Determination of famciclovir concentrations in compounded formulations

Phoebe G. Weaver, Lynelle R. Johnson, Lauren R. Eichstadt, Sara M. Thomasy, Heather K. Knych
Veterinary Medical Teaching Hospital, University of California, Davis

INTRODUCTION

Famciclovir is an anti-viral medication that has revolutionized control of diseases associated with feline herpesvirus, a disease of world-wide significance to the cat population. Anti-viral medications are typically given for multiple weeks, which is problematic in both domestic and wild cats because of the difficulty in chronic administration of medications. Efficacy of therapy in feline viral infection is often based on resolution of clinical signs because of the difficulty in monitoring the presence or absence of viral infection.[1] Hence it is critical to know if the concentration of compounded famciclovir formulations remains consistent over time.

Pharmacokinetic studies have demonstrated complex metabolism in the cat [2] and a multitude of dosing regimens have been used clinically.[3,4,5] Most recently a dose of 90 mg/kg twice daily by mouth has been recommended to ensure appropriate concentrations in the tears and plasma. [2] While commercially available tablet sizes are somewhat appropriate for use in a standard sized adult cat, smaller cats and kittens are more difficult to dose. Also, because of the difficulties in giving medications to cats, famciclovir is often compounded. However, there are few studies validating the multiplicity of products available on the market. [6]

HYPOTHESES

This study was designed to test the following hypotheses:

- All compounded products would be within 10% of the labeled concentration
- Concentrations of compounded products would remain stable over 2 months

MATERIALS & METHODS

Famciclovir was obtained as oral oil suspensions in concentrations of 25 to 400 mg/ml and in unflavored, tutti frutti, and anchovy flavors. Additional formulations included fish flavored oral paste in concentrations of 125 to 400 mg/ml, tiny tabs, and chew treats of varying concentrations.

On days 0, 7, 14, and 28, drug was extracted from each compound, and these samples were diluted to concentrations, measurable by liquid chromatography mass spectrometry (1.25 ng/µL to 4 ng/µl), twice with 100% acetone, and once with a 1:1 acetone : water solution.

Famciclovir concentrations were then determined by liquid chromatography tandem mass spectrometry. Detection and quantification were conducted using selective reaction monitoring of the initial precursor ion for famciclovir (mass to charge ratio (m/z) 322.207). The response for the product ions for famciclovir (m/z 136.1, 262.2 and 280.2) was plotted and peaks at the proper retention time integrated using Quanbrowser software (Thermo Scientific). Quanbrowser software was then used to generate calibration curves and quantitate famciclovir in the samples by linear regression analysis.

DATA ANALYSIS

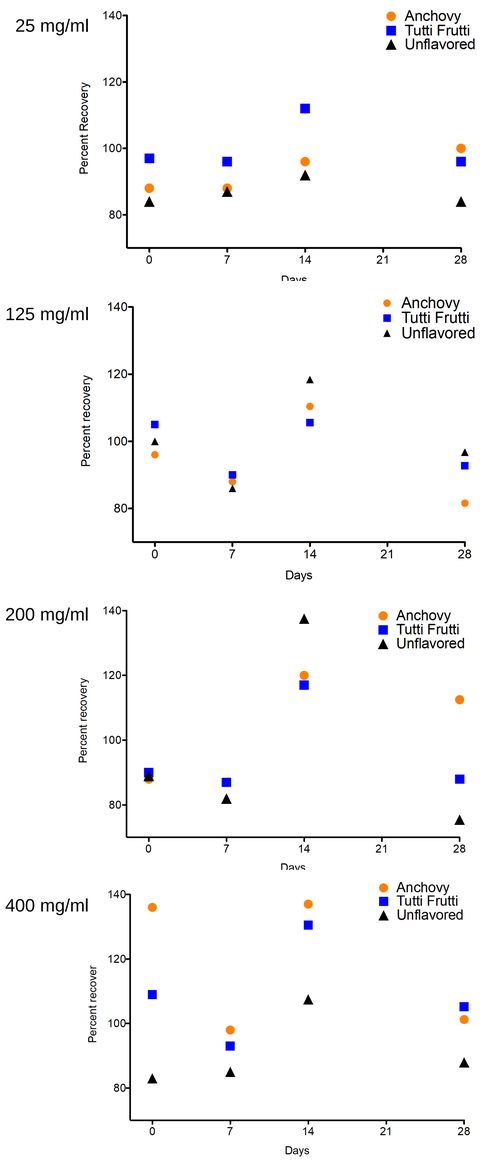
Mean values for samples run in triplicate were calculated and determined using a standard curve based on calibration samples with a known concentration of famciclovir, providing calculated concentrations of famciclovir for each product on each day. Percent concentration was calculated by comparison to the reported value of the compound.

RESULTS

Erratic results were obtained for famciclovir concentrations in chew tabs and paste, with percent recovery ranging from 1-200%. Alternate extraction experiments are ongoing using blank products spiked with known concentrations of famciclovir.

RESULTS

Oral oil suspensions:



Tiny tabs: 62.5mg

day	0	7	14
mg extracted	56	59	62

DISCUSSION

Results of this study showed marked variabilities in the concentrations of famciclovir in compounded formulations over time. For oil suspensions:

Day of experiment	No (%) with concentration >10% lower	No (%) with concentration >10% higher
0	5/12 (42%)	1/12 (8%)
7	8/12 (67%)	0/12 (0%)
14	0/12 (0%)	8/12 (67%)
28	4/12 ((33%)	1/12 (8%)

All samples will be evaluated on day 56.

An increase in famciclovir recovery was detected on day 14 in each oil preparation. Follow up experiments are currently being performed using aliquoted solutions of new oil suspensions to investigate the possibility of dehydration due to evaporation resulting from multiple openings of the vial, although the decline in concentration on day 28 makes this less likely.

Tiny tabs remained within 10% of the stated concentration for 14 days.

CONCLUSION

Ongoing investigations are needed to establish the accuracy and stability of compounded famciclovir.

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