DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY OF MIRTAZAPINE TRANSDERMAL OINTMENT FOR THE MANAGEMENT OF FELINE WEIGHT LOSS

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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 sequalae 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.

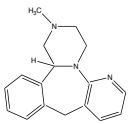
Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant with antiemetic and appetite-stimulating properties. Its presynaptic α2- adrenergic receptor antagonism results in increased norepinephrine which likely contributes to its appetite stimulating effects [2].

Mirtazapine blocks three serotonin (5-HT2A, 5-HT2C and 5-HT3) and histamine (H1) receptors. Antagonism of 5-HT2C 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 has been demonstrated to achieve clinically relevant plasma concentrations in cats.

Figure 1. Chemical structure of mirtazapine



Molecular Formula: $C_{17}H_{19}N_3$

Molecular Weight: 265.35 g/mol

OBJECTIVE

The purpose of this study was to evaluate the effectiveness and safety of mirtazapine transdermal ointment for the management of weight loss in cats.

METHODS

This study was a multi-center, double-blind, placebo-controlled, randomized field study in client owned cats.

Cats at least 1 year of age, weighing ≥ 2 kg, with a documented medical history of ≥ 5% body weight loss that was deemed clinically significant were enrolled.

Cats could not have a serum creatinine > 5.0 mg/dL or diagnosed neoplasia.

Randomization was 1:1 (mirtazapine:control product).

Mirtazapine was dosed at 2 mg per cat (equiv. to 0.1 mL volume of 2% ointment), regardless of body weight (BW).

Control product (placebo) ointment was dosed at the same volume.

METHODS (CONT'D)

Application

Dose volume was applied to the inner pinna once a day for 14 ± 3 days (approximately 1.5 inch ribbon).

Assessments

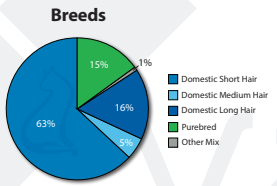
Case reviews were done prior to unblinding to select the effectiveness population based on adherence to the protocol.

Effectiveness was demonstrated by comparison of mean percent change in body weight between the Day 1 and Week 2 visits using a two-sided t-test with significance set at $p < 0.05$, where the percent change in body weight in the mirtazapine group was ≥ 0.

Clinical pathology data from all cases receiving mirtazapine or control product were included in the safety analysis. Each variable was analyzed using Analysis of Covariance, with treatment as a fixed effect and the baseline value as a covariate.

RESULTS

Study population



- 115 Treated with Mirtazapine [90 cats in the effectiveness analysis]
- 115 Treated with Control Product [97 cats in the effectiveness analysis]

Sex: Female spayed: 123, Female intact: 1, Male Neutered: 107

Baseline mean weight (kg)		Baseline mean age (years)	
Mirtazapine 4.1 ± 1.2	Control Product 4.3 ± 1.0	Mirtazapine 14.2 ± 3.7	Control Product 13.4 ± 3.0

Table 1. Pre-existing conditions at enrollment (incidence > 5%) - safety population

Pre-existing Condition	Mirtazapine (n=115) n (%)	Control Product (n=115) n (%)	All (n=230) n (%)
Renal insufficiency	49 (42.6)	35 (30.4)	84 (36.5)
Hyperthyroidism	21 (18.3)	15 (13.0)	36 (15.7)
Hyposthenuria	6 (5.2)	13 (11.3)	19 (8.3)
Diarrhea	10 (8.7)	4 (3.5)	14 (6.1)
Regurgitation	2 (1.7)	9 (7.8)	11 (4.8)
Hypercalcemia	0 (0)	6 (5.2)	6 (2.6)

RESULTS (CONT'D)

Table 2. Dose and effectiveness outcomes - effectiveness population

	Mirtazapine (n=90)		Control Product (n=97)	
	Mean ± SD	Median (range)	Mean ± SD	Median
Dose (mg/kg)	0.5 ± 0.2	0.5 (0.2 to 1.0)	0.0	0.0
Baseline BW (kg)	4.1 ± 1.2	3.9 (2.1 to 9.2)	4.3 ± 1.0	4.3 (2.3 to 7.5)
BW change(%)	4.1 ± 5.3	4.5 (-10.7 to 16.7)	0.3 ± 3.5	0.0 (-14.6 to 7.7)
BW change (kg)	0.2 ± 0.2	0.2 (-0.6 to 0.5)	0.01 ± 0.2	0.0 (-0.7 to 0.3)

SD=standard deviation

Table 3. Percent change in body weight: Day 1 to week 2 - effectiveness population

	Mirtazapine (n=90)	Control Product (n=97)
Mean percent change (SD)	4.1 (0.6)	0.3 (0.4)
Difference in mean percent change (95% Confidence Interval)	3.8 (2.5, 5.1)	
p-value	<0.0001	

Figure 2. Mean body weight from baseline - effectiveness population

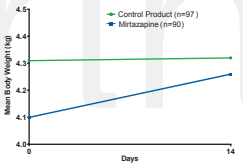
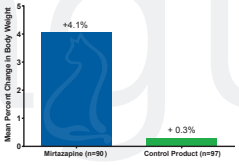


Figure 3. Mean % change in body weight from baseline - effectiveness population



Adverse Events

BUN was the only clinical pathology parameter significantly different between mirtazapine and control that was out of the normal range and was likely due to the increased incidence of renal disease at the time of enrollment in the mirtazapine group. All other significantly different parameters were within the normal range and not considered clinically relevant.

Nine cats (3 mirtazapine, 6 control) experienced serious adverse events related to their underlying disease.

Table 4. Total incidence (%) and summary of adverse events (AE) occurring in >5% - safety population

Description of AE	Mirtazapine (n=115)	Control Product (n=115)
Total incidence	70 (60.9)	75 (65.2)
Vomiting	13 (11.3)	15 (13.0)
Pinnal erythema	12 (10.4)	20 (17.4)
Abnormal behavior	8 (7.0)	3 (2.6)
Vocalization	7 (6.1)	1 (0.9)
Dehydration	6 (5.2)	5 (4.3)
Heart murmur	5 (4.3)	7 (6.1)
Diarrhea	5 (4.3)	6 (5.2)

DISCUSSION

Enrolled cats had a variety of underlying conditions responsible for their weight loss that represent diseases commonly seen in veterinary practice including renal insufficiency, dental or periodontal disease, hyperthyroidism, and arthritis. It is common for these diseases to persist or progress resulting in continued weight loss requiring long-term treatment.

Of the 9 cats that died during the course of the study, 8 were euthanized due to progression of their underlying disease, 6 control and 3 mirtazapine treated cats. One cat with pre-existing cardiac disease, inflammatory bowel disease, and hyperthyroidism died at home.

The most common adverse event reported was vomiting and was likely due to the underlying disease (26.1% of enrolled cats had pre-existing vomiting). Incidence was similar in both treatment groups.

Local, transient erythema at the application site was also reported in both treatment groups (more frequent in control group) and could be expected with topical application on the inner pinnae of cats.

CONCLUSIONS

Mirtazapine transdermal ointment was effective in managing weight loss in cats.

Use of mirtazapine transdermal ointment resulted in a mean body weight gain of 4.07% compared to 0.29% for control after two weeks of transdermal treatment.

DISCLOSURES

Kristy Longpre, William Buhles, Ming Yin, Tianhua Hu, 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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