Determination of mirtazapine 2% ointment dislodged upon petting following repeated topical (transdermal) administrations in cats

Authors

Olivier Szkuta[1], Melinda Poole O'Banion[2], Mireille Vila[1], Michela Cantiello[1]

[1]Avogadro LS, France; [2]Kindred Biosciences, Inc, USA

Introduction

Mirtazapine is an antagonist of three serotonin (5-HT2A, 5-HT2C and 5-HT3) and histamine (H1) receptors primarily used to treat depression in humans. Mirtazapine also has anxiolytic, sedative, antiemetic, and appetite stimulant proprieties.

Mirtazapine is used in cats to increase food intake and weight gain and decrease vomiting to allow a better recovery after surgery or during some chronic disease. A mirtazapine transdermal ointment was developed to overcome difficulties of repeated oral administration in cats with dysorexia or vomiting. However, the potential for unintentional dermal and subsequent oral hand-to-mouth drug exposure to care takers or others in the household as a result of petting their cat following transdermal application of mirtazapine was unknown and had to be evaluated to make a quantitative user risk assessment.

The purpose of this study was to determine the amount of mirtazapine residues dislodged by petting treated cats following 14 repeated daily application of a mirtazapine transdermal ointment.

Materials and Methods

Animals and treatments

Eight female domestic shorthair cats ranging in age from 13 – 14.5 months and weighing between 3.0 and 4.5 kg received a daily dose of 2 mg mirtazapine transdermal ointment (0.1 mL ointment; 2% mirtazapine) applied to the inner pinna of the right ear for 14 consecutive days. Cats were individually housed to avoid cross-contamination and were observed daily throughout the study.

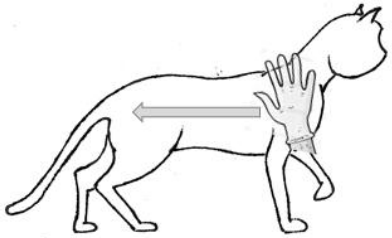
Petting procedures

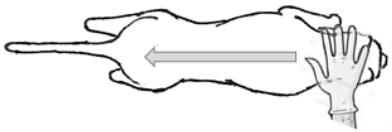
Petting procedures were performed before the first application (pre-dose) and 0.5h, 1h, 2h, 4h, 8h, 12h, 24h, 48h and 96h after the last application. Dye free 100% cotton gloves were used to collect the dislodgeable residues. At each sampling time and for each location (ear and body), one cotton glove was placed over a nitrile protective glove on a mannequin hand.

The inner (anterior) surface of the pinna of the right ear was stroked with the mannequin index with uniform medium pressure from the base of the ear to the apex. The sample from each time interval on each cat included 20 petting simulations, which consisted of 20 strokes.

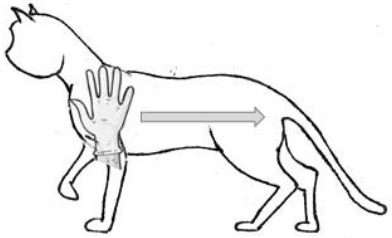
The body surfaces were stroked with the palmar surface of the mannequin hand with uniform medium pressure running with the lay of the cat hair coat for 20 strokes including each side along the ribcage and along the back from the base of the head/neck to the tail.

Ear Petting





Body Petting



Samples Processing

Excessive hair removal

+ Methanol

Agitation

Solvent aliquoting

-80°C

Samples Analysis

Mirtazapine residues were assayed in the cotton gloves using a validated HPLC/MS/MS method with a LLOQ of 250 ng/glove. Control gloves (no drug) were used for the calibration standard and quality control (QC) samples for the specimen analysis. The system suitability, the interference check, the calibration curves and the precision of the QC samples were within acceptable limits for all analytical runs.

Study parameters

The Percent Dislodgeable Residue (PDR), defined as the percent of the daily applied dose of the drug removed (i.e., dislodged) from the cat upon petting, was determined for each sample and averaged for each sampling time point.

Results

Clinical observations

Redness of the ear and in rare cases a slight amount of blood on the sampling glove was observed in the first 24h sampling. This irritation was likely caused by excessive petting to a sensitive portion of the ear, as occurred most dramatically on the first day of sampling post dosing and resolved when petting intensity reduced.

Percent Dislodgeable Residue

Time after last administration	Mean mirtazapine percent dislodgeable residue (% ± SD)	
	Ear petting	Body petting
Pre-dose	0	0
0.5 h	19.95 ± 10.64	0.51 ± 0.31
1 h	2.37 ± 1.90	0.12 ± 0.12
2 h	1.24 ± 0.85	0.29 ± 0.16
4 h	0.50 ± 0.28	0.16 ± 0.11
8 h	0.23 ± 0.16	0.08 ± 0.05
12 h	0.08 ± 0.06	0.05 ± 0.02
24 h	0.04 ± 0.03	0.03 ± 0.01
48 h	0.03 ± 0.04	0.01 ± 0.01
96 h	0	0

Table 1: Mean mirtazapine percent dislodgeable residue (± SD) vs sampling time

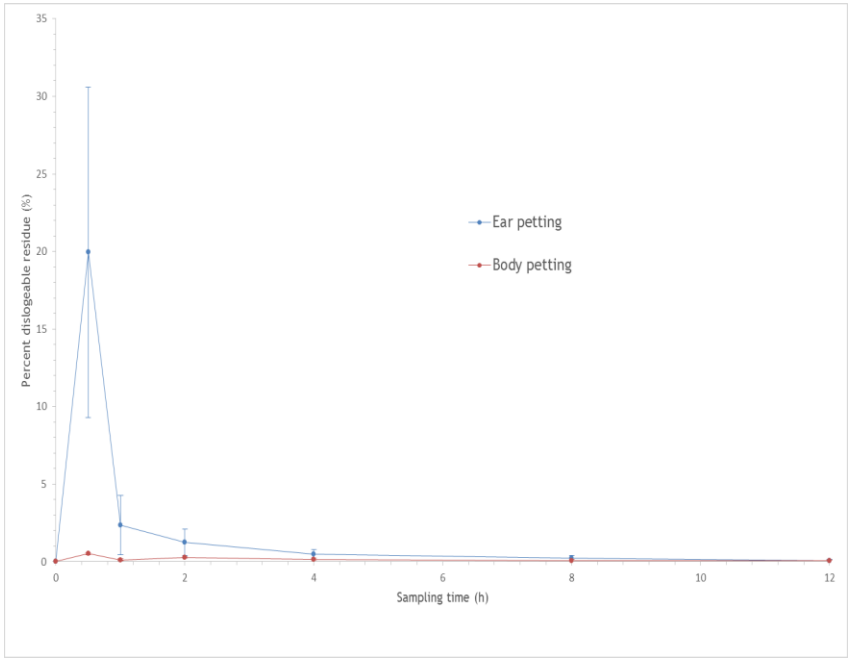


Figure 1: Mean mirtazapine percent dislodgeable residue (± SD) vs sampling time (first 12h)

Conclusion

Residues of mirtazapine from body petting following application of 2 mg of mirtazapine transdermal ointment to the inner pinna of the ear for 14 consecutive days in cats were low (lower than 1.0% of the daily administered dose whatever the cat) from 0.5 h after the last administration. For ear petting, the residues were high (around 20% of the daily administered dose) at 0.5h after the last administration, then reduced to on average 2.37% from 1 h after the last administration.