SINGLE DOSE PHARMACOKINETICS FOLLOWING TRANSDERMAL APPLICATION AND ORAL ADMINISTRATION OF MIRTAZAPINE OINTMENT IN CATS

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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

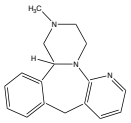
Mirtazapine is a noradrenergic and specific serotonergic antidepressant with antiemetic and appetite-stimulating properties. Its presynaptic α2- adrenergic receptor antagonism results in increased norepinephrine which likely contributes to its appetite stimulating effects [2].

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].

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 single dose pharmacokinetics (PK) of a novel formulation of mirtazapine transdermal ointment in cats.

METHODS

This study was a randomized, masked, cross-over single dose PK study.

Eight healthy purpose-bred cats were acclimated for 7-days.

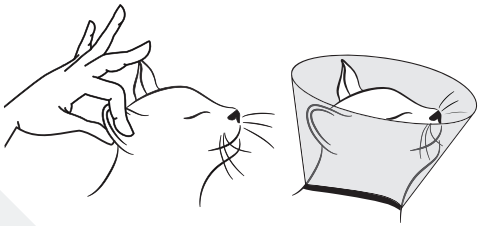
Baseline physical examination, hematology and serum chemistry were evaluated.

METHODS (CONT'D)

Application

Cats received 0.5 mg/kg by mouth (oral administration) or to the inner pinna (transdermal application). Following a 5-day washout, each cat received the alternate treatment.

All cats wore Elizabethan collars throughout the course of the study.



Assessments

Plasma was collected pre-dose and at 1, 2, 4, 6, 8, 12, 24, 48, 72 and 96 h after administration.

Mirtazapine concentrations were measured using an LC-MS/MS method.

The following PK parameters were calculated (via standard methods WinNonlin Professional 5.3) and statistically compared (via Wilcoxon Signed Rank test with significance set at $p < 0.05$).

- T_{max}: time to maximum (peak) concentration
- C_{max}: maximum (peak) concentration
- $T_{1/2}$: elimination half-life
- $AUC_{0-\infty}$: area under the concentration-time curve

RESULTS

Eight cats participated in the study.

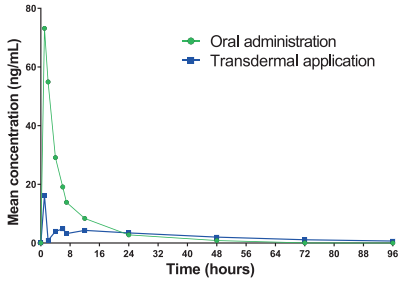
Mean age was 9.9 (6.0-12.3) years.

Cat #	Age (yr)	Gender	Day 0 Treatment	Day 5 Treatment
1	8.0	M	O	T
2	6.0	M	T	O
3	12.1	F	T	O
4	11.5	F	T	O
5	12.0	F	T	O
6	8.0	F	O	T
7	8.9	F	O	T
8	12.3	F	O	T

F = Female, spayed; M = Male neutered; T = Transdermal mirtazapine; O = Oral mirtazapine

RESULTS (CONT'D)

Figure 2. Mean plasma concentrations (ng/mL) of mirtazapine



Oral mirtazapine was rapidly absorbed from the gastrointestinal tract.

The absorption of transdermal mirtazapine was slower compared to oral administration.

The mean ± standard deviation relative bioavailability of transdermal mirtazapine compared to oral mirtazapine was 64.9%.

Table 1. Mirtazapine PK parameters

	Transdermal Application (n=8)		Oral Administration (n=8)		p-value
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	
T_{max} (h)	15.9 (15.6)	9.0 (1.0-48.0)	1.13 (0.35)	1.0 (1.0-2.0)	0.02†
C_{max} (ng/mL)	21.5 (43.5)	5.6 (2.1-129)	83.1 (31.2)	83.2 (43.4-128)	0.04†
$AUC_{0-\infty}$ (ng*h/mL)	260 (69.8)*	247 (204-397)*	434 (149.0)	494 (208-590)	0.09
T ½ (h)	26.8 (6.0)	27.4 (19.0-34.5)*	10.1 (4.2)	9.1 (4.7-17.0)	0.03†

SD=standard deviation; * n=6; $AUC_{0-\infty}$ was not calculated for 2 cats because the terminal elimination half-life could not be determined. † Statistically significant difference between oral and transdermal mirtazapine.

DISCUSSION

Absorption of mirtazapine was faster and more consistent following oral administration as compared to topical application.

The mean extent of absorption following oral administration was about 2-fold higher than following topical application of mirtazapine.

The longer apparent terminal elimination half-lives seen with topical versus oral administration appears consistent with 'flip-flop kinetics', which occurs when the rate of systemic absorption from the topical application site is slower than the rate of elimination from the systemic circulation.

CONCLUSIONS

Mirtazapine transdermal ointment applied to the inner pinna achieved measurable plasma concentrations in cats. Absorption of mirtazapine was faster, more consistent, and about 2-fold higher compared to transdermal application.

DISCLOSURES

Beasley Mason, William Buhles, Daizie Labelle, Donald Jung, Melinda Poole are/were employees/contractors of Kindred Biosciences, Inc. Jessica Quimby is a consultant for Kindred Biosciences, Inc.

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