Title

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Journal

Journal of Feline Medicine and Surgery, 19(12)

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Publication Date

2017-12-01

DOI

10.1177/1098612X16688807

Peer reviewed

Original Article

Journal of Feline Medicine and Surgery
2017, Vol. 19(12) 1245–1248

DOI: 10.1177/1098612X16688807
journals.sagepub.com/home/jfms

This paper was handled and processed by the American Editorial Office (AAFP) for publication in *JFMS*

Assessment of absorption of transdermal ondansetron in normal research cats

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Abstract

Objectives The objective of this study was to assess the absorption of transdermal ondansetron in healthy cats.

Methods Five research cats with unremarkable complete blood count, biochemistry and urinalysis were used for both single- and multiple-dose application studies. For single-dose application, 4 mg ondansetron in 0.1 ml Lipoderm gel was applied once to the internal ear pinna. Blood samples were collected via jugular catheter over a 48 h period following administration (0, 15 mins, 30 mins, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h and 48 h). For multiple-dose application, 4 mg ondansetron in 0.1 ml Lipoderm gel was applied for five consecutive days before blood samples were obtained in the same manner. Serum was separated and frozen prior to analysis. Ondansetron was measured via liquid chromatography coupled to tandem mass spectrometry.

Results Analysis revealed no clinically relevant drug levels in serum after either single- or multiple-dose administration of 4 mg transdermal ondansetron.

Conclusions and relevance Transdermal application of 4 mg ondansetron does not result in clinically relevant serum concentrations of drug. Despite characteristics of the drug that imply suitability for transdermal application, this does not appear to be an acceptable method of drug delivery for this medication at this dose. This study highlights the importance of assessing the suitability of each medication for transdermal administration.

Accepted: 16 December 2016

Introduction

Ondansetron is a 5-HT_3 receptor antagonist designed to treat chemotherapy-induced nausea in humans, and has been shown to be an effective antiemetic and antinausea medication in cats.[1] 5-HT_3 receptors are present both on abdominal vagal afferent nerves and centrally in the chemoreceptor trigger zone, and therefore ondansetron has both peripheral and central antiemetic effects.[2,3] Controlling nausea and providing adequate nutrition to feline patients is critical when managing cases of acute and chronic illness.

In a recent study that compared oral, subcutaneous and intravenous administration of ondansetron, it was shown that the bioavailability of oral ondansetron (32%) was much lower than that of subcutaneous ondansetron (75%).[4] Moreover, the elimination of subcutaneous ondansetron was significantly longer (3 h) than oral or intravenous administration (1 h).[4] Owing to the poor bioavailability of oral ondansetron and the impracticality of giving multiple subcutaneous doses (more than three doses a day) at home, due to a short half-life, owners are often not able to medicate with ondansetron at home, resigning it to mostly in-hospital administration. Transdermal ondansetron would therefore be of great advantage to owners who struggle with medication administration for the palliation of vomiting or nausea in feline patients, and this route of

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administration might result in longer clinically relevant drug serum concentrations.[5]

To date, no investigations have been performed on the use of transdermal ondansetron. The use of transdermal medications has been demonstrated to be effective in feline patients for a few drugs such as methimazole and mirtazapine, with weaker evidence for amlodipine.[5–8] However, it has also become clear that transdermal absorption of drugs can be lower than with oral dosing and that absorption of transdermal drugs can be inconsistent between patients.[9–11] Therefore, although this is an extremely attractive method of drug administration, additional studies are warranted.

According to the modified 'rule of five', in order for a drug to be amenable to transdermal application, it needs to be administered at a small dose, have a small molecular size (<500 Daltons [Da]), be moderately lipophilic with a logP between 1 and 3, and have fewer than two hydrogen donors and fewer than five hydrogen acceptors.[12] Ondansetron is a candidate for assessment as a transdermal medication because a common dose is 2–4 mg, and it meets the rule of five as it is 294 Da in size, has zero hydrogen bond donors and two hydrogen bond acceptors, and has a logP of approximately 2.4 (http://www.drugbank.ca/drugs/DB00904).

The purpose of this study was to assess the absorption of single-dose and multiple-dose transdermal ondansetron in young healthy cats.

Materials and methods

Drug preparation

All ondansetron transdermal gels were prepared at the Colorado State University Veterinary Teaching Hospital Pharmacy by a single member of the pharmacology staff using ondansetron hydrochloride dehydrate USP powder (Lot #123190/C; Medisca) and Lipoderm gel (Professional Compounding Centers of America). The study was completed in two phases, a single-dose administration phase, and a multiple-dose administration phase. Transdermal gel for all cats was prepared immediately prior to each phase.

Drug administration and sample collection

Five apparently healthy research cats with unremarkable physical examination, complete blood count, chemistry and urinalysis were used, and all aspects of the project received approval by the Colorado State University Institutional Animal Care and Use Committee. For single-dose administration, 4 mg ondansetron in 0.1 ml Lipoderm gel was applied once to the internal ear pinna at time zero before blood samples were collected. For multiple-dose administration, 4 mg ondansetron in 0.1 ml Lipoderm gel was applied once daily to the internal ear pinna for five consecutive days before the study was performed. All cats wore double e-collars (one soft and one hard) to prevent removal of the jugular catheter and grooming of the ears throughout the time period of the study. Drug administration for phase 2 was initiated 2 weeks after phase 1 was completed. Pinnae were monitored for any irritation subsequent to administration.

For both study phases, cats were sedated using a ketamine/butorphanol protocol (20 mg ketamine/cat intravenous, 0.1 mg/kg butorphanol intravenous) and jugular catheters were placed approximately 16 h prior to time zero in order to facilitate repeated blood sampling. Blood samples were collected via jugular catheter at 0, 0.5, 1, 2, 4, 8, 12, 24 and 48 h once the study was underway. Serum was separated and stored at −80°C prior to analysis.

Serum ondansetron analysis

Serum concentrations of ondansetron were measured using liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS), as previously described.[4] For the current analyses the lower limit of quantitation based on analytical method validation guidelines was 1 ng/ml. Although sample replicates are not typically performed, duplicate aliquots were analyzed in four samples to recheck the measured concentration for accuracy. The analysis was performed at the Pharmacology Core at the Colorado State University Veterinary Teaching Hospital.

Ondansetron gel concentration analysis

Ondansetron gels compounded for use in the study were analyzed to determine dose accuracy. To confirm transdermal gel concentration, 10 mg dosing solution gel was diluted 1:100 with solution of 50:50, Methanol:Milli-Q water (v:v). Samples were vortex mixed, sonicated for 5 mins and diluted an additional 1:100 with 50:50 Methanol:Milli-Q. In total, samples were diluted $1{:}1 \times 10^4$ and quantified using a standard curve of ondansetron prepared in 50:50 Methanol:Milli-Q using the LC/MS/MS method described previously.[4]

Results

All compounded transdermal ondansetron Lipoderm gels used in the study were analyzed to verify appropriate ondansetron concentration. Average gel concentration was 90% (range 84–97%) of the target 4 mg dose. When ondansetron serum levels were analyzed after single- and multiple-dose administration of 4 mg ondansetron in 0.1 ml Lipoderm gel, the majority of samples had no appreciable drug levels measured. Ten samples had drug levels just above the lower limit of quantitation (range 1–6 ng/ml), five from the single-dose administration and five from the multiple-dose administration. A single preadministration (time zero) baseline sample contained 36 ng/ml ondansetron, which was confirmed with analysis of a duplicate aliquot. No irritation

subsequent to gel administration was noted in any cat after single- or multiple-dose administration.

Discussion

The original goal of this study was to assess the pharmacokinetic parameters of single-dose and multiple-dose transdermal ondansetron in young healthy research cats, in order to determine if transdermal application could potentially be used in the palliation of nausea and vomiting in feline patients. However, unexpectedly this could not be performed because no clinically relevant serum levels of ondansetron were detected in any feline patients after single- or multiple-dose application of 4 mg transdermal ondansetron. Only a few samples contained detectable drug, with concentrations just over the lower limit of quantitation. As serum samples were obtained via jugular catheter it should be considered that drug concentration could possibly have been falsely elevated owing to proximity to the ear, a finding described in a previous study.[13] The cause of the inadequate absorption of transdermal ondansetron in the five cats used in this study is not known. A variety of causes for inconsistent transdermal drug delivery of drug have been identified, including hydration status, concurrent illness or health of the stratum corneum.[14] Other factors such as tissue temperature, circulation status of the underlying tissue, and interactions between the drug itself and the gel delivery vehicle could all decrease absorption.

The measured concentration of ondansetron in the compounded gels was found to be slightly less than the 10% variability from target dose considered acceptable for compounded medications; however, there still should have been adequate drug to result in absorption. These results are similar to a previous study in which transdermal mirtazapine in Lipoderm gel was measured for compounding accuracy and found to be quite variable.[5] This variability from target dose once again highlights the potential inaccuracy of compounded transdermal medications, despite preparation by qualified staff with Professional Computing Centers of America-approved methodology. Previous experience with compounding transdermal medications using Food and Drug Administration (FDA)-approved tablets has made us aware of problematic inconsistencies in the gel due to the percentage of excipient in tablets.[5] Therefore, for proof of concept for the current study it was deemed necessary to use a bulk 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.[15]

Although pharmacokinetic data for transdermal drugs in feline patients is sparse, previous studies have shown that higher doses of transdermal drug may be required to match the serum drug concentrations attained after oral administration.[7,11,16] Mechanisms for this necessary increase in dose remain unclear, although it has been hypothesized to be related to some degree of dermal metabolism or interactions between the drug and its gel delivery.[14] With this previous observation in mind, the current study used double the dose (4 mg) of ondansetron typically prescribed orally for a feline patient,[17] yet no clinically relevant serum ondansetron levels were measured. When 2 mg ondansetron is given to cats via intravenous or subcutaneous routes, maximum serum concentrations range from 228–1310 ng/ml, yet when administered via the transdermal route in the current study, no serum levels greater than 6 ng/ml were measured.[4]

Previous studies have also indicated that repeated application of a transdermal drug may result in increased absorption and higher drug serum concentrations, and should be a part of assessment of the applicability of the drug to transdermal administration.[6,10] Transdermal methimazole is without question the most studied feline transdermal medication; however, initial evaluation of a single transdermal dose indicated bioavailability was poor and made it seem unlikely that the medication would be amenable to transdermal application. However, further studies with repeated dosing confirmed a therapeutic effect.[10,18] Therefore, in the current study both single and repeated daily doses of transdermal ondansetron were evaluated. However, 5 days of repeated daily dosing of 4 mg transdermal ondansetron did not increase the amount of drug detected in the serum of the cats in this study, even though blood sampling started 15 mins after the fifth daily dose was administered.

During the analysis of samples from this study, a single preadministration (time zero) blood sample was found to contain measureable ondansetron levels at a level that would be clinically applicable. This finding has been attributed to contamination via handling of the sample, despite that fact that all personnel were required to wear gloves during sample processing in case they had been inadvertently exposed to gel from the cats' ears during sample collection from the jugular catheter. This observation serves as a cautionary note for future studies involving transdermal medications.

The results of this study highlight the importance of assessing the absorption capability of each individual drug that is desired to be used for transdermal administration. Moreover, this study substantiates that although a drug appears to have appropriate characteristics that would make it amenable to transdermal application (small dose, small molecular size and moderate lipophilicity), one cannot assume that it will be adequately absorbed.

Conclusions

Transdermal application of 4 mg ondansetron does not result in clinically relevant serum concentrations of drug. Despite characteristics of the drug that imply suitability

for transdermal application, this does not appear to be an acceptable method of drug delivery for this medication at this dose. This study highlights the importance of assessing the suitability of each medication for transdermal administration, regardless of characteristics of the drug that imply that it would adequately pass the skin barrier.

Acknowledgements The authors gratefully acknowledge Sabina Ligas and Leigh Davis for assistance with cat handling.

Conflicts of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding This study was funded, in part, via a grant from the Young Investigator Grant program in the Center for Companion Animal Studies at Colorado State University.

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