Comparison of Compounded, Generic, and Innovator-Formulated Itraconazole in Dogs and Cats

Janelle Renschler, DVM, PhD, DACVP, Amanda Albers, BS, Hanna Sinclair-Mackling, BS, Lawrence Joseph Wheat, MD

ABSTRACT

The triazole antifungal itraconazole may be cost prohibitive in brand name form; therefore, compounded and generic products are often used as alternatives. Itraconazole blood concentrations have not been studied in clinical patients receiving these formulations. Itraconazole bioassay was performed on serum/plasma from 95 dogs and 20 cats receiving itraconazole (compounded from bulk powder, generic pelletized, or brand name) for systemic mycosis treatment. Mean itraconazole concentration was lower in the compounded group (n = 42) as compared with the generic (n = 40) or brand name (n = 33) groups (0.5 μg/mL versus 8.3 μg/mL and 6.5 μg/mL, respectively; P < .001). No statistical difference was observed between itraconazole concentrations in the generic and brand name groups. Forty animals (95.2%) in the compounded group had subtherapeutic (<1.0 μg/mL) values. All cats in this group (n = 10) had undetectable itraconazole concentrations. Some animals in the generic and brand name groups had subtherapeutic values (12.5 and 12.1%, respectively) or potentially toxic values (>10 μg/mL; 37.5 and 24%, respectively). Compounded itraconazole should be avoided, but generic itraconazole appears to serve as a reasonable alternative to brand name itraconazole. Therapeutic drug monitoring may be beneficial in all cases. (J Am Anim Hosp Assoc 2018; 54:195–200. DOI 10.5326/JAAHA-MS-6591)

Introduction

Itraconazole is a synthetic triazole antifungal that is commonly used in the treatment of systemic fungal infections such as blastomycosis and histoplasmosis in dogs, cats, and humans. This drug is a very weak base (pKa 3.7), requiring a low pH for absorption, and it is highly lipophilic (nearly insoluble in water). The commercially available innovator-formulated capsules contain 100 mg itraconazole coated on spheres (composed of sucrose, maize starch, and purified water) and inactive ingredients including polyethylene glycol that facilitate absorption. Bioavailability of the drug in capsule form is low during fasting and increases greatly when taken with food, with previous human studies showing fasting absorption to be about 60% of postprandial absorption. An oral solution is also commercially available from the innovator, and this solution contains cyclodextrin in order to improve bioavailability as compared with the capsule form. Despite these formulations, variable intestinal absorption of itraconazole remains problematic for both capsule- and solution-based products.

Treatment of systemic fungal infections in dogs and cats may be cost prohibitive for many pet owners. Brand name itraconazole capsules typically cost >$1000/mo for a 20 kg dog and require an extended treatment duration (often >90 days). For this reason, lower-cost compounded products (estimated to be as low as <$100/mo for a 20 kg dog) containing bulk itraconazole powder have been marketed by various compounding pharmacies. In addition, human generic capsules containing pelletized itraconazole (both approved by the FDA and non-FDA approved) are available and have been used in domestic animals. The FDA-approved human generic capsules cost approximately one-quarter the cost of the brand name capsules, and the nonapproved generic capsules may cost as little as one-eighth that of brand name capsules.
The use of compounded itraconazole has been discouraged by veterinary specialists due to perceived treatment failures in dogs, as well as documented treatment failure in a parrot. Poor oral absorption of compounded itraconazole was previously demonstrated in black-footed penguins. In a study using nine healthy beagle dogs, Mawby et al. showed that one compounded itraconazole product produced a very low mean plasma concentration in dogs and was not bioequivalent to brand name itraconazole. Although a generic itraconazole was also not statistically bioequivalent in that study (possibly due to low number of dogs in the study), the generic product could produce plasma concentrations similar to brand name itraconazole. No previous published studies have documented itraconazole blood concentrations in dogs and/or cats being treated with these products for systemic mycoses.

A steady state concentration of itraconazole is achieved in dogs and cats 14–21 days after starting oral therapy. Due to unpredictable intestinal absorption, evaluation of the serum or plasma itraconazole concentration at steady state is recommended and may be assessed through various microbiological or high-performance liquid chromatography (HPLC) methods. Based on human studies, therapeutic plasma concentrations of itraconazole by HPLC should be at least 0.5–1.0 μg/mL. Because results by microbiological assay (bioassay) are typically 3–10-fold higher than by HPLC (with most references describing results on the lower end of that range), it could be assumed that therapeutic itraconazole blood concentrations should be at least approximately 3 μg/mL by bioassay. Depending on the relationship between HPLC and bioassay results, concentrations of 1–3 μg/mL by bioassay may potentially be therapeutic. Solid evidence is lacking on upper limits of the therapeutic range; however, results from a human study suggest that concentrations >17.1 μg/mL by bioassay are associated with a higher risk of toxicity. Toxicity is dose dependent and usually presents as nausea, anorexia, vomiting, and increased activity of liver enzymes (due to hepatotoxicity), as well as ulcerative dermatitis. In dogs, activities of serum alkaline phosphatase and alanine aminotransferase are positively correlated with itraconazole blood concentration, and higher enzyme activities are observed with values above approximately 10 μg/mL by bioassay.

The objective of this study was to compare itraconazole blood concentrations in dogs and cats undergoing treatment for systemic mycoses with either compounded, generic, or brand name itraconazole, in order to determine if either compounded or generic products might serve as lower-cost alternatives to the innovator-formulated itraconazole.

**Materials and Methods**

**Patient Population**

Serum or plasma samples were obtained from dogs and cats for clinical testing of itraconazole concentration at the authors’ diagnostic laboratory (MiraVista Diagnostics, Indianapolis, Indiana) between December 2012 and April 2014. Fax or telephone surveys were conducted with the submitting veterinary clinic to obtain consent and gather additional information including patient weight, daily itraconazole dosage, date of treatment initiation, category of itraconazole (compounded from bulk powder, generic pelletized, or brand name), and source (if known) of compounded or generic products. Information on breed and sex of patients was not recorded. In order to increase the amount of study samples, testing was encouraged for patients with a positive Blastomyces or Histoplasma antigen test at the authors’ laboratory. Testing was performed within 7 days of sample acquisition from the patient. Collection of blood samples at steady state concentration (at least 2 wk [dogs] or 3 wk [cats] after initiation of therapy or dosage change) at the trough time point was recommended. In addition, administration of itraconazole capsules with food was recommended, but owner compliance cannot be assumed and was not verified.

**Itraconazole Formulations**

Itraconazole products were classified as compounded, generic, or brand name. Compounded products contained bulk itraconazole powder in any form (oral suspension, capsule, chewable tablet, etc.). To be classified as generic, the product had to contain pelletized itraconazole inside capsules. Brand name products were innovator formulated and included both oral solution and capsules.

**Bioassay Procedure**

Itraconazole concentration was assessed by a microbiological assay (bioassay). *Candida kefyr* strain American Type Culture Collection 46764 was inoculated into Yeast Nitrogen Broth to a dilution of 0.5 McFarland and incubated at 33–37°C for approximately 5 h until a dilution of 2 McFarland was obtained. A volume of 1.5 mL of *C. kefyr* broth was added to 85 mL of 2X Yeast Nitrogen Broth, and this mixture was added to melted Noble agar and then allowed to harden for 15–20 min. Five-millimeter holes were bored in the agar. Holes were inoculated with 65 μL of either patient serum or plasma, standards or controls. Plates were incubated at 33–37°C for 16–18 h, and the clearing zones with no yeast growth were measured in millimeters with calipers. A standard curve was generated, and the patient result in millimeters was converted to itraconazole concentration in μg/mL. Result was reported as “None Detected” if there was no measurable zone or “<0.3 μg/mL” if there was a clearing zone but the measurement was below that for the 0.3 μg/mL standard. Results between 0.3 and 20 μg/mL were reported as the calculated value. Results above 20 μg/mL were reported as “>20 μg/mL.” For study purposes, results reported as “None Detected” were classified as 0 μg/mL, those reported as “<0.3 μg/mL” were...
classified as 0.29 μg/mL and those reported as “>20 μg/mL” were classified as 20.1 μg/mL. Results were categorized as subtherapeutic (<1 μg/mL), equivocal (1–2.9 μg/mL), therapeutic (3–10 μg/mL), or potentially toxic (>10 μg/mL).

Statistical Analysis
Statistical calculations were performed using MedCalc Statistical Software version 12.7.6. A two-tailed Fisher’s exact test was applied to the data, and P values of ≤ .05 were considered significant.

Results
The study group included 115 animals, including 95 dogs and 20 cats. Species and product distributions among the three groups are shown in Table 1. Compounded products were reported to have been attained from a wide variety of compounding pharmacies, and most were in oral suspension form. Some patients had received bulk itraconazole powder compounded in capsule form or chewable tablets. One dog in the compounded group had samples analyzed at two different time points while receiving different dosages of itraconazole (thus totaling the number of samples analyzed at 116). Generic products had also been attained from a variety of sources. Because generic capsules marketed for human use are only available in 100 mg size, in some cases (particularly for felines), the capsules were resized by weighing the pellets to create lower-dose capsules. Due to owner acquisition of many generic products, veterinarians were often uncertain of the source of the generic product being used for the patient.

Brand name products included both capsule and oral solution formulations. All cats in the brand name group were receiving the oral solution.

Mean dosage of itraconazole administered to patients in the generic group (6.0 mg/kg/day) was lower than that for the compounded and brand name groups (8.0 and 7.4 mg/kg/day, respectively; P = .013 and .015). Mean serum or plasma itraconazole concentration was subtherapeutic in the compounded group (0.5 μg/mL) but was within the therapeutic range for both the generic and brand name groups (8.3 and 6.5 μg/mL, respectively). The mean itraconazole concentration for the generic group was not statistically different from the brand name group (P = .184).

The distribution of results is shown in Figure 1. The single outlier for the compounded group with an itraconazole concentration above 3 μg/mL (11.3 μg/mL) was a 12-kg dog undergoing treatment for blastomycosis with 8.3 mg/kg/day itraconazole from a veterinary compounding pharmacy. At least three other dogs in the study were reportedly receiving a product from the same pharmacy, and these dogs all had subtherapeutic itraconazole concentrations. Subtherapeutic itraconazole concentrations were found in 5 patients out of 40 (12.5%) in the generic group as well as 4 patients out of 33 (12.1%) in the brand name group. Equivocal itraconazole concentrations (1–2.9 μg/mL) were also found in five patients from the generic group and four patients from the brand name group. In addition, 15/40 animals (37.5%) in the generic group had results in the potentially toxic range (>10 μg/mL), along with 8/33 (24%) in the brand name group and the single outlier in the compounded group.

### TABLE 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>P Value</th>
<th></th>
<th></th>
</tr>
</thead>
</table>
| Total no. of animals | 42 | 40 | 33 | N/A
| No. of dogs | 32 | 36 | 27 | N/A
| No. of cats | 10 | 4 | 6 | N/A
| Mean weight, kg | 23.15 | 24.8 | 19.5 | .631
| Mean dosage itraconazole, mg/kg/day ± SD (median) | 8.0 ± 4.4 (7.1) | 6.0 ± 2.1 (5.5) | 7.4 ± 2.6 (6.7) | .013*
| Feline | 12.6 ± 7.2 (10.7) | 6.0 ± 3.7 (4.7) | 7.5 ± 3.1 (7.1) | .118
| Canine | 6.7 ± 2.0 (5.8) | 6.0 ± 1.9 (5.5) | 7.4 ± 2.6 (6.7) | .147
| Mean blood itraconazole, μg/mL ± SD (median) | 0.5 ± 1.7 (0.0) | 8.3 ± 5.9 (7.4) | 6.5 ± 5.3 (4.9) | <.001*
| Range blood itraconazole, μg/mL | 0.0–11.3 | 0.3–20.1 | 0–20.1 | N/A

* Statistically significant.
N/A, not applicable; SD, standard deviation.
Although the mean dosage for cats receiving compounded itraconazole was relatively high at 12.6 mg/kg/day, all of these cats had an undetectable itraconazole concentration. Four cats had received generic itraconazole (at dosages of 3.6, 5.8, 3.2, and 11.4 mg/kg/day) and had itraconazole concentrations of 0.3, 0.3, 0.7, and 17.4, respectively. Six cats had received brand name itraconazole (at dosages of 4.3, 5.0, 4.8, 10.4, 11.3, and 9.2 mg/kg/day) and had itraconazole blood concentrations of 0.3, 0.6, 1.0, 4.9, 7.7, and 9.7, respectively.

The relationship between itraconazole dosage and blood concentration for the generic and brand name groups is shown in Table 2. Animals with a subtherapeutic or equivocal blood concentration were receiving a lower dosage of brand name itraconazole (P = .02) or generic itraconazole (P = .03) as compared with those with therapeutic blood concentrations. There was no significant difference between administered dosages for animals with therapeutic blood concentrations as compared with toxic blood concentrations.

**Discussion**

In this study, we demonstrated very low itraconazole blood concentration in clinical patients receiving compounded itraconazole. Compounding from bulk itraconazole for animal use is currently not permitted under the most recent (2003) Compliance Policy Guide of the FDA. Bulk medications are considered unapproved substances, as they are the active pharmaceutical ingredients intended to be used in the manufacturing of the final FDA-approved product. Compounding of a drug may lead to reduced systemic availability, quality, and stability as compared with the approved product. The American Veterinary Medical Association only supports compounding from bulk pharmaceutical ingredients when the approved product is not commercially available, the appropriate compounded preparation cannot be produced from the approved product, or there is no approved product from which to compound the needed preparation. None of these criteria are applicable to itraconazole.

![Distribution of blood itraconazole results for dogs and cats receiving compounded, generic, or brand name itraconazole. Dashed lines indicate limits of therapeutic range (3–10 μg/mL), and dotted line indicates lower limit of equivocal range (1–2.9 μg/mL). ND, none detected.](image)

**TABLE 2**

<table>
<thead>
<tr>
<th>Itraconazole Concentration</th>
<th>Mean Dosage Itraconazole, mg/kg/day ± SD (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtherapeutic + equivocal (0–2.9 μg/mL)</td>
<td>4.5 ± 1.4 (4.3) 4.9 ± 0.9 (4.8)</td>
</tr>
<tr>
<td>Therapeutic (3.0–10.0 μg/mL)</td>
<td>6.3 ± 1.5 (6.4) 8.5 ± 2.6 (8.6)</td>
</tr>
<tr>
<td>Potentially toxic (&gt;10 μg/mL)</td>
<td>6.7 ± 2.6 (5.7) 7.5 ± 2.3 (8.2)</td>
</tr>
</tbody>
</table>

SD, standard deviation.
as both the innovator-formulated product and FDA-approved generic products are available for use in domestic animals. Despite these factors, compounded products prepared from bulk powder itraconazole are widely available through compounding pharmacies. Veterinary practitioners apparently continue to use these compounded products with some frequency, as the largest number of cases in our study were receiving compounded itraconazole. This is most likely attributed to cost concerns and possibly a lack of understanding of the problems associated with compounded medications.

Generic itraconazole capsules are identical in formulation to the brand name capsules and should have the same quality, strength, purity, and stability. Because of these identical characteristics, both generic and brand name itraconazole would reasonably be expected to have similar bioavailability. The generic products used in this study were from a wide variety of sources (including some non-FDA-approved pelleted itraconazole capsules) and produced similar blood concentrations (despite being administered at a lower mean dose) as compared with brand name products. These results support the use of pelleted generic itraconazole as a lower-cost substitute for innovator-formulated itraconazole.

The finding of subtherapeutic itraconazole blood concentrations in some animals in the generic and brand name groups (12.1 and 12.7%, respectively), as well as the poor correlation between prescribed dose and measured blood concentration, supports the recommendation that therapeutic drug monitoring should be performed despite the type of itraconazole product used. Subtherapeutic blood levels in these animals might be due to owner noncompliance (e.g., not administering capsules with food), higher gastric pH, or other unknown causes for reduced bioavailability. In addition, many animals in the generic and brand name groups had itraconazole blood concentrations in the potentially toxic range. Monitoring of itraconazole blood concentrations in these cases allows for a dosage reduction (and therefore a lower cost of treatment). At the time of press, the cost of the itraconazole bioassay was only $39 in the authors’ laboratory. This cost is minimal in comparison with the cost of additional months of itraconazole products (hundreds to thousands of dollars) due to prolonged therapy from subtherapeutic itraconazole concentration, or additional diagnostics (e.g., serial serum biochemistry profiles) and therapy due to itraconazole toxicity. Veterinary practitioners should be aware of the method (HPLC versus bioassay) used for measuring itraconazole by the diagnostic laboratory, as it will impact the therapeutic range.

Although only 20 feline cases were available for this study, some interesting trends were apparent from this group. All 10 of the cats receiving compounded bulk itraconazole had an undetectable blood concentration (despite the majority receiving itraconazole at >10 mg/kg/day). Three out of four cats in the generic group had a subtherapeutic blood concentration, although these cats were all receiving a lower dose (<6 mg/kg/day) of itraconazole. Results suggest that a higher dose (>10 mg/kg/day) may be necessary to achieve therapeutic blood levels in some cats. The generic products administered to cats were all likely pelleted itraconazole compounded inside capsules, as generic capsules are not commercially available in the appropriate size for domestic feline body weight. We chose to include these animals in the "generic" group rather than the "compounded" group because they were receiving pelleted itraconazole. We cannot exclude the possibility that compounding of a generic product resulted in reduced bioavailability, instability, contamination, etc., and perhaps should have been included in the "compounded" group. The cats in the brand name group were all receiving the oral suspension (which has greater bioavailability than capsules in general); however, three out of six cats still had a subtherapeutic blood concentration. Again, these three cats were all receiving a lower dose (≤5.0 mg/kg/day) of the itraconazole suspension. Additionally, the proprietary oral suspension may be poorly tolerated by cats, leading to owner difficulty in administering the complete prescribed dose to the cat.19 Alternate-day dosing of cats with brand name itraconazole capsules was recently described as a possible alternative to the brand name oral suspension or compounded products, although we did not include any cats on this dosing regimen in the present study.19

One limitation of this study was the use of the bioassay technique as compared with HPLC methods, which are more sensitive and lack potential interference from other antifungal agents. The bioassay has been used clinically in the authors’ laboratory and provides a reasonable estimation of itraconazole levels without the need for expensive instrumentation and reagents, thus allowing the cost of testing to remain low. Increased sensitivity of HPLC over bioassay is not clinically relevant, as the bioassay can detect a concentration as low as 0.3 µg/mL, which is well below the lower therapeutic limit. Bioassay methods typically result in higher estimated itraconazole concentration as compared with HPLC. This is due (in part) to the presence of an active metabolite, hydroxyitraconazole, which contributes to bioassay results. Hydroxyitraconazole may also be measured by HPLC, and bioassay results are still higher than combined itraconazole and hydroxy-itraconazole concentrations by HPLC. One explanation for this may be the insolubility of itraconazole in standards prepared in serum, leading to reduced zone sizes of standards (and thus overestimation of drug concentrations in clinical samples).13 In previous comparisons of HPLC with various bioassay techniques, an approximately 3–10-fold difference in itraconazole concentration was observed.13,14 Bioassay/HPLC ratios may vary depending on the laboratory and method and thus should be established locally.
Another limitation of the study is the lack of clearly defined limits for therapeutic range of itraconazole levels. We are unaware of any canine or feline studies evaluating the lower therapeutic limit for itraconazole blood concentration. Several human studies have been used to make projections to veterinary patients. In a study of patients with human immunodeficiency virus and cryptococcal meningitis, better treatment response was observed with mean itraconazole blood concentration $>1\ \mu g/mL$ (by HPLC).$^{10}$ In a study of 250 patients with oral mucosal candidiasis, trough itraconazole blood concentration by HPLC $>0.5\ \mu g/mL$ was associated with the highest rate of treatment success.$^{12}$

Conclusions from these two studies form the basis for the most widely accepted minimum therapeutic itraconazole concentration by HPLC (0.5–1.0 $\mu g/mL$). Neither of the previous studies, however, addressed therapeutic concentrations for histoplasmosis or blastomycosis. One study of itraconazole therapy for histoplasmosis in patients with acquired immunodeficiency syndrome showed treatment failure in a patient with plasma itraconazole concentration of 1.8 $\mu g/mL$ by bioassay.$^{20}$ The authors had arbitrarily chosen a therapeutic target concentration of at least 2 $\mu g/mL$ by bioassay. In the current study, we chose a target concentration of at least 3 $\mu g/mL$ for our bioassay with an equivocal range of 1–2.9 $\mu g/mL$. Ultimately, lowering the therapeutic target from 3 to 1 or 2 $\mu g/mL$ would have minimal impact on study results, as the mean itraconazole blood concentration in the compounded group was only 0.5 $\mu g/mL$.

**Conclusion**

We demonstrated that compounded itraconazole from a variety of sources failed to produce therapeutic itraconazole blood concentrations in dogs and cats undergoing treatment for systemic mycoses. Generic pelletized itraconazole did produce similar results as compared with the brand name product. These results support the concept that compounded bulk itraconazole should be avoided, but that generic itraconazole may serve as a lower-cost treatment alternative to the innovator-formulated itraconazole. Some animals receiving either the generic or the brand name itraconazole had a subtherapeutic (or potentially toxic) blood concentration; therefore, therapeutic drug monitoring for itraconazole is recommended in all cases.

**FOOTNOTES**

a Sporanox capsules 100 mg; Capsule contents manufactured by Janssen Pharmaceutica N.V., Olen, Belgium; Manufactured by JOLLIC, Gurabo, Puerto Rico; Manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey

b MedCalc Software bvba, Ostend, Belgium

**REFERENCES**


