

Comparison of absorption characteristics of oral reference and compounded itraconazole formulations in healthy cats

Dianne I. Mawby DVM, MVSc

Jacqueline C. Whittemore DVM, PhD

Leanne E. Fowler BS

Mark G. Papich DVM, MS

From the Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, TN 37996 (Mawby, Whittemore, Fowler); and the Department of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27607 (Papich).

Address correspondence to Dr. Mawby (dmawby@utk.edu).

OBJECTIVE

To compare absorption characteristics of orally administered compounded itraconazole capsules and suspension with those of reference (brand-name) formulations in healthy cats.

DESIGN

Randomized crossover study.

ANIMALS

8 healthy adult cats.

PROCEDURES

After 12 hours of food withholding, cats received 50 mg of itraconazole (reference capsule, reference solution, compounded capsule, and compounded suspension) in a randomized crossover design, with a 21-day wash-out period. Capsules were administered with a small meal. Blood samples were collected at predetermined intervals for high-pressure liquid chromatography analysis of plasma itraconazole concentrations. Area under the concentration-time curve, maximum concentration, and terminal half-life of itraconazole were determined and compared among formulations.

RESULTS

7 cats completed the study. Mean half-life of itraconazole in reference formulations was 18 to 26 hours. Absorption of the reference solution was 3 times that of the reference capsule. Compounded formulations were absorbed poorly and inconsistently. Complete pharmacokinetic results for the compounded capsule were obtained for only 3 of 6 cats and for the compounded suspension for only 1 of 5 cats, precluding bioequivalence analysis. Relative absorption of compounded formulations was only 2% to 8% of reference formulation values.

CONCLUSIONS AND CLINICAL RELEVANCE

Compounded oral formulations of itraconazole should not be used for cats because of poor absorption. The differences in absorption between the 2 reference formulations suggested that doses required to meet human target serum concentrations in cats are markedly different (capsules, 12.5 mg/kg [5.7 mg/lb], q 24 h, with food; solution, 4 mg/kg [1.8 mg/lb], q 24 h, without food). (*J Am Vet Med Assoc* 2018;252:195–200)

Systemic fungal infections, such as blastomycosis and histoplasmosis, can be fatal in cats if not treated promptly with effective antifungal agents such as itraconazole.^{1–4} Itraconazole is a broad-spectrum, synthetic triazole antifungal drug with variable bioavailability and absorption, partly because it is highly lipophilic and essentially insoluble in water.⁵ The reference (brand-name) formulation of itraconazole is available for oral administration in capsules and solution. For the solution, hydroxypropyl- β -cyclodextrin (400 mg/mL) is used as a molecular inclusion complex to maintain solubility of itraconazole. Absorp-

tion of itraconazole from the capsules is improved in an acidic environment, and coupling administration with a meal is recommended to increase bioavailability.^{6–8} In contrast, absorption of itraconazole solution, which is already in solution because of complexing with cyclodextrin, does not require administration with food.

Reference formulations of itraconazole are expensive. Therefore, the drug has been compounded for veterinary use from the bulk chemical substance by compounding pharmacists as a less expensive alternative. Although this practice violates US federal regulations that prohibit compounding from bulk chemicals for animals, the FDA generally has not enforced this regulation. Compounded itraconazole products for dogs, cats, zoo animals, and exotic animals are widely available to veterinarians and pet owners. Veterinarians must exercise due diligence in examining pub-

ABBREVIATIONS

AUC	Area under the concentration-time curve
C _{MAX}	Maximum plasma concentration
t _{1/2}	Terminal half-life
T _{MAX}	Time to maximum plasma concentration

lished research to understand the quality of the compounded products they might prescribe.

Administration of compounded itraconazole formulations is not recommended because of unknown pharmacokinetics and bioavailability, uncertain quality of the compounded products, and anecdotal accounts of treatment failure.¹ Our research group found negligible absorption of compounded itraconazole capsules (5.5% compared with reference formulation values) in a previous study⁹ involving healthy dogs. Similar findings have been reported^{10,11} for oral compounded formulations in birds.

The purpose of the study reported here was to compare absorption of 4 oral formulations of itraconazole (2 reference formulations and 2 compounded formulations) in healthy cats. To achieve this, the same parameters used in bioequivalence tests accepted by the FDA were chosen for pharmacokinetic analysis: AUC and C_{MAX} . A secondary objective was to determine the pharmacokinetics of the reference formulations for the purpose of developing recommended dose administration strategies for cats.

Materials and Methods

Animals

Eight healthy adult research cats with body weights ranging from 3.1 to 5.0 kg (6.8 to 11.0 lb; mean, 4.0 kg [8.8 lb]) were used in the study. Cats were deemed healthy on the basis of results of a physical examination and routine hematologic analysis. The research protocol was approved by the University of Tennessee Institutional Animal Care and Use Committee (protocol No. 2149).

Experimental protocol

A randomized crossover design was used in which cats received 4 itraconazole formulations with the sequence determined by random number selection, with a 21-day washout period separating treatments. Formulations included the reference capsule^a (repackaged at the University of Tennessee College of Veterinary Medicine pharmacy from 100-mg capsules into 50-mg capsules), reference liquid solution,^b compounded capsule,^c and compounded liquid suspension.^c Compounded itraconazole formulations were prepared by a licensed pharmacist at the University of Tennessee. The active pharmaceutical ingredient used for compounding was a bulk chemical substance obtained from an approved source.^c The powder was authenticated with a certificate of analysis. The oral suspension was formulated in a commercially available compounding vehicle.^{d,e} The bulk chemical was transferred into gelatin capsules for the oral capsule formulation. Compounded formulations were prepared 24 hours before the first dose was administered and stored at room temperature (approx 21°C).

Twelve hours before treatment administration, food was withheld from each cat and a jugular or femoral catheter was aseptically placed and secured with

bandages. Nasoesophageal catheters were placed in cats receiving liquid formulations to ensure complete receipt of each dose and then removed after treatment administration. Time 0 blood samples were collected, and the assigned itraconazole formulation was administered as a 50-mg dose (mean dose, 12.5 mg/kg [5.7 mg/lb]). Capsules were administered with a small meal (approx 30 mL of canned food^f), whereas liquid formulations were not. Blood samples (1 to 2.5 mL) were again collected at predetermined intervals (1, 2, 4, 8, 12, 24, 36, 48, 72, 84, 96, and 120 hours). Catheters were removed after the last sample was collected.

Sample processing

Blood samples were immediately transferred to glass tubes containing heparin, placed on ice, and then centrifuged at 1,500 X g in batches. Plasma was separated and stored in plastic cryogenic vials at -70° to -80°C. Plasma samples were shipped frozen on ice to the North Carolina State University Clinical Pharmacology Laboratory for itraconazole analysis.

Itraconazole analysis

Quantitative analysis of itraconazole in plasma samples was performed by means of high-pressure liquid chromatography with a previously validated technique.^{9,11-13} Fresh calibration samples and quality control samples were prepared daily. Control (blank) feline plasma was fortified (spiked) with standard solutions of itraconazole to prepare all quality control and calibration samples. Fortified feline plasma, calibration samples, incurred samples, and blank plasma samples were prepared identically.

Pharmacokinetic analysis

Concentrations of itraconazole following oral administration of each formulation to each cat were analyzed by means of compartmental or noncompartmental analysis and pharmacokinetic software.⁸ Plasma drug concentrations were plotted on linear and semi-logarithmic graphs for visual inspection and initial selection of appropriate models for pharmacokinetic analysis. Plasma drug concentrations were weighted by a factor of 1/(predicted plasma concentration)² for pharmacokinetic analysis. The specific model (ie, 1 or 2 compartments) was selected for best fit on the basis of the smaller Akaike information criterion value.¹⁴

For the orally administered reference formulations, pharmacokinetic parameters were calculated by use of the following formula:

$$C = \frac{Ka \times F \times D}{V(Ka - K)} \times [e^{-K \times t} - e^{-Ka \times t}]$$

where C is the plasma concentration, Ka is the non-IV absorption rate assuming first-order absorption, K is the elimination rate constant, V is the apparent volume of distribution, F is the fraction of drug absorbed, D is the non-IV dose, e is the base of the natural logarithm,

Table 1—Geometric mean pharmacokinetic values and coefficients of variation (CV; %) for itraconazole determined from compartmental (reference formulation) or noncompartmental (compounded formulation) analysis of plasma samples from healthy cats after oral administration of 4 formulations (compounded capsule,^c n = 6; reference capsule,^a 6; compounded suspension,^c 5; and reference solution,^b 6) containing 50 mg of itraconazole (mean dose, 12.5 mg/kg [5.7 mg/lb]).

Parameter	Compounded capsule			Reference capsule			Compounded suspension			Reference solution		
	n	Mean	CV	n	Mean	CV	n	Mean	CV	n	Mean	CV
AUC _{0-C_n} (μg•h/mL)	6	0.49	94.70	6	—	—	3	0.60	80.70	—	—	—
AUC _{0-∞} (μg•h/mL)	3	1.29	29.70	6	16.97	24.37	1	1.74	—	6	70.19	19.10
C _{MAX} (μg/mL)	6	0.03	79.62	6	0.54	37.16	3	0.02	59.65	6	1.69	48.15
t _{1/2} (h)	3	34.06	80.62	6	18.04	21.24	1	37.49	—	6	25.53	41.87
K (h ⁻¹)	3	0.02	106.98	6	0.04	21.24	1	0.02	—	6	0.03	41.87
Mean residence time (h)	3	53.47	73.44	—	—	—	1	48.92	—	—	—	—
T _{MAX} (h)	6	9.16	65.67	6	6.00	28.93	3	8.32	49.49	6	3.45	58.79

— = Insufficient data for compartmental analysis. AUC_{0-∞} = Area under the curve from time 0 to infinity. AUC_{0-C_n} = Area under the curve from time 0 to the last measurement point. K = Elimination rate. n = Number of cats with measurable plasma itraconazole concentration.

and t is time. In this model, it is assumed that K_a was considerably greater than K because there was no flip-flop effect caused by slow absorption from the gastrointestinal tract. A lag time was added to the model to account for dissolution of capsules and stomach emptying time. Secondary parameters obtained from the model included C_{MAX} , T_{MAX} , AUC, and the respective absorption $t_{1/2}$ and elimination $t_{1/2}$. Because no IV administered dose was given to accompany the orally administered dose, values for systemic clearance and apparent volume of distribution would be meaningless and are not reported.

Plasma concentrations for the compounded itraconazole formulations were sparse and largely undetected for most sample collection points. Therefore, noncompartmental analysis was performed.⁸ The AUC from time 0 to the last measured concentration (AUC_{0-C_n}), defined by the limit of quantification, was calculated by use of the log-linear trapezoidal method. The AUC from time 0 to infinity (AUC_{0-∞}) was calculated by adding the terminal portion of the curve to AUC_{0-C_n}. The terminal portion of the curve was estimated from the relationship C_n/λ_z , where λ_z is the terminal slope of the curve and C_n is the last measured concentration. For some cats, insufficient sample collection points with concentrations above the detection limit were available to estimate the terminal slope. Mean residence time and $t_{1/2}$ were determined as secondary parameters. The values for C_{MAX} and T_{MAX} were obtained directly from the observed data.

Results

Animals

No vomiting or regurgitation was observed. One cat did not readily eat the small meal after administra-

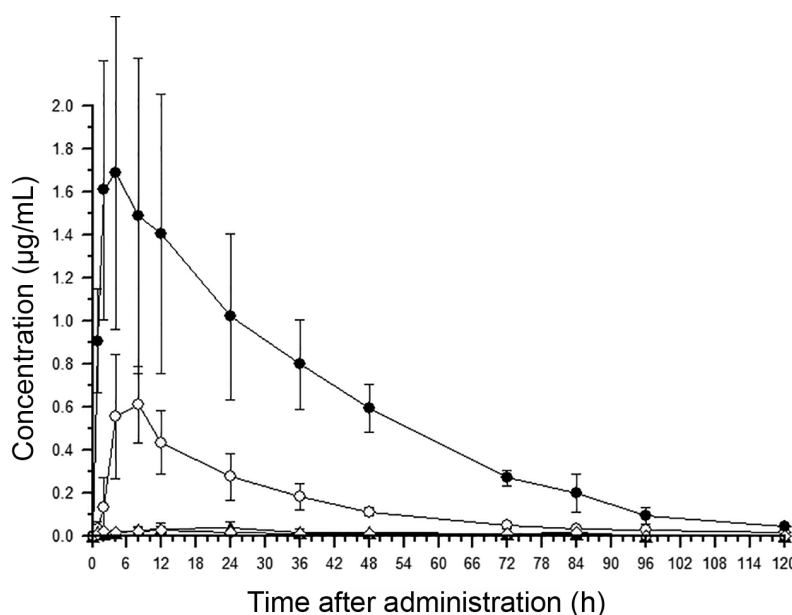


Figure 1—Mean plasma itraconazole concentrations over time in healthy cats after oral administration of 50 mg (mean dose, 12.5 mg/kg [5.7 mg/lb]) of itraconazole in 4 different itraconazole formulations (reference capsule^a [white circles, n = 6], reference solution^b [black circles, 6], compounded capsule^c [black triangles, 6], and compounded suspension^c [white triangles, 5]). Error bars represent SD. Cats received each treatment in random order, with a 21-day washout period separating treatments. Symbols for the compounded formulations overlap because they were all close to 0.

tion of the original capsule formulation and required syringe feeding. One cat was excluded from the study prior to the last data collection period because of its temperament. Blood samples were successfully collected from the remaining 7 cats at the predetermined points and processed for analysis. On the basis of preliminary results from the first data collection period, the final sample collection point was reduced from 120 to 84 hours. Interim analysis after the third data collection period revealed that compounded itraconazole was not being absorbed, whereas the reference product was consistently absorbed. On the basis of these data, it was considered unnecessary to subject

the remaining cats to an additional data collection period; therefore, the study was terminated. This resulted in data for 5 cats in the compounded suspension group and 6 cats in all other treatment groups.

Pharmacokinetic analysis

Pharmacokinetic values for each parameter and concentration-time curves for each itraconazole formulation were summarized (**Table 1**; **Figure 1**). The AUC and C_{MAX} for the compounded formulations were considerably less than those for the reference formulations. Many plasma samples obtained after cats received compounded formulations had undetectable itraconazole concentrations. Complete pharmacokinetic results could be obtained for only 3 cats following compounded capsule administration and for only 1 cat following compounded suspension administration. As such, bioequivalence calculations could not be performed.

Absorption of the reference solution was approximately 3 and 4 times that of the reference capsule, as indicated by the C_{MAX} and the AUC, respectively (Table 1). Relative absorption of compounded itraconazole, compared with that of the corresponding reference formulation, was 8% for the capsule and 2% for the suspension in the few cats in which it could be measured.

Discussion

The compounded capsule and liquid suspension formulations were both poorly and inadequately absorbed in cats, and we therefore cannot recommend them for oral administration. Itraconazole in the reference solution was much better absorbed than that in the reference capsule.

Itraconazole is commercially available for oral administration in a capsule or solution. Both products are expensive, and the 100-mg capsule^a is often too large for some cats. The FDA defines repackaging as the act of taking a finished drug product from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the drug.¹⁵ Repackaging of an approved oral dose is allowed by the FDA to allow tailoring of doses for small patients without compromising oral absorption.¹⁵⁻¹⁸ In contrast, compounding is defined as the manipulation of a drug or chemical substance to create a different drug to meet the special needs of a patient.^{16,17} Compounding from bulk chemicals has produced preparations inferior to the proprietary formulation.¹⁶ Moreover, federal regulations prohibit the compounding of veterinary itraconazole from a bulk chemical substance when an approved FDA formulation is available.¹⁶ However, some compounding pharmacies prepare and promote compounded products made from bulk chemical substances in violation of federal regulations, and veterinarians have relied on compounding pharmacists to compound products from the bulk itraconazole powder.

Ordinarily, bioequivalence analysis involves statistical comparison of AUC and C_{MAX} between a test and reference formulation by means of two 1-sided test procedures.¹⁸ Because there were undetectable plasma itraconazole concentrations at many sample collection points for all but 3 cats that received compounded capsules and 1 cat that received compounded suspension orally, AUC and C_{MAX} could not be calculated for most cats. As such, it was not possible to calculate relative bioequivalence for the compounded itraconazole formulations. For the few cats available for analysis, relative absorption of the compounded products was only 2% (suspension) and 8% (capsule) of reference formulation values. These results were similar to those of a previous bioequivalence study⁹ of compounded and reference capsules of itraconazole administered orally to healthy dogs, in which compounded itraconazole formulations resulted in AUC and C_{MAX} values that were only 5% of those for the reference formulation.

Because we sought to determine whether oral administration of itraconazole formulations compounded by use of best practices could result in therapeutic blood concentrations in cats, compounded medications were prepared by a licensed university pharmacist according to the standards published by the United States Pharmacopeia.¹⁹ An aliquot of the powder was assayed for content and quality, and the powder was confirmed to contain itraconazole and meet or exceed quality standards. The vehicles used in the study to create the compounded drugs were the vehicles most commonly used for this process. Characteristics of the vehicles, such as excipients and pH, likely differed greatly from those of the reference products, potentially worsening their solubility and contributing to their poor absorption.

The compounded formulations were prepared in a single batch for the entire study. They were stored at room temperature after preparation; we did not determine whether degradation of the product occurred during storage. Plasma itraconazole concentrations following compounded product administration did not differ among measurement points, suggesting that degradation did not affect the results. Because of the poor results achieved with the compounded bulk formulations, such products should not be used as substitutes for the FDA-approved itraconazole formulations for cats.

Itraconazole is a weak base and is classified as practically insoluble by the United States Pharmacopeia.¹⁹ For the capsule formulation of the drug, gastric acidity is required for dissolution and absorption. The hydroxypropyl- β -cyclodextrin used to maintain solubility of itraconazole in the solution formulation is an oligosaccharide in the form of a cylindrical structure that is hydrophilic on the outside and hydrophobic on the inside, thereby positioning the itraconazole molecule within the hydrophobic tunnel. As a result, absorption is not dependent on the presence of an acid pH and bioavailability is greater than that of the

capsule formulation in humans.⁷ Consistent with findings in humans, absorption of the reference solution was approximately 3 times as great as that of the reference capsule in cats.

As identified in other species, high interindividual variation in absorption of both the reference capsule and solution was identified in the present study. For our study, the contents of reference capsules were repackaged into 50-mg capsules for administration. The reference itraconazole product was not manipulated or changed during this procedure, and the gelatin capsules that were used are not known to interfere with absorption. Therefore, the observed difference in absorption was unlikely a result of repackaging.

The terminal slopes observed on the concentration-time curve (Figure 1) were similar for the 2 reference itraconazole formulations, indicating that the products produced concentrations that declined at the same rate; therefore, we presume that clearance was similar for each formulation (although clearance could not be measured directly).

Therapeutic plasma concentrations of itraconazole are undetermined for cats, and veterinarians have extrapolated values on the basis of recommendations for humans.^{20,21} Blood samples can be tested to ensure that adequate plasma concentrations are attained in veterinary patients.²² In humans, trough serum itraconazole concentrations of ≥ 0.5 to $1.0 \mu\text{g/mL}$ as measured by high-pressure liquid chromatography have been associated with therapeutic success.^{20,21} On the basis of findings in the present study, reference itraconazole capsules given to cats with food at a dose of approximately 12.5 mg/kg once daily should achieve this target. Similar trough concentrations were achieved after administration of 100-mg itraconazole capsules every other day (dose range, 12.3 to 26.3 mg/kg [5.6 to 12.0 mg/lb]) for 3 weeks in another study¹² involving cats, although 20% of the cats developed clinically relevant adverse effects. The high incidence of adverse effects could limit application of that administration regimen.

On the basis of our calculations, and assuming linear clearance, an oral solution dose of approximately 4 mg/kg (1.8 mg/lb), given once daily without food to cats, should achieve plasma drug concentrations similar to those achieved with the reference capsule given at a dose of 12.5 mg/kg , once daily with food. This would markedly decrease the volume of medication an owner must administer, potentially improving cat and owner compliance, and might decrease the likelihood of adverse drug effects such as hyporexia, without compromising patient outcome. One other study²³ has been reported regarding the pharmacokinetics of an itraconazole solution administered orally at a dose of 5 mg/kg (2.3 mg/lb) to cats. However, detail was lacking regarding whether the solution was manufactured as a cyclodextrin complex, in an organic vehicle, or in another manner. The solution evaluated in that study had a mean \pm SD bioavailability of $52.1 \pm 11.6\%$. The C_{MAX} was $0.70 \mu\text{g/mL}$, which is proportional to the dose difference identified in the present study, but the $t_{1/2}$ and

AUC differed from our results. Without more information about the specific formulation used in that study,²³ these differences cannot be explained.

One limitation of the present study was the small number of healthy cats used. It remains undetermined whether the absorption characteristics reported here would apply to sick cats or to a larger population.

Given our findings, we do not recommend compounded oral itraconazole formulations for administration to cats. Absorption of the reference solution was markedly higher than that of the reference capsules, allowing for a substantially lower dose of itraconazole solution to be administered to cats to achieve the same plasma drug concentration as achieved with a larger dose of the capsule (4 mg/kg vs 12.5 mg/kg). In addition, the solution does not require administration with food, which may be relevant for ill cats with poor appetites. It should be noted that subsequent to acceptance of this report for publication, the FDA approved an oral itraconazole solution formulation^h for treatment of dermatophytosis in cats. As such, that formulation is recommended for initial treatment of cats with systemic fungal infections.

Acknowledgments

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Footnotes

- Sporanox capsules (100 mg), manufactured for PriCara, Division of Ortho-McNeil-Janssen Pharmaceuticals Inc, Raritan, NJ; capsule contents manufactured by Janssen Pharmaceutica NV, Olen, Belgium.
- Sporanox solution (10 mg/mL), manufactured for Janssen Pharmaceuticals Inc, Titusville, NJ; manufactured by Janssen Pharmaceutic NV, Beerse, Belgium.
- Itraconazole powder (certificate of analysis item 30-4325; lot No. C163344), PCCA USA, Houston, Tex.
- Acidophilus lactobacillus* (1 billion units/g; certificate of analysis item 30-4244; lot No. C171833), PCCA USA, Houston, Tex.
- PCCA syrup vehicle (No.30-3521), PCCA USA, Houston, Tex.
- Science Diet, Adult Feline Gourmet Beef Entrée, Hill's Pet Nutrition Inc, Topeka, Kan.
- Phoenix WinNonlin, version 6.1, Certara, St Louis, Mo.
- Itrafungol, Elanco US Inc, Greenfield, Ind.

References

- Legendre AM. Blastomycosis. In: Greene CE, ed. *Infectious diseases of the dog and cat*. 4th ed. St Louis: Elsevier Saunders, 2012;606-614.
- Brömel C, Greene CE. Histoplasmosis. In: Greene CE, ed. *Infectious diseases of the dog and cat*. 4th ed. St Louis: Elsevier Saunders, 2012;614-621.
- Hodges RD, Legendre AM, Adams LG, et al. Itraconazole for the treatment of histoplasmosis in cats. *J Vet Intern Med* 1994;8:409-413.
- Aulakh HK, Aulakh KS, Troy GC. Feline histoplasmosis: a retrospective study of 22 cases (1986-2009). *J Am Anim Hosp Assoc* 2012;48:182-187.
- Davis JL, Papich MG, Heit MC. Antifungal and antiviral drugs. In: Riviere JE, Papich MG, eds. *Veterinary pharmacology and therapeutics*. 9th ed. Ames, Iowa: Wiley-Blackwell, 2009;1013-1049.

6. Barone JA, Koh JG, Bierman RH. Food interaction and steady-state pharmacokinetics of itraconazole capsules in healthy male volunteers. *Antimicrob Agents Chemother* 1993;37:778-784.
7. Koks CHW, Meenhorst PL, Bult A, et al. Itraconazole solution: summary of pharmacokinetic features and review of activity in the treatment of fluconazole-resistant oral candidiasis in HIV-infected persons. *Pharmacol Res* 2002;46:195-201.
8. Willems L, van der Geest R, de Beule K. Itraconazole oral solution and intravenous formulations: a review of pharmacokinetics and pharmacodynamics. *J Clin Pharm Ther* 2001;26:159-169.
9. Mawby DI, Whittemore JC, Genger S, et al. Bioequivalence of orally administered generic, compounded, and innovator-formulated itraconazole in healthy dogs. *J Vet Intern Med* 2014;28:72-77.
10. Molter CM, Zuba JR, Papendick R. *Cryptococcus gattii* osteomyelitis and compounded itraconazole treatment failure in a Pesquet's parrot (*Psittichas fulgidus*). *J Zoo Wildl Med* 2014;45:127-133.
11. Smith JA, Papich MG, Russell G, et al. Effects of compounding on pharmacokinetics of itraconazole in blackfooted penguins (*Spheniscus demersus*). *J Zoo Wildl Med* 2010;41:487-495.
12. Middleton SM, Kubier A, Dirikolu L, et al. Alternate-day dosing of itraconazole in healthy adult cats. *J Vet Pharmacol Ther* 2016;39:27-31.
13. Davis JL, Salmon JH, Papich MG. Pharmacokinetics and tissue distribution of itraconazole after oral and intravenous administration to horses. *Am J Vet Res* 2005;66:1694-1701.
14. Yamaoka K, Nakagawa T, Uno T. Application of Akaike's information criterion (AIC) in evaluation of linear pharmacokinetic equations. *J Pharmacokinetic Biopharm* 1978;6:165-175.
15. US FDA. Repackaging of certain human drug products by pharmacies and outsourcing facilities. Guidance for industry. Silver Spring, Md: FDA, 2017;2. Available at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm434174.pdf. Accessed Jun 21, 2017.
16. US FDA. Compounding animal drugs from bulk drug substances. Draft Guidance for Industry #230. Available at: www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM446862.pdf. Accessed Jun 21, 2017. Withdrawn by the FDA on Nov 7, 2017.
17. US FDA. Compounding and the FDA: questions and answers. Guidance, compliance, regulatory information. Compounding. Available at: www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm. Accessed Jun 21, 2017.
18. US FDA. Guidance for FDA staff and industry: compliance policy guides manual. Section 608.400: compounding of drugs for use in animals. Rockville, Md: FDA, 2003. Available at: www.fda.gov/OHRMS/DOCKETS/98fr/03d-0290-gdl0001.pdf. Accessed Jan 5, 2016.
19. United States Pharmacopeial Convention. *USP pharmacists' pharmacopeia: 2008-2009*. 2nd ed. Rockville, Md: United States Pharmacopeia Convention, 2009;85-874.
20. Goodwin ML, Drew RH. Antifungal serum concentration monitoring: an update. *J Antimicrob Chemother* 2008;61:17-25.
21. Ashbee HR, Barnes RA, Johnson EM, et al. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother* 2014;69:1162-1176.
22. Sykes JE, Papich MG. Antifungal drugs. In: *Canine and feline infectious diseases*. St Louis: Elsevier/Saunders, 2014;87-96.
23. Liang C, Shan Q, Zhong J, et al. Pharmacokinetics and bioavailability of itraconazole oral solution in cats. *J Feline Med Surg* 2016;18:310-314.



From this month's AJVR

Evaluation of the diagnostic yield of dental radiography and cone-beam computed tomography for the identification of dental disorders in small to medium-sized brachycephalic dogs

Sophie Döring et al

OBJECTIVE

To evaluate the diagnostic yield of dental radiography (Rad method) and cone-beam CT (CBCT) methods for the identification of 31 predefined dental disorders in brachycephalic dogs.

ANIMALS

19 client-owned brachycephalic dogs admitted for evaluation and treatment of dental disease.

PROCEDURES

31 predefined dental disorders were evaluated separately and scored by use of dental radiography and 3 CBCT software modules (serial CBCT slices and custom cross sections, tridimensional rendering, and reconstructed panoramic views). A qualitative scoring system was used. Dental disorders were grouped into 10 categories for statistical analysis. Point of reference for presence or absence of a dental disorder was determined as the method that could be used to clearly identify the disorder as being present. Accuracy, sensitivity, specificity, and positive and negative predictive values were calculated with the McNemar χ^2 test of marginal homogeneity of paired data.

RESULTS

When all 3 CBCT methods were used in combination, the diagnostic yield of CBCT was significantly higher than that of dental radiography for 4 of 10 categories (abnormal eruption, abnormally shaped roots, periodontitis, and tooth resorption) and higher, although not significantly so, for all categories, except for 1 (loss of tooth integrity).

CONCLUSIONS AND CLINICAL RELEVANCE

CBCT provided more detailed information than did dental radiography. Therefore, CBCT would be better suited for use in diagnosing dental disorders in brachycephalic dogs. (*Am J Vet Res* 2018;79:62-72)



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