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Drug exposure and clinical effect of transdermal mirtazapine in healthy young cats: a pilot study

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Abstract

Objectives—Measure drug exposure and clinic effects after administration of transdermal mirtazapine (TMZ) in healthy cats.

Methods—Phase I: Seven healthy research cats received A) 3.75 mg and 7.5 mg TMZ once aurally with 48 hour serum sampling (serum samples were obtained via jugular catheter at 0, 0.5, 1, 2, 5, 9, 12, 24, 36 and 48 h), B) 7.5 mg TMZ and placebo daily aurally for six days then 48 h serum sampling C) 1.88 mg mirtazapine orally once with serum sampling at 1, 4 and 8 h. Phase II: Twenty client-owned cats were enrolled in a randomized double-blind placebo-controlled three-way crossover clinical effect study. Treatments consisted of six days of aural 7.5 mg TMZ or placebo gel at home, and 1.88 mg mirtazapine orally once in clinic. Owners documented appetite, rate of food ingestion, begging, activity and vocalization daily at home. On day six, food consumed, activity and vocalization were documented in hospital and trough and peak serum mirtazapine levels obtained. Serum mirtazapine and gel concentrations were measured using liquid chromatography/tandem mass spectrometry.

Results—Phase I: Administration of TMZ achieved measureable serum mirtazapine concentrations. $AUC_{0\text{-}48}$ of multidose 7.5 mg TMZ was significantly higher than single dose 1.88 mg OMZ ($P = 0.02$). Phase II: Client-owned cats administered TMZ had a significant increase in appetite ($P = 0.003$), rate of food ingestion ($P = 0.002$), activity ($P = 0.002$), begging ($P = 0.002$) and vocalization ($P = 0.002$) at home. In hospital there was a significant increase in food ingested with both TMZ and OMZ compared to placebo ($P < 0.05$). Gel concentrations ranged from 87%–119% of target dose.

Conclusions and relevance—7.5 mg daily TMZ achieves measureable serum concentrations and significant appetite stimulation despite variance in compounded gel concentrations, but side effects denote a lower dose is indicated.

Keywords

feline; appetite stimulant; remeron; transdermal; compounding

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Conflict of interest The authors do not have any potential conflicts of interest to declare.

Introduction

Although originally developed as a human antidepressant, mirtazapine has become widely used as an appetite stimulant in veterinary medicine. The mechanism of action for appetite stimulation is not well described and may involve antagonism of the $5HT_{2c}$ receptor, which is known for its appetite inhibition activity as well as antagonism of the H_1 receptor which also plays a role in appetite regulation.[1,2] Antagonism of the $5\text{-}HT_3$ receptor, which is an important receptor in the physiology of emesis, is likely responsible for mirtazapine's anti-emetic properties, and may also serve to palliate inappetence.[3]

Mirtazapine is frequently used in feline patients with acute and chronic diseases experiencing dysrexia. Not all feline patients are amenable to oral administration of medications and this often becomes a source of frustration for a feline owner that ultimately affects the human-animal bond. The use of mirtazapine in a transdermal gel form is appealing in order to ease stress of application for owners and ultimately benefit more feline patients. The question then becomes if mirtazapine can be absorbed via the transdermal route. Lipinksi's "Rule of Five" describes the four physiochemical parameters of an oral drug that predict the likelihood of its absorption and permeation.[4] Poor absorption or permeation is expected if: 1) >5 hydrogen bond donors are present; 2) the molecular weight (MW) is over 500 Daltons; 3) the log p >5 (n-octanol/water partition coefficient, i.e. lipophilicity); and 4) >10 hydrogen bond acceptors are present.[4]

If two of the four parameters are out of range, then poor absorption and permeability is expected.[4] In a recent retrospective analysis of various ophthalmic, inhaled and transdermal medications, transdermal delivery systems appear to require more stringent properties for absorption as the stratum corneum is highly selective.[5] Based on this retrospective analysis, the investigators statistically developed stricter thresholds of the physiochemical parameters for transdermal drug systems which include the following modifications to the "Rule of Five": 1) <2 hydrogen donors; 2) MW < 335 Daltons; 3) log p <5; 4) <5 hydrogen acceptors.[5] Mirtazapine has no hydrogen donors, is of appropriate size at 265 Daltons, has a coefficient of log P 2.9–3.2, and has only three hydrogen acceptors, making it theoretically suitable to transdermal administration (http://www.drugbank.ca/drugs/DB00370). The purpose of this study was to assess whether transdermal mirtazapine (TMZ) achieves therapeutic serum concentrations and results in a clinical effect in healthy cats. Specific aims to explore this objective included a) to determine whether drug exposure after administration of single dose TMZ (3.75 mg and 7.5 mg) was similar to administration of single dose oral mirtazapine in healthy research cats b) to determine how drug exposure changes after daily administration of TMZ in healthy research cats, c) to assess the clinical effect of TMZ in client-owned cats in the home and hospital environment and d) to compare the drug exposure of client-owned cats to that of research cats after daily administration of TMZ.

Materials and Methods

Drug Preparation

All mirtazapine and placebo transdermal gels were prepared at the Colorado State University Veterinary Teaching Hospital (CSU VTH) Pharmacy by a single individual. TMZ gels for

Phase I were prepared using USP grade mirtazapine powder (Sigma Aldrich, St. Louis. MO) in Lipoderm gel (Professional Compounding Centers of America, Houston, TX). Due to the significant cost of USP grade powder subsequent TMZ gels for Phase II were prepared using pharmaceutical grade mirtazapine powder (Attix Pharmaceuticals, Toronto, ON: NDC# 75839-108-00; Batch 131218 certificate of analysis: 99.5%: meets specifications) in Lipoderm gel. For dosing of oral mirtazapine, generic mirtazapine (Aurobindo Pharma, Dayton, NJ) was compounded into a 1.88 mg capsule by the CSU VTH Pharmacy according to Professional Compounding Centers of America protocol. The method used is theoretically guaranteed to produce accurate compounding to within 10% of the target dose.

Phase I

The specific aims of Phase I were a) to determine whether drug exposure after administration of single dose TMZ (3.75 mg and 7.5 mg) was similar to administration of single dose oral mirtazapine in healthy research cats and b) to determine how drug exposure changes after daily administration of TMZ in healthy research cats. Seven healthy research cats with unremarkable physical examination, CBC, chemistry and urinalysis were used. All portions of the project were approved by the Institutional Care and Use Committee at Colorado State University. For all serum sampling studies a jugular catheter was placed under ketamine/butorphanol sedation (20 mg ketamine/cat intravenous, 0.1 mg/kg butorphanol intravenous) 16 h prior to study initiation for ease of sample collection. Procedures consisted of A-D. A) 3.75 mg/0.1 ml TMZ was administered once aurally to four cats with 48 h serum sampling. Serum samples were obtained via jugular catheter at 0, 0.5, 1, 2, 5, 9, 12, 24, 36 and 48 h. All four cats received Lipoderm gel compounded with USP mirtazapine powder. B) 7.5 mg/0.1 ml TMZ was administered once aurally to five cats with 48 h serum sampling. Serum samples were obtained via jugular catheter at 0, 0.5, 1, 2, 5, 9, 12, 24, 36 and 48 h. All five cats received Lipoderm gel compounded with USP mirtazapine powder. C) 1.88 mg mirtazapine was administered orally once to seven cats with limited serum sampling at 1, 4 and 8 h. D) 7.5 mg/0.1 ml TMZ was administered daily aurally, rotating ears, to seven cats for six consecutive days then 48 hour serum sampling was performed. Mirtazapine was last administered aurally on the morning the serum sampling started. Serum samples were obtained via jugular catheter at 0, 0.5, 1, 2, 5, 9, 12, 24, 36 and 48 h, and in four cats samples were also obtained at 60 and 72 h. All seven cats had Lipoderm gel compounded with bulk mirtazapine powder. A washout period of at least one week was present between each experiment in Phase 1.

Phase II

The specific aims of Phase II were a) to assess the clinical effect of TMZ in client-owned cats in the home and hospital environment and b) to compare the drug exposure of client-owned cats to that of research cats after daily administration of TMZ. This was a randomized, double-blinded, placebo-controlled crossover study. Twenty apparently healthy cats recruited from the student pet population with unremarkable physical examination, CBC, chemistry and urinalysis were enrolled. All portions of the project were approved by the Institutional Care and Use Committee at Colorado State University and owners gave informed consent before participation. Each cat received three total treatments in a pre-randomized order: transdermal placebo (TP), TMZ and oral mirtazapine (OMZ) with at least

a seven-day wash-out period. Randomization was determined by assigning each treatment a number and using an online random order generator to randomly determine each cat's treatment sequence (List Randomizor; Randomness and Integrity Services Ltd; https://www.random.org/lists/). For the two transdermal treatments, owners applied 0.1ml of gel, containing either placebo or mirtazapine to alternating ears for six consecutive days (without wiping off the ears). Protective gloves were provided and were discarded after each use. Owners completed daily questionnaires to record appetite, activity level, begging and vocalization (Appendix 1). On day seven, cats were brought to the CSU VTH. A baseline behavioral assessment was performed by a single blinded observer for each cat (Appendix 2). A blood sample was collected for serum mirtazapine concentration. The gel was then applied as described above. After application of the gel, one-half cup of the cat's usual food was weighed with a gram scale (Ohaus Scout Pro SP202, Ohaus Corporation, Parsippany, NJ) and was provided in the cage. A second blood sample was collected one hour after gel administration. Behavioral assessments and food weights were performed at one-hour intervals for eight hours by a single blinded observer. For administration of OMZ, cats were brought to the CSU VTH and a baseline behavioral assessment performed. Cats received 1.88 mg OMZ followed by 3 ml water administered by a syringe. Blood was collected one hour after OMZ capsule administration for serum mirtazapine concentration. The cat's pre-weighed one-half cup food was provided after blood collection. Behavioral assessment and food weight was monitored at one-hour intervals for eight hours by a single blinded observer. Administration of medication for all three treatments was performed by a single individual who was not involved in scoring the cats. Serum alanine aminotransferase (ALT) was performed at the CSU Diagnostic Laboratories on samples from the day of in hospital assessment after daily transdermal mirtazapine administration.

Mirtazapine analysis

Mirtazapine was measured using liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS) as previously described.[6] The analysis was carried out in the Pharmacology Core at the CSU VTH.

Gel concentration analysis

Mirtazapine concentration was analyzed in all TMZ gels compounded for use in Phase I and II studies. Additionally, the mirtazapine concentration of four TMZ gels purchased from commercial compounding pharmacies were analyzed. To confirm transdermal gel concentration, approximately 10 mg of dosing solution gel was diluted 1:100 with solution of 50:50, ACN:Milli-Q (v:v). Samples were vortex mixed, sonicated for 5 mins, diluted an additional 1:10,000 with 50:50, ACN:Milli-Q. In total, samples were diluted 1:1 ×10^6 and quantified using a standard curve of mirtazapine prepared in 50:50, ACN:Milli-Q using the LC/MS/MS method described previously.[6]

Drug exposure analysis

Due to the nature of the transdermal medication, standard pharmacokinetic analysis was not possible. Instead, a drug concentration curve was generated and Prism software (GraphPad Software, Inc., La Jolla, CA, USA) was used for calculation of $AUC_{0\text{-}48}$ from administration of 3.75 mg single dose TMZ, 7.5 mg single dose TMZ and 7.5 mg multiple dose TMZ. For

development of a limited-sampling model of mirtazapine exposure following oral administration, the mirtazapine serum concentration versus time data for five cats administered a fixed 1.88 mg oral dose was utilized for calculation of drug exposure ($AUC_{0\text{-}\infty}$) by noncompartmental methods. The resulting AUC values were analyzed as a response to time point mirtazapine concentration values as a predictor by best subset multiple linear regression. This method evaluates all single time points as well as all possible combinations of multiple time points (2, 3, 4, 5, 6, or 7) as predictors of the outcome ($AUC_{0\text{-}\infty}$). Data utilized in the best subset linear regression analysis were those time points corresponding to post-administration samples and were designated as 15, 30, 60, 240, 480 and 1140 corresponding to the number of minutes the samples were collected after administration. The combination of statistical correlation and number of samples required were considered in choosing the optimal limited-sampling scheme. The results of best subset multiple linear regression revealed that using three points as predictors of $AUC_{0\text{-}\infty}$ (60, 240 and 480 mins) could provide the best combination of statistical correlation ($r^2 = 0.995$) while minimizing sample number. The final model utilizing the identified time points is described by the equation:

$$\mathrm{AUC}_{0-\infty}=6870.2+106.4(\mathrm{C}_{60\mathrm{min}})-196.7(\mathrm{C}_{240\mathrm{min}})+1404.9(\mathrm{C}_{480\mathrm{min}})$$

where C_{60min}, C_{240min} and C_{480min} represent the serum concentrations at 60, 240 and 480 minutes respectively, following oral administration. AUC predictions for seven cats administered an oral dose of mirtazapine in Phase I (D) were generated with the previously described limited sampling model.

Statistical analysis

Phase I: All regression analysis for the limited-sampling model development was carried out using Minitab® v 16 software (Minitab, State College, PA, USA). $AUC_{0\text{-}48}$ from administration of 3.75 mg single, 7.5 mg single and 7.5 mg multidose TMZ and OMZ was compared using Wilcoxon Matched pair test (ANOVA could not be performed as not all cats participated in each category of dose administration).

Phase II: Prism software (GraphPad Software, Inc., La Jolla, CA, USA) was used for analysis. Daily scores were calculated as follows: an increase in appetite or activity, begging or vocalization behaviors received a score of one (1), a decrease received a score of negative one (−1) and no change received a score of zero (0). The individual observation scores for the six days were summed, resulting in a total score. Owner observation scores between TMZ and TP were compared using a Wilcoxon Matched Pair test. Percent food ingested between TMZ, TP and OMZ while in hospital was compared using a Friedman test with Dunn's post-hoc comparison. Data were assessed for normality using D'Agostino & Pearson normality test and were not found to be normally distributed hence non-parametric tests were used for analysis. For all analyses, a *P* value of <0.05 was considered to be statistically significant.

Results

Phase I

All seven cats were domestic shorthairs: four neutered males and three spayed females. Ages ranged from 1–2 years (median 2 years) and weights ranged from 3.2–6.2 kg (median 5.0 kg). Mirtazapine concentrations were measurable in serum after all TMZ administrations. TMZ did not display a typical drug concentration curve, rather maintained a steady state serum concentration for at least 48 h after administration (Figure 1). In four cats who had serum levels obtained at 60 and 72 h, mirtazapine was still detectable. The $AUC_{0\text{-}48}$ of multidose 7.5 mg TMZ was significantly higher than single dose 1.88 mg OMZ ($P = 0.02$), and approached being significantly higher than single dose 7.5 mg TMZ ($P = 0.06$) (Figure 2). There was no significant difference in $AUC_{0\text{-}48}$ between administration of single dose 3.75 mg TMZ, single dose 7.5 mg TMZ and single dose 1.88 mg OMZ. The median trough and peak serum mirtazapine concentration after multidose 7.5 mg TMZ administration and the median peak serum mirtazapine concentration after single dose 1.88 mg OMZ are summarized in Table 1.

Overall TMZ gel concentrations for Phase I varied by 75–116% of target dose. Gel concentrations of mirtazapine for each treatment and the four commercial compounding pharmacies are summarized in Table 2.

Phase II

Of the twenty cats enrolled in the clinical effect study twelve cats were spayed females and eight were neutered males. Breeds included nine domestic shorthairs, ten domestic longhairs and one Siamese. Ages ranged from 1–7 years (median 2 years). Weights ranged from 2.86–7.19 kg (median 4.65 kg). Four cats were excluded from blood collection for serum mirtazapine levels but participated in all other aspects of the study: One cat was excluded from blood collection due to participation in the blood donor program and three cats were excluded due to demeanor during venipuncture. Due to incomplete questionnaire data some cats were excluded from some statistical analysis of the home scores. Two cats were excluded from the appetite and activity score analysis, one cat was excluded from the rate of ingestion score analysis and three cats were excluded from the begging score and vocalization analysis.

When 7.5 mg TMZ was given daily at home, there was a statistically significant increase in appetite scores ($P = 0.003$; Figure 3) and rate of food ingestion scores ($P = 0.002$; Figure 4). There was also a statistically significant increase in undesired effects such as, begging scores ($P = 0.002$; Figure 5), vocalization scores ($P = 0.002$; Figure 6) and activity scores ($P = 0.002$) of TMZ when compared to TP. Two cats were observed by owners to have a significant increase in undesirable food-seeking behavior. While cats were observed in hospital after six days of 7.5 mg TMZ administration, there was a statistically significant increase in percent food ingested compared to TP ($P < 0.05$). A statistically significant difference increase in percent food ingested was also seen after administration of OMZ in hospital in comparison to placebo ($P < 0.05$). (Figure 7). There was no statistically significant difference between TMZ, TP and OMZ for interaction scores and vocalization

scores in hospital. Two cats were significantly vocal regardless of treatment arm. No tremors or twitching were observed during the 8 h observation period.

The median trough and peak serum mirtazapine concentrations for client-owned cats after multidose 7.5 mg TMZ administration and median peak serum mirtazapine concentration after single dose 1.88 mg OMZ are described in Table 1. Overall TMZ gel concentrations for Phase 2 varied by 87 – 119% of target dose and are detailed for comparison in Table 2. Serum ALT for 17 of the cats after six days of daily TMZ administration ranged from 21–97 IU/L (Reference Interval 30–140 IU/L).

When trough and peak serum mirtazapine concentrations were compared between the healthy research cat multidose 7.5 mg drug exposure study and the client-owned cat multidose 7.5 mg clinical effect study, client-owned cats had significantly higher peak ($P = 0.02$) and trough ($P = 0.02$) serum mirtazapine levels (Figure 8). However, the analyzed TMZ gel concentration was also significantly higher in the clinical effect study than in the drug exposure study ($P = 0.02$).

Discussion

The purpose of this pilot study was to determine if mirtazapine is amenable to transdermal application and is effective in stimulating appetite in healthy cats. Results indicated that administration of a single 3.75 mg or 7.5 mg TMZ dose achieved serum concentrations similar to administration of 1.88 mg oral mirtazapine, while repeated daily dosing of 7.5 mg TMZ resulted in significantly higher drug exposure after six days. Serum concentrations after administration of TMZ were relatively consistent over at least a 48 h period in comparison to OMZ which leads to an initial spike in serum drug concentration followed by elimination (Figure 1). In the clinical effect study in client-owned cats the efficacy of TMZ as an appetite stimulant was demonstrated by a statistically significant increase in food consumption in both the home and hospital setting in comparison to placebo. At a dose of 7.5 mg given daily for six consecutive days, a significant number of the cats were observed by their owners to have an increase in their appetite and rate of food ingestion. However cats also showed a significant increase in undesirable side effects such as increased vocalization, begging behavior and increased activity with two cats subjectively showing a marked increase in their food seeking behaviors, indicating a lower dose would be more appropriate. Significant variation from target dose was documented in the TMZ gel preparations, highlighting known concerns with compounding medications. However, this study still provides evidence that transdermal mirtazapine could be beneficial for sick cats who are not amenable to pill administration. Additional studies are necessary to determine optimal dosing.

Concerns with the compounding of veterinary and human medications have received a significant amount of press recently, but are not a new concept.[7,8] Consistency and purity of product, bioavailability and efficacy are largely unproven for literally hundreds of transdermal medications potentially available from commercial pharmacies. These issues were certainly prominent in the current study with marked variability in TMZ concentrations both in gels prepared at CSU VTH Pharmacy and by commercial pharmacies. However,

once this issue was identified in Phase I, Phase II gels were able to be prepared much closer to target simply with awareness and attention to the duration of gel mixing during the compounding process. Earlier pilot studies involved making a compounded product with the FDA approved tablet in a pluronic lecithin organogel (PLO) gel. Although this product achieved measurable serum concentrations, use of tablets resulted in inconsistencies in the gel due to the percentage of excipient that made both accurate application and analysis of gel concentration challenging. For the purposes of the study and proof of concept it was therefore deemed necessary to use a bulk mirtazapine powder. Current FDA recommendations are that compounding of drugs from bulk substances is acceptable when the FDA approved product is demonstrated to result in inefficacy.[9] However the USP powder product was prohibitively expensive for large-scale use and could only be used for initial exploration studies. A pharmaceutical grade powder was located and was successfully and effectively used, but subsequent to the finish of the study this product was recalled for possible penicillin contamination. Therefore despite the promising efficacy of TMZ in these pilot studies, recommendations for cautious and judicious use (i.e only when no other option exists) of compounded transdermal medications are only strengthened by the study results.

Based on the limited pharmacokinetic data of other veterinary drugs used for transdermal delivery, it is assumed that the bioequivalence and duration of action is not equivalent to the oral or intravenous form of the drug due to some degree of dermal metabolism and properties of the vehicle for delivery.[10] Previous single-dose pharmacokinetic studies of transdermal medications in cats have shown low bioavailability compared to a single oral dose.[11–13] Previous anecdotal experience with transdermal mirtazapine at the equivalent oral dose of 1.88 mg implied little clinical effect. Therefore for this study, two higher doses of transdermal mirtazapine, 3.75 mg (equivalent to one quarter of 15 mg tablet) and 7.5 mg (equivalent to one half of 15 mg tablet) were explored. In addition, single-dose pharmacokinetics are likely not appropriate for evaluating transdermal delivery systems, a concept that was supported by a study assessing transdermal amlodipine in cats where repeated transdermal dosing resulted in a clinical response.[8] Therefore in this study both single dose and multiple dose pharmacokinetics were evaluated. It was indeed confirmed that multiple dose regimen significantly increases drug exposure. In retrospect also assessing repeated dosing of 1.88 mg and 3.75 mg TMZ would have been ideal as, in comparison to other transdermal medications that have been studied, mirtazapine appears to be relatively more bioavailable even with a single dose.

The dose for the clinical effect study in client-owned cats (7.5 mg) was initially chosen based on the results of the drug exposure study in healthy research cats. However, the significant increase in mirtazapine serum levels in client-owned cats in comparison to healthy research cats was not anticipated and implies a lower dose would be more appropriate. Lower serum concentrations after daily dosing in healthy research cats could have been present for a number of reasons. Firstly the presence of ear tattoos in the healthy research cats could have affected drug uptake and this was the reason the design of the clinical effect study in client-owned cats included obtaining serum levels, which in retrospect was quite important. Secondly, the blood samples were taken from the healthy research cats via indwelling jugular catheter and from the client-owned cats via direct jugular venipuncture in the hospital setting. Either the excitement of the journey to the

hospital and/or the venipuncture process could have resulted in increased aural circulation and increased drug absorption. Lastly, there was a statistically significant difference in the gel concentrations between the two groups which could have resulted in the difference. Regardless of the cause the end result was that the dose necessary for appetite stimulation was likely overestimated in the clinical effect study.

Future studies aimed at dose titration are warranted to decrease undesirable side effects (vocalization, begging behavior, activity level, obsessive food seeking behavior). While the doses explored in this study did achieve adequate serum levels and appetite stimulation in healthy cats, side effects seen in the clinical effect study in the home environment indicate that a lower dose would be more appropriate. Additionally more information is needed to determine the appropriate dose for cats with illnesses and geriatric cats. Cats with chronic kidney disease have been shown to have a prolonged half-life of mirtazapine and therefore require a lower dose and increased dosing interval and the doses used in this pilot study are unlikely to be appropriate for this patient group.[14] Other factors that could contribute to alterations in transdermal drug delivery include concurrent illness, hydration status and stratum corneum health. These factors may play an additional role when exploring the use of transdermal mirtazapine in geriatric ill cats.[10]

This study has a few limitations which should be taken into account when interpreting the results. Serum samples to determine drug exposure were obtained via jugular catheter or jugular venipuncture and may have been falsely elevated due to proximity to the ear, a finding described in a recent study of buccal mucosal absorption of buprenorphine utilizing sampling from 10 cm jugular catheters in feline subjects.[15] In Phase 1 of the current study, significantly longer 32 cm long-line jugular catheters were utilized in the healthy research cats, while direct venipuncture was utilized in client-owned cats in Phase II. It is unknown if the longer jugular catheters used in the current study would produce similar biased results as the previous report. However, the difference between use of jugular catheters in the healthy research cats and direct venipuncture in client-owner animals does provide an additional explanation for why drug exposure concentrations may have been higher in client-owned cats. Placement of jugular or other long-line catheters in client-owned cats for the purpose of the study was not clinically feasible.

Phase I procedures were performed as sequential pilot studies and a randomized cross over of treatment arms was not performed. This may have had an unappreciated effect on the results of this portion of the study. Despite non-randomization and the use of multiple sources of mirtazapine, it was elected to include the data gathered in this portion of the study because it demonstrates that transdermal mirtazapine reaches serum concentrations resulting in a clinical effect regardless of the source of mirtazapine or gel utilized. Current commercially available transdermal mirtazapine gels use a variety of mirtazapine sources and gel types.

Despite repeated efforts of the CSU VTH pharmacy staff and utilization of techniques approved by Professional Compounding Centers of America as standard protocol for gel compounding, not all tested gel samples fell within the stipulated guidelines of 10% of target dose (however accuracy was superior to products tested from commercial pharmacies). As

the purpose of this study was to inform the practitioner of the possible utility of the currently available transdermal mirtazapine gel product, and not technological development, further effort was not made to develop a solution to this problem. The end result of this study was appreciable drug levels in the cat and a significant clinical effect which may be beneficial to patients with no other feasible option for appetite stimulation. Given the inherent variability of delivery methodology (varied syringe dispensing and application with glove to pinna by a pet owner) it should also be considered that testing performed on the gel is likely not representative of what is available for absorption by the cat; transdermal gel application is currently an inexact science at best.

Conclusion

Mirtazapine is amenable to administration in a transdermal gel and achieves therapeutic serum levels. Despite variability in compounded gel concentrations, transdermal mirtazapine administered at a dose of 7.5 mg daily resulted in significant increases in appetite, but resulted in undesirable dose-related side effects. It was therefore concluded that the transdermal dose necessary for appetite stimulation was likely over estimated and future dose titration studies for elderly and diseased patient populations are necessary to optimize efficacy while minimizing side effects.

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Appendix 1: At-Home Assessment

Cat's Name:_____

Date: _____

Treatment Group: _____

Did you apply the transdermal gel today? Yes No

Time of application:

Which ear was the gel applied to? Right ear Left ear

Did your cat tolerate receiving the medication? Yes No

Did you notice any redness or irritation of the ears? Yes No

Describe your cat's appetite today: Decreased Unchanged Increased

How quickly did your cat eat his/her food today? Slower than normal Unchanged Faster than normal

Describe your cat's activity level today: Decreased Unchanged Increased

Described your cat's begging/food seeking behavior today: Decreased Unchanged Increased

Described your cat's vocalization behavior today: Decreased Unchanged Increased

Did you notice any unusual behavior today? Yes No

Appendix 2: Behavioral Assessment

Interaction

1. Hiding/sits at back of cage
2. Gets up to greet you when cage is opened
3. Soliciting attention at front of cage

Vocalization (meows per minute)

1. 0–10
2. 10–15
3. 15+

Activity

1. Sedentary/Hiding
2. Walking around normally
3. Frantic/hyperactivity

Tremors

1. None
2. Mild twitch/bobble (subtle)
3. Noticeable head bobble or twitching

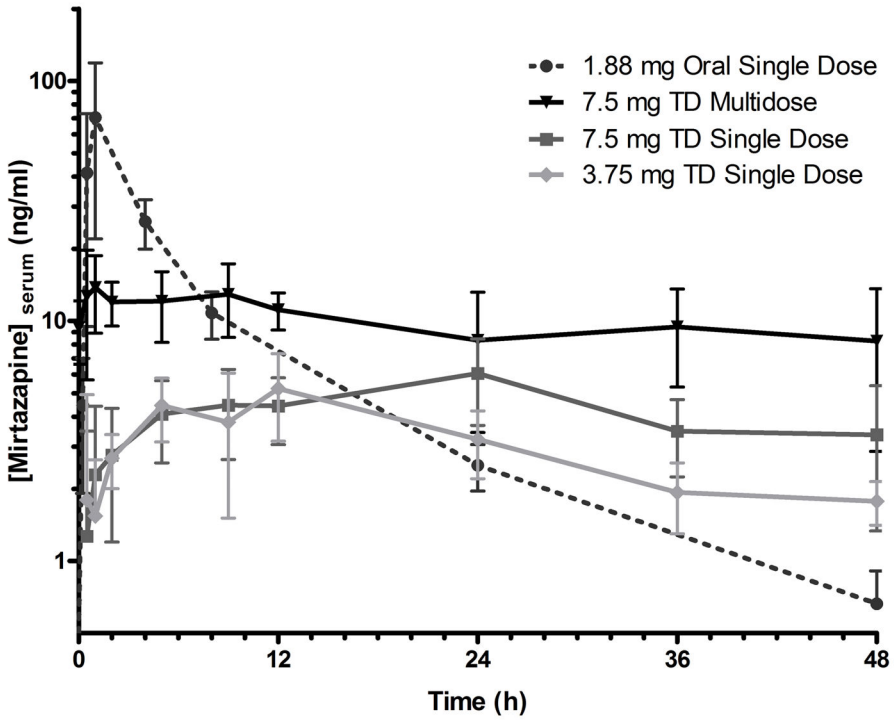

Figure 1.

Serum mirtazapine concentration curve (+/− SD) after administration of single dose 3.75 mg transdermal mirtazapine (TMZ), single dose 7.5 mg transdermal mirtazapine, single dose 1.88 mg oral mirtazapine (OMZ) and multiple dose 7.5 mg transdermal mirtazapine to healthy research cats. Serum concentrations after administration of TMZ were relatively consistent over at least a 48 hour period in comparison to OMZ which shows an initial spike in drug concentration followed by a typical drug concentration curve.

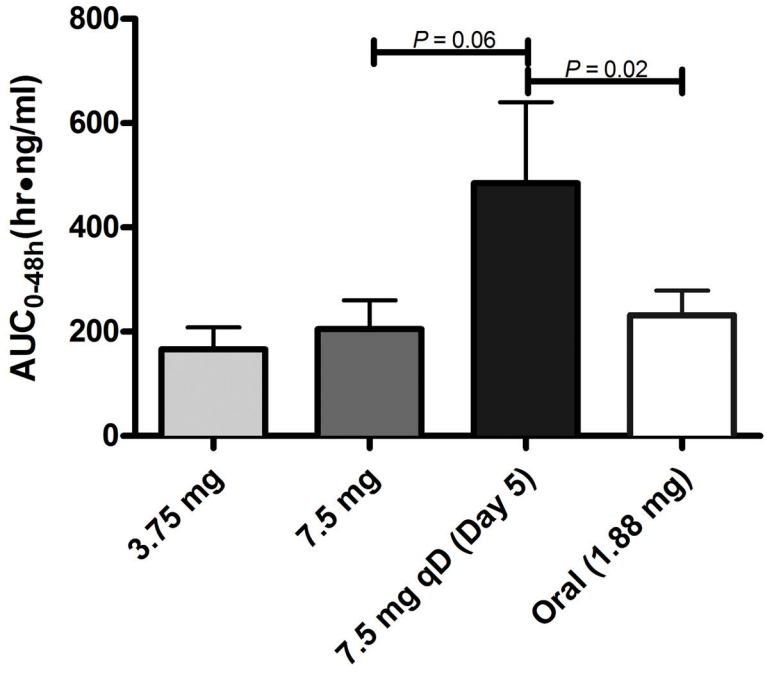

Figure 2.

Comparative calculated serum mirtazapine exposure over 48 h after single dose 3.75 mg transdermal mirtazapine (TMZ), single dose 7.5 mg transdermal mirtazapine, single dose 1.88 mg oral mirtazapine (OMZ) and multidose 7.5 mg transdermal mirtazapine in healthy research cats. The $AUC_{0\text{-}48}$ of multidose 7.5 mg TMZ was significantly higher than single dose 1.88 mg OMZ ($P = 0.02$), and approached being significantly higher than single dose 7.5 mg TMZ ($P = 0.06$).There was no significant difference in $AUC_{0\text{-}48}$ between administration of single dose 3.75 mg TMZ, single dose 7.5 mg TMZ and single dose 1.88 mg OMZ.

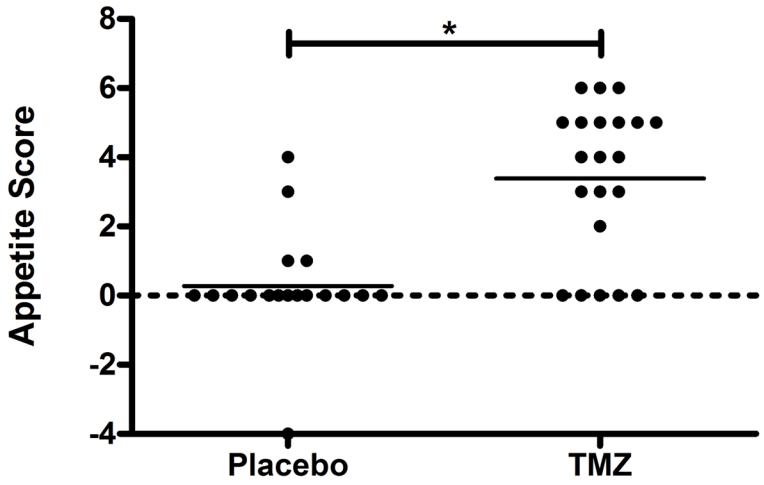

Figure 3.

Appetite score based on daily owner assessment after administering 7.5 mg transdermal mirtazapine (TMZ) or placebo daily for five days in a blinded cross-over design. There is a statically significant difference in appetite score between TMZ and placebo (**P* = 0.003; n = 18).

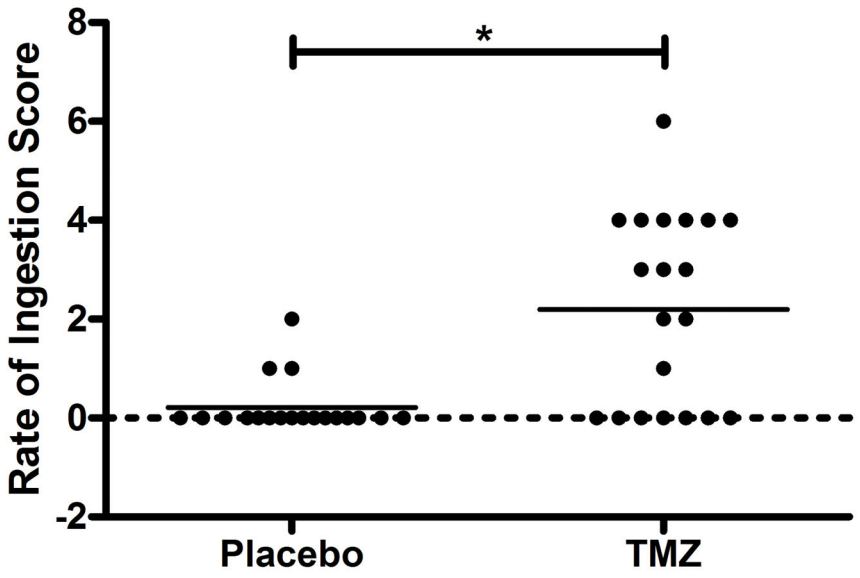

Figure 4.

Rate of food ingestion score based on daily owner assessment after administering 7.5 mg transdermal mirtazapine (TMZ) or placebo daily for five days in a blinded cross-over design. There is a statistically significant difference in rate of food ingestion score between TMZ and placebo (*P = 0.002; n = 19).

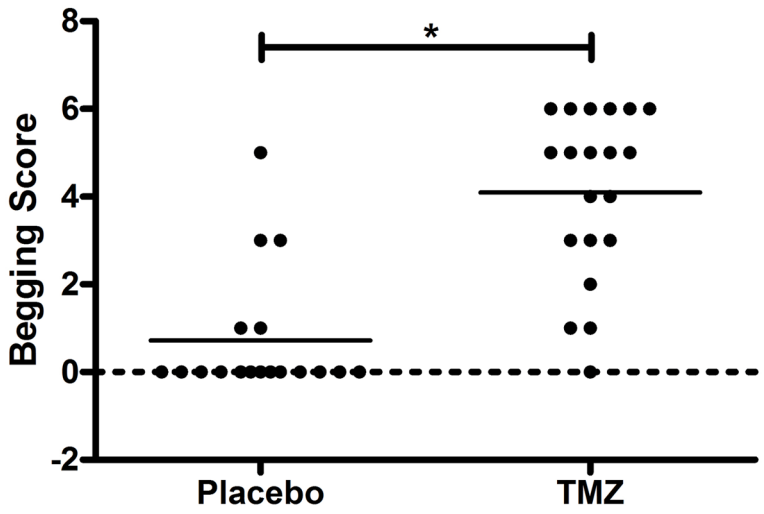

Figure 5.

Begging score based on daily owner assessment after administering 7.5 mg transdermal mirtazapine (TMZ) or placebo daily for five days in a blinded cross-over design. There is a statically significant difference in begging score between TMZ and placebo (**P* = 0.002; n = 17).

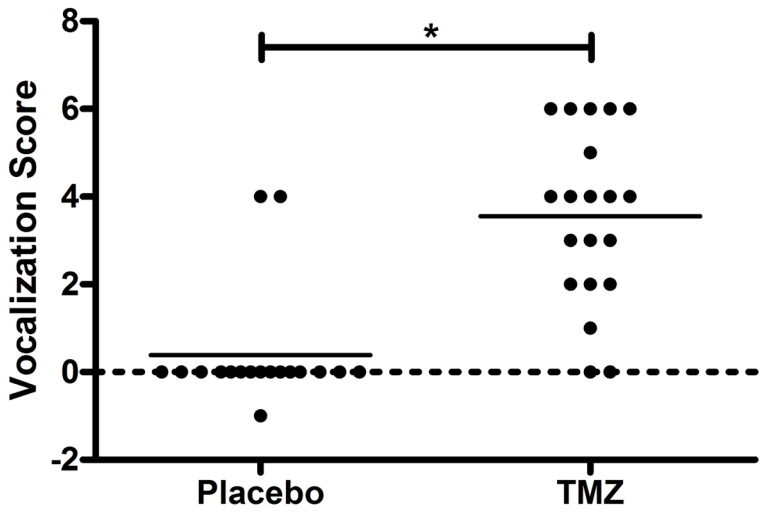

Figure 6.

Vocalization score based on daily owner assessment after administering 7.5 mg transdermal mirtazapine (TMZ) or placebo daily for five days in a blinded cross-over design. There is a statically significant difference in vocalization score between TMZ and placebo (* $P = 0.002$; n = 17).

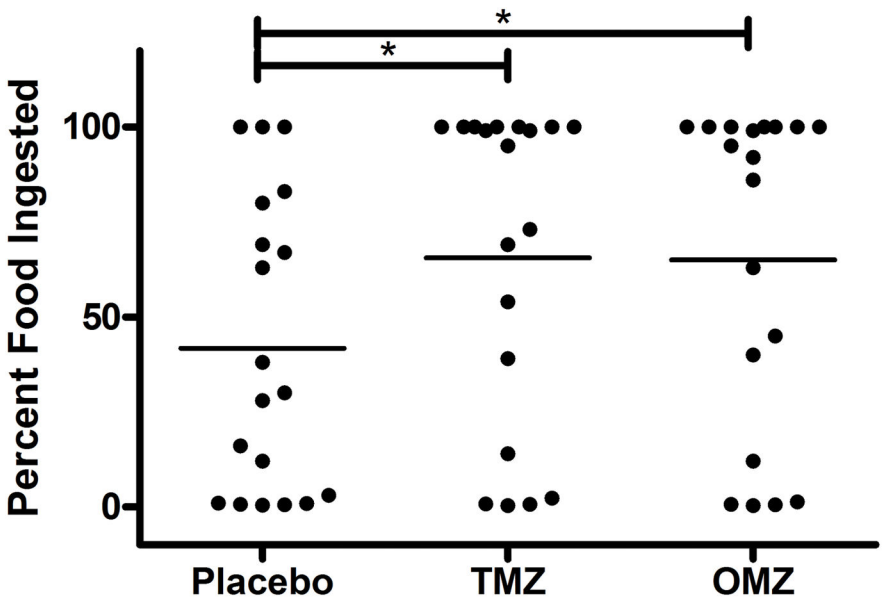

Figure 7.

Comparison of percent food ingested when client-owned cats were observed in the hospital environment after six days of transdermal mirtazapine (TMZ) or transdermal placebo and a single oral mirtazapine dose (OMZ). There was a statically significant difference in percent food ingested between placebo and TMZ and placebo and OMZ (*$P < 0.05$).

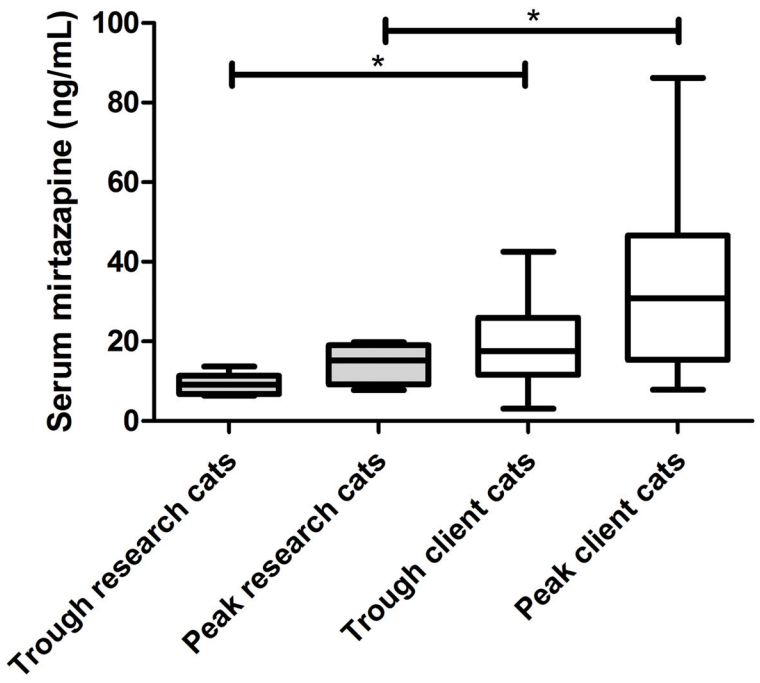

Figure 8.

Trough and peak serum mirtazapine concentrations compared between the healthy research cat multidose 7.5 mg drug exposure study and the client-owned cat multidose 7.5 mg clinical effect study; client-owned cats had significantly higher peak (**P* = 0.02) and trough (**P* = 0.02) serum mirtazapine levels.

Table 1

Comparison of multidose 7.5 mg TMZ and single dose 1.88 mg OMZ median trough and peak serum mirtazapine concentrations in healthy cats.

Treatment	Median Trough (ng/ml) [range]	Median Peak (ng/ml) [range]
Healthy Research Cats		
Multidose 7.5 mg TMZ (n=7)	9.1 [6.3 – 13.7]	15.2 [7.8 – 19.8]
Single dose 1.88 mg OMZ (n=7)	Not applicable	30.1 [20.1 – 64.7]
Client-Owned Cats		
Multidose 7.5 mg TMZ (n=16)	17.5 [3.1 – 42.5]	37.4 [7.9 – 86]
Single dose 1.88 mg OMZ (n=15)	Not applicable	47.3 [0.5 – 112]

Table 2

Summary of the average percent (+/− SD) and range of mirtazapine gel concentrations in respect to target dose.

Gel type and dose	Average (%) +/− SD	Range (%)
Phase 1		
3.75 mg single dose (n=4) Lipoderm/USP mirtazapine	106 +/− 11	94 – 116
7.5 mg single dose (n=5) Lipoderm/USP mirtazapine	95 +/− 18	75 – 109
7.5 mg multidose (n=7) Lipoderm/bulk mirtazapine	95 +/− 1	87 – 106
Phase 2		
7.5 mg multidose (n=18) Lipoderm/bulk mirtazapine	107 +/− 9	87 – 119
Commercial pharmacies		
-Lipoderm (n=2)	65 +/− 14	55 – 75
-PLO (n=2)	66 +/− 31	44 – 87

PLO: pluronic lecithin organogel