MULTIPLE DOSE PHARMACOKINETICS OF MIRTAZAPINE TRANSDERMAL 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

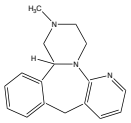
Mirtazapine is a noradrenergic and specific serotonergic antidepressant with antiemetic and appetite-stimulating properties. Its presynaptic α2-adrenergic receptor antagonism results in increased norepinephrine which likely contributes to its appetite stimulating effects [2].

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 multiple dose pharmacokinetics (PK) of mirtazapine in a novel ointment formulation following 14 days of transdermal application in cats.

METHODS

This study was a masked, randomized, three-arm parallel study to determine the plasma PK of two doses (0.5 and 2.0 mg/kg) of mirtazapine ointment applied transdermally once daily for 14 days.

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

Baseline physical examination, hematology and serum biochemistry were evaluated.

METHODS (CONT'D)

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

Application

Cats received 0.5 or 2.0 mg/kg mirtazapine transdermal ointment to the inner right pinna for 14 days per the randomization schedule.

Assessments

Blood was collected pre-dose and 1, 2, 4, 6, 8, 12, 24, 48, 72 and 96 h following the last dose.

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

Analyses

The following PK parameters were calculated (via non-compartmental 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

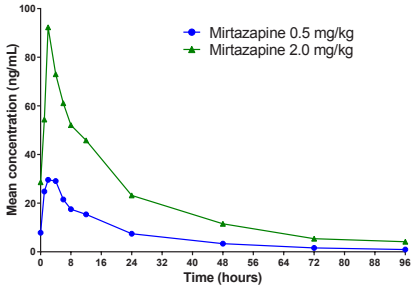
Twenty cats participated in the study (11 female, 9 male). Mean age was 8.65 years (range 6.2-13 years).

Table 1. Mirtazapine PK parameters

Treatment Groups	# of cats	Sex	Day -1 mean BW kg (range)
Control	4	2F / 2M	5.8 (4.6-7.0)
mirtazapine 0.5 mg/kg	8	5F / 3M	5.4 (3.8-7.1)
mirtazapine 2.0 mg/kg	8	4F / 4M	5.3 (4.0-7.3)

BW = Body Weight; F = female, spayed; M=male, neutered

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



RESULTS (CONT'D)

Table 2. Mirtazapine PK parameters

	0.5 mg/kg (n = 8)		2.0 mg/kg (n = 8)		p-value
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	
T_{max} (h)	2.1 (1.3)	2.0 (1.0-4.0)	3.0 (1.1)	3.0 (2.0-4.0)	0.2188
C_{max}(ng/mL)	39.6 (9.7)	40.9 (27.2-56.5)	98.2 (55.0)	73.9 (56.6-212)	0.0156
$AUC_{0-\infty}$ (ng*h/mL)	647 (225)	590 (453-1167)	2045 (525)	1778 (1576-2909)	0.1484
T ½ (h)	20.7 (4.0)	21.0 (15.8-25.5)	28.4 (8.6)	27.2 (20.3-47.5)	0.0156

Mean ± SD body weight for cats that received 0.5 mg/kg mirtazapine was 5.4 ± 1.1 kg prior to treatment and 5.7 ± 1.2 kg after 14 days of treatment.

Mean ± SD body weight for cats that received 2.0 mg/kg mirtazapine was 5.3 ± 1.1 kg prior to treatment and 5.7 ± 1.2 kg after 14 days of treatment.

Mean ± SD body weight for control cats was 5.8 ± 1.2 kg at baseline and 6.1 ± 1.2 kg after 14 days.

Mild redness of the pinna (application site) was noted in all control and treated cats, but no pinnal excoriation or ulceration was observed in any cat.

DISCUSSION

The absorption of both 0.5 and 2.0 mg/kg transdermal mirtazapine after 14 days was relatively consistent and rapid with a mean T_{max} between 2.1 to 3.0 h and mean C_{max} of 39.6 to 98.2 ng/mL, respectively.

Mean terminal half-lives were similar between the 0.5 and 2.0 mg/kg groups (20.7 and 28.4 hours, respectively).

In the 0.5 mg/kg group, average concentration over the dosing interval was 16.4 ng/mL and the mean fluctuation in plasma concentrations over the dosing interval was 210%.

In the 2.0 mg/kg group, average concentration over the dosing interval was 47.4 ng/mL and the mean fluctuation in plasma concentrations over the dosing interval was 142%.

Weight gain was seen in both groups receiving mirtazapine but statistical comparison was not performed in this pilot study.

As age and kidney affect pharmacokinetics of oral mirtazapine, a possible limitation of the study is the variable age of the cats and unknown urine specific gravity. However it is not known if age and early kidney disease affect the pharmacokinetics of transdermal mirtazapine in the same manner.

CONCLUSIONS

The daily transdermal administration of mirtazapine ointment for 14 days achieved clinically relevant concentrations in cats and results in weight gain.

Mean terminal half-lives were similar between the 0.5 and 2.0 mg/kg groups (20.7 and 28.4 hours, respectively).

DISCLOSURES

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

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