appetite-stimulating properties. Its presynaptic α_2 -adrenergic receptor antagonism results in increased norepinephrine which likely contributes to its appetite stimulating effects [2].

Mirtazapine blocks three serotonin (5-HT_{2A}, 5-HT_{2C} and 5-HT₃) and histamine (H₁) receptors. Antagonism of 5-HT_{2C} and/or H₁ receptors potentially stimulate appetite regulated by the hypothalamus, thus leading to weight gain [5].

Antagonism of 5-HT₃ reduces nausea and vomiting in humans [6].

Mirtazapine has been shown to increase food intake and weight gain in both humans [7] and cats [2, 8]. Mirtazapine transdermal ointment achieves clinically relevant serum concentrations in cats and results in increased body weight at a dose of 0.5 mg/kg.

Figure 1. Chemical structure of mirtazapine

Molecular Formula: C₁₇H₁₉N₃

Molecular Weight: 265.35 g/mol

OBJECTIVE

The purpose of this study was to evaluate the safety profile of mirtazapine at an exaggerated dose.

METHODS

This study was a non-randomized, unmasked, laboratory safety study in purpose-bred cats.

Seven female cats that were clinically normal on examination were included in this study.

Although clinically normal, 2/7 cats had elevated BUN and creatinine as indication of mild to moderate kidney dysfunction.

METHODS (CONT'D)

Study Drug Application

Formulation	Subjects	Dose	Duration
mirtazapine transdermal ointment	5 healthy 2 CKD	5mg/kg 1x per day	28 days

Each 1 mL of mirtazapine ointment contains 20 mg (2%). Mirtazapine was applied topically to the inner pinna of the ear.



Assessments

- Days -7 through 27: twice daily health and behavioral assessments
- Days -5, -1, 6, 13, 20 and 27: body weight
- Days -5, 13 and 27: physical examinations, EKG, blood pressure, hematology and serum chemistry
- Days -6 and 26: abdominal and scanning echocardiogram and abdominal ultrasound (Day 26 only)

Table 1. Behavioral assessment scoring key

Interaction: 0=Hiding/sits at back of cage 1=Gets up to greet you when cage is opened 2=Soliciting attention at front of cage	Activity: 0=Sedentary/hiding 1=Walking around normally 2=Frantic/hyperactivity
Vocalization (per 15 seconds): 0=0; 1=1 to 5; 2=6 to 10; 3=>10	Tremors: 0=None 1=Mild twitch/bobble (subtle) 2=Noticeable head bobble or twitching

Statistical Analysis

Body weight, blood pressure, and serum ALT were compared between time points using a Wilcoxon Signed Rank Test for paired samples.

Sum of pre-dose mean behavior scores were compared to mean behavior scores at Day 27 using a Wilcoxon Signed Rank Test for paired samples.

Statistical significance was set at p<0.05 for all tests.

RESULTS

Overall Safety Findings

No significant health abnormalities were observed in any of the enrolled cats.

RESULTS (CONT'D)

Table 2. Summary of clinical findings

Clinical Assessment ¹	Incidence
Body Weight: weight gain	7 cats
Clinical Observations:	
Erythema of inner pinna	7 cats
Increased urination ²	2 cats
Vomiting	1 cat
Ataxia/Spasms	1 cat

¹ There were no clinically relevant findings following blood pressure, hematology, serum chemistry, or cardiovascular assessment in any enrolled cat.

² CKD cats. Normal urine specific gravity.

Other Safety Findings

Abdominal and Thoracic Ultrasound:

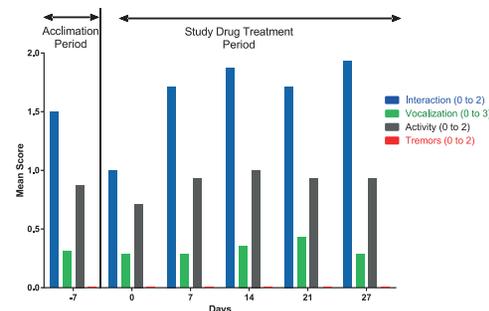
There was no clinically relevant findings in treated cats at the beginning or end of the study.

Body Weight :

Treated cats gained a significant amount in body weight from Day 0 to Day 28 (p=0.016).

- Mean weight at Day -7: 3.48 kg
- Mean weight at Day 27: 3.94 kg

Figure 2. Behavioral assessment



There were no statistically significant changes in animal behavior over the course of the study.

DISCUSSION

Mirtazapine transdermal ointment was well tolerated in cats when administered at approximately 10x (dose range 15.0-22.8 mg) the recommended dose for both oral and transdermal mirtazapine [8, 9].

A previous retrospective study of oral mirtazapine toxicity demonstrated significant adverse effects with accidental administration of an entire 15 mg tablet [9].

CONCLUSIONS

Mirtazapine transdermal ointment was well tolerated in cats when administered at 5 mg/kg for 28 consecutive days.

DISCLOSURES

Allyson Avenatti, William Buhles, Daizie Labelle, Melinda Poole are/were employees/contractors of Kindred Biosciences, Inc. Jessica Quimby is a consultant for Kindred Biosciences, Inc.

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