Treatment of Blastomycosis With Itraconazole in 112 Dogs

Alfred M. Legendre, Barton W. Rohrbach, Robert L. Toal, Michael G. Rinaldi, Linda L. Grace, and Janet B. Jones

One hundred twelve client-owned dogs with blastomycosis were treated with itraconazole, 5 or 10 mg/kg/d. The first group of 70 dogs treated in 1987 and 1988 received 10 mg/kg/d (group 1), and the second group of 42 dogs treated after October 1988 received 5 mg/kg/d (group 2). Even though the groups were treated at different times, the dogs were similar in age and gender distribution, number of sites involved, and percent and severity of pulmonary involvement. The proportion of dogs cured with a 60-day course of itraconazole was similar for both groups (53.6% versus 54.3%) and for a second historical control group treated with amphotericin B (57%); the recurrence rate was also similar, 20%, 21.4%, and 20%, respectively. Dogs treated with itraconazole had similar mortality rates (25.7% at 5 mg/kg/d; 25% at 10 mg/kg/day) to those treated with amphotericin B (23%). Seventeen of the 23 dogs that died (74%), did so during the first week of treatment; these early deaths were usually attributed to respiratory failure. The only site of infection that was significantly associated with failure (death or recurrence) was the brain. There was a marked difference in survival times between dogs without lung disease or with mild lung disease compared with dogs with moderate or severe lung disease. Serum itraconazole concentrations reached steady state by 14 days of treatment. Dogs receiving 5 mg/kg/d of itraconazole (group 2) had mean serum concentrations of 3.55 ± 2.81 mg/mL (range, 0.67 to 10.8 μg/mL), whereas dogs receiving 10 μg/kg/d (group 1) had mean concentrations of 13.46 ± 8.49 μg/mL (range, 1.8 to 28 μg/mL) ($P \leq .001$). There was no association between cure and serum itraconazole concentrations. Dogs in group 1 had significantly more adverse effects than dogs in group 2 ($P = .046$). Anorexia was the most common adverse effect, occurring in 14.9% of dogs in group 1. Only 8% of dogs in group 2 had adverse effects. Serum concentrations of itraconazole were positively correlated with serum alkaline phosphatase and alanine aminotransferase activities. Our findings indicate that itraconazole administered at a dose of 5 mg/kg/d is the drug of choice for blastomycosis in dogs.

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Blastomycosis is a systemic fungal infection of the dog. The disease is common in the Mississippi, Missouri, and Ohio river basins, as well as in Wisconsin and the central Atlantic states.[1-5] Amphotericin B administered IV has been the treatment of choice since the 1960s.[6-8] However, renal toxicosis often occurs during amphotericin B treatment; therefore, an easier-to-use and less toxic treatment has been sought. Ketoconazole, an imidazole administered PO, is effective in dogs with blastomycosis,[9,10] but the responses to treatment occur more slowly, and the cure rate is less than that obtained with amphotericin B.[10]

Itraconazole, a triazole, was developed by Janssen Pharmaceutica in 1980 and became available for treatment of fungal infections in humans in October 1992. We report the results of treatment with itraconazole PO in 112 dogs with blastomycosis.

Materials and Methods

Dogs

The 112 dogs in this study were client-owned animals. Some dogs were brought directly to the Veterinary Teaching Hospital but most were referred by area veterinarians. Dogs were treated from January 1987 to June 1990.

Inclusion Criteria

To be included in the itraconazole study, a cytological or histopathologic diagnosis of blastomycosis was required, and owners had to sign a consent form to use an investigational drug, and agree to return the dog for re-evaluation.

Clinical Evaluation

A history, physical examination, CBC, and serum biochemical analysis were obtained in all dogs. Ophthalmic evaluation was performed if ocular disease was suspected during initial examination. Thoracic radiographs were taken in all patients, and radiographs of specific bones were taken if there was evidence of lameness. Any dog with neurological signs referable to the brain was considered to have brain involvement. Prior to receiving itraconazole, a work sheet was completed by the clinician identifying the sites of infection found during the clinical evaluation. Owners were asked to return their dogs for re-evaluation after 30 and 60 days of treatment and to report any problems. Thoracic radiographs were repeated at the end of the treatment period (60 days).

Itraconazole Treatment

Dogs in group 1 (n = 70) evaluated in 1987 and 1988 received itraconazole 10 mg/kg/d PO for 60 days divided into 2 doses and administered with food. Starting in October of 1988, the remaining dogs in group 2 (n = 42) received itraconazole 5 mg/kg/d PO with food. After the change in protocol, there were 7 dogs that received a dose of 10 mg/kg/d. This occurred because participating clinicians were unaware of the change in protocol or feared that the dogs would not be adequately treated with a lower dose.

Itraconazole Toxicity

Dogs were routinely evaluated at 30-day intervals during the itraconazole treatment, and owners were asked to notify us if the patient

From the Department of Small Animal Clinical Sciences (Legendre, Grace and Jones) and the Department of Large Animal Clinical Sciences (Rohrbach and Toal), The University of Tennessee, Knoxville, TN and the Fungus Testing Laboratory (Rinaldi), The University of Texas Health Science Center at San Antonio, Department of Pathology, San Antonio, Texas.

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Reprint requests: Alfred M. Legendre, DVM, Department of Small Animal Clinical Sciences, University of Tennessee, Knoxville, TN 37901-1071.

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was anorexic, vomiting, or had other problems. In addition to physical examination, serum biochemical analysis was performed to monitor liver enzyme activities. Increase in serum alkaline phosphatase (SAP) activity was classified as mild (73 to 200 IU/L; reference range, 12 to 72 IU/L), moderate (201 to 400 IU/L), and severe (>400 IU/L). Increase in serum alanine aminotransferase (ALT) activity was classified as mild (76 to 200 IU/L; reference range, 20 to 75 IU/L), moderate (201 to 400 IU/L), and severe (>400 IU/L).

Procedures for Handling Complications

The attending clinician was given the option to continue treatment if clinical signs had not resolved at the end of the treatment period. The dose of itraconazole was usually decreased from bid to sid (10 mg/kg/d to 5 mg/kg/d) if signs of drug-associated toxicosis (anorexia, lethargy, ulcerative dermatitis, increases in ALT activity above 300 U/L) occurred. If toxicosis was suspected in the dogs receiving 5 mg/kg/d (group 2), the drug was discontinued and restarted at the same dose after the signs had abated. Treatment was discontinued if toxic effects occurred late in the course of treatment (after 45 days) and the signs of blastomycosis had resolved.

Serum Itraconazole Concentrations

Serum itraconazole was quantified by one of the authors (MGR) using a yeast-nitrogen base agar diffusion bioassay method modified from the technique described by Bodet et al.[11] *Candida fefyr* was added to a solution of yeast nitrogen base (YNB) broth and incubated at 37°C for 6 hours. The solution was adjusted to a No. 2 McFarland standard and 0.5 mL was added to 35 mL of melted YNB agar deeps. The YNB was poured into 150 × 15 mm Petri plates. Each 7-mm well bored in the agar was filled with standards (0.5, 2, 5, and 20 μg/mL), control, or patient unknowns, and the plates were incubated overnight at 37°C. The standard curve was plotted on semi-logarithmic paper. Patient samples and the control were read against the standard curve. This bioassay method measures total itraconazole activity, including the hydroxyitraconazole metabolite, which also has antifungal activity. Blood samples for serum itraconazole concentration were taken 4 to 7 hours after administration of the drug. Blood samples were collected weekly from 9 dogs during the first month of treatment to evaluate time needed to reach a steady state of itraconazole in serum. Serum itraconazole concentration was quantified in 37 dogs 30 days after treatment began.

Follow-Up Evaluation

When the owners were willing to return the dogs, they were re-evaluated monthly for 6 months after starting treatment, and 1 year after completion. Follow-up evaluations were carried out by telephone interview when owners were reluctant to return patients for examination. Response to therapy was categorized as cured, relapsed, or died, and the date of death was recorded. A cure was defined as a dog still alive, or a dog that was normal when lost to follow-up after a minimum of 426 days from the start of treatment. The 426-day follow-up was based on a 12-month period after completion of a 60-day course of treatment. This time was chosen based on previous studies that reported that most dogs treated with amphotericin B, ketoconazole, or amphotericin B and ketoconazole had recurrence of disease within 14 to 240 days after completion of treatment.[10] Dogs that had a recurrence of disease after apparent recovery were classified as relapses, regardless of their eventual outcome (eg, cure on retreatment, death, euthanasia, lost to follow-up). Dogs that had a recurrence of disease and were euthanized or died because of an illness suspected to be blastomycosis by the attending veterinarian were also considered relapses. Dogs that died without veterinary examination were considered relapses if one of the authors (AML) suspected blastomycosis from a description given by the owner, even though the diagnosis was not confirmed. Dogs in those cases where contact with the owners had been lost, dogs that ran away from home, or dogs that died from defined causes unrelated to blastomycosis less than 426 days after the start of treatment were classified as lost to follow-up. In our analysis, these dogs were given credit for the time they spent under observation. For analysis of the risk factors, the groups with a negative response (death and relapse) were combined into a treatment failure group and compared with the cured group (no relapse and alive and well for at least 426 days after the start of treatment).

Severity of Lung Disease

The severity of lung disease at the time of initial examination was determined by review of lung radiographs by one radiologist (RLT). Severity of lung disease was classified by previously published criteria as: no lesions, 0; mild or localized lung mass, 1; moderate, 2; moderate to severe, 3; severe, 4.[10]

Statistical Analysis

Interval data were tested for normal distribution using the W test developed by Shapiro and Wilk.[12] The level of alpha error to determine statistical significance for all tests was >0.05. Where possible, non-normally distributed interval data were transformed using square root or log transformation. Differences in means of interval characteristics among groups were tested for statistical significance using the *t*-test procedure. When we were unable to transform to a normal distribution, the Mann-Whitney test for nonparametric data was used.[13] Categorical data were evaluated using a χ-square or Fisher's Exact Test, depending on whether expected cell values were less than 5. A χ-square test for 1 × 2 tables was used to compare categorical characteristics among 3 or more groups.[14] Estimates of survival time among subgroups of patients was done using the product-limit method, and difference in survival time among subgroups was evaluated with the log rank test.[15] Covariables were tested for association with failure time using log rank scores.[16] Changes in serum concentration of itraconazole over time were evaluated by repeated measures of analysis of variance using a mixed model procedure and the Fisher's Least Significant Difference Test for specific contrasts. (SAS Institute Inc. SAS Technical Report P-229, SAS/STAT Software: Changes and Enhancements, Release 6.07. Cary, NC: SAS Institute Inc; 1992:287–368.) Correlation of liver enzyme activity with itraconazole concentration was evaluated using the method of Spearman.[17]

Results

Dogs Treated

There were 112 dogs included in the study, of which 71 (63%) were male (15 castrated) and 41 (37%) were female (26 spayed). Study patients ranged in age from 6 months to 11 years, with mean and median ages of 3.8 and 3.0 years, respectively. Thirty-seven breeds were represented, and 21% of the patients were of mixed breed. The most common breeds were Doberman Pinscher (11%), Labrador Retriever (9%), Cocker Spaniel (9%), and Golden Retriever (5%).

Characterization of the 5 and 10 mg/kg/d Treatment Groups

There were no marked differences between the treatment groups in age or gender distribution, number of sites involved, or percent and severity of pulmonary involvement

Table 1. Scores for Severity of Lung Disease in the Treatment Groups

Score	Group 1 n = 64	Group 2 n = 37
0	6 (9.4%)	3 (8.1%)
1	16 (25%)	15 (40.5%)
2	14 (21.9%)	7 (18.9%)
3	13 (20.3%)	4 (10.8%)
4	15 (23.4%)	8 (21.6%)

Severity of lung disease was classified as: no lesions, 0; mild or localized lung mass, 1; moderate, 2; moderate to severe, 3; severe, 4.[10] The radiographs of 11 dogs were not available for review.

(Table 1). Sixty-one percent of the dogs in group 1 (n = 70) (10 mg/kg/d) completed at least 60 days of treatment, compared with 60% of those in group 2 (n = 42) (5 mg/kg/d). There was no marked difference between the number of dogs in group 1 (15%) and those in group 2 (9%) that were treated for longer than 60 days.

Effectiveness of Itraconazole Treatment

The results of treatment for both groups were compared with a historical cohort treated with amphotericin B (Table 2). The results are similar. There were 14 dogs (20%) lost to follow-up from group 1 and 7 dogs (16.7%) lost from group 2 before the mandatory 426 day post-treatment evaluation period. These dogs were excluded from Table 2, but included in the survival analysis (Fig 1). Three dogs from group 1 and 2 dogs from group 2 were excluded from the survival analysis because they were lost to follow-up immediately after the initial examination (no points of follow-up). As seen in Fig 1, 17 of the 23 dogs that died did so during the first week of treatment. Eighty-four percent of patients in both treatment groups survived 7 days. There was no marked difference in survival times between the 2 groups of dogs ($P > .05$).

Blastomycosis recurred in group 1 at a mean and median time of 226 ± 153 and 169 days (range, 107 to 550 days), whereas in group 2, infection recurred at a mean and median

Table 2. The Outcome of Treatment With Itraconazole in 91 Dogs With Blastomycosis

	Itraconazole Groups*		Amphotericin B†
	Group 1 n = 56	Group 2 n = 35	8-9 mg/kg n = 35
Cured	30 (53.6%)	19 (54.3%)	20 (57%)
Recurrence	12 (21.4%)	7 (20%)	7 (20%)
Died	14‡ (25%)	9 (25.7%)	8 (23%)

* Group 1 received 10 mg/kg/d of itraconazole and group 2 received 5 mg/kg/d. The 21 dogs that were lost to follow-up before 426 days were excluded from the calculations.

† A previous study of blastomycosis treatment carried out at the same institution.[10] The 8 to 9 mg/kg dose is a cumulative dose.

‡ One dog died after 26 days of treatment with fulminating liver disease that may have been related to itraconazole.

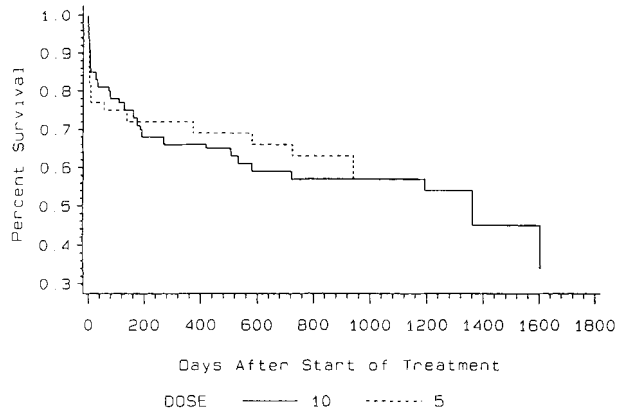

Fig 1. Survival of 112 dogs with blastomycosis administered itraconazole 10 mg/kg/d (group 1, n = 67) and 5 mg/kg/d (group 2, n = 40).

time of 313 ± 188 and 289 days (range, 97 to 583 days) ($P > .05$). Relapse was usually a clinical diagnosis; only 4 of the 19 dogs that relapsed had cytological or histopathologic confirmation of blastomycosis. Fifteen of 19 (79%) dogs had recurrent infection within 426 days of the start of treatment. In 4 dogs with late onset of recurrent blastomycosis, the signs occurred at 508, 518, 550, and 583 days, respectively. Of the 19 dogs with recurrent infection, 9 were euthanized, 2 died at the time of recurrence of blastomycosis, 7 were cured with further itraconazole treatment, and 1 was lost to follow-up.

Sites of Involvement

The site of infection was not statistically associated with failure (relapse or death), except for dogs with brain involvement ($P = .042$) All 4 dogs with brain involvement died. The lung as a site of infection had a P value of .06, and there was a marked association between severity of lung disease and survival time (Fig 2).

When 5 groups of dogs classified by severity of lung lesions were collapsed into 2 groups (0, 1, 2 and 3, 4), those with more severe lung disease (3 and 4) were significantly more likely to fail therapy (21 of 30, 70%) (χ^2 $P \leq .006$) than dogs with less severe lung disease (16 of 52, 31%).

Itraconazole

Serum itraconazole concentrations were quantified weekly for 4 weeks in 9 dogs in group 1 (Table 3). Serum itraconazole concentrations were quantified after 30 days of treatment in 23 dogs in group 1 and in 14 dogs in group 2. Dogs in group 1 had a mean concentration of 13.46 μg/mL ± standard error of the mean (SEM) 8.49 μg/mL, median 12.1 μg/mL (range, 1.8 to 28 μg/mL); those in group 2 had a mean serum concentration of 3.55 μg/mL ± 2.81 μg/mL, median 2.7 μg/mL (range, 0.67 to 10.8 μg/mL). The mean itraconazole concentrations were markedly different ($P \leq .001$).

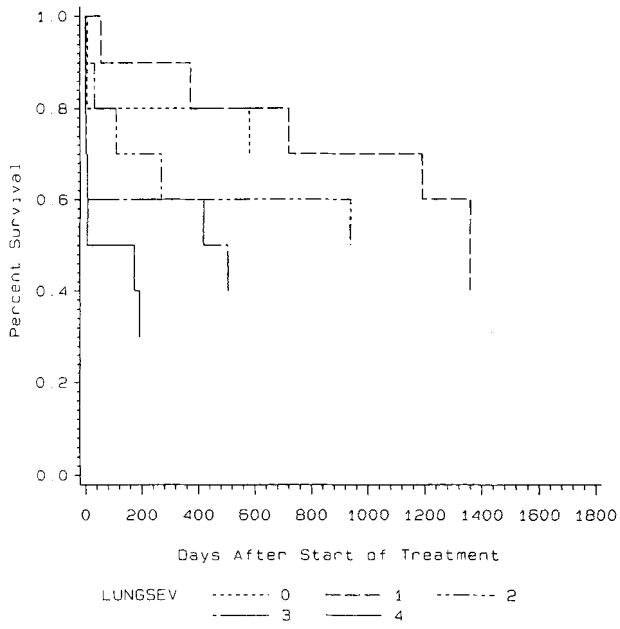

Fig 2. Survival of 82 dogs with blastomycosis is shown as cumulative proportion surviving (%). Dogs have been grouped as to lung severity: 0, no lung lesions (n = 9); 1, mild lesions or localized lung mass (n = 27); 2, moderate lesions (n = 16); 3, moderate to severe lesions (n = 15); and 4, severe lesions (n = 15).

Relationship of Drug Concentration to Effectiveness

The serum concentrations of itraconazole after 30 days of treatment were compared between dogs that were cured and those that failed therapy. The dogs that were cured (n = 23) had a mean concentration of 10.22 μg/mL ± SEM 1.71 μg/mL, compared with the dogs in the failed group (n = 11) mean of 9.39 μg/mL ± SEM 3.01 μg/mL ($P > .05$). Fourteen of 20 (70%) dogs with serum itraconazole concentrations of ≥5 μg/mL were cured compared with 9 of 14 (64%) dogs with serum itraconazole concentrations of <5 μg/mL ($P > .05$).

Adverse Effects

Three dogs from group 1 and 2 dogs from group 2 were excluded because they were lost to follow-up at the time they left the clinic after the initial examination. The 67 dogs given itraconazole at a dose of 10 mg/kg/d (group 1) had more adverse effects than the 40 dogs treated with 5 mg/kg/d (group 2) ($P < .006$). The most common adverse effects in dogs in group 1 were anorexia and skin ulceration (Table 4). Itraconazole-induced adverse effects usually developed after 30 days of therapy. Itraconazole was temporarily discontinued in 7 dogs in group 1 and in 1 dog in group 2.

Itraconazole-induced anorexia usually resolved in 3 or 4 days after the drug was discontinued. Therapy was restarted after the dogs had been off treatment for a week. One of the dogs with an increase in blood urea nitrogen (BUN) had been previously treated with amphotericin B. The ulcerative skin lesions detected in dogs were usually 1 to 2.5 cm in diameter and circular, and the skin was necrotic. When the necrotic skin was removed or sloughed, there was an ulcer (Fig 3). One dog had more extensive lesions (Fig 4). Skin lesions underwent biopsy in 2 dogs and vasculitis was observed.

Table 3. Serum Itraconazole Concentrations in Dogs With Blastomycosis Receiving 10 mg/kg/d of Itraconazole

	Days of Treatment			
	7	14	21	28
Dogs	n = 9	n = 9	n = 9	n = 7
Mean concentration (μg/mL) ± SEM	16.1 ± 1.7*	19.4 ± 1.7	20.2 ± 1.7	20.1 ± 1.8

* The 7-day time point was significantly different from all other days ($P \leq .05$).
Abbreviation: SEM, standard error of the mean.

Table 4. Adverse Effects Observed During Itraconazole Treatment

Effect	Group 1 n = 67	Group 2* n = 40
None	47 (70%)	37 (92.5%)
Anorexia	10 (14.9%)	1 (2.5%)
Vomiting	3 (2.8%)	1 (2.5%)
Diarrhea	2 (3.0%)	0
Lethargy	3 (4.5%)	0
Increased blood urea nitrogen	2 (3.0%)	0
Skin ulceration	5 (7.5%)	0
Pollakiuria	0	1 (2.5%)
Flaky skin	1 (1.5%)	0
Hair loss	1 (1.5%)	0

* Group 1 received itraconazole 10 mg/kg/d and group 2 received 5 mg/kg/d. There is a marked difference in number of adverse effects between the groups ($P = .006$).

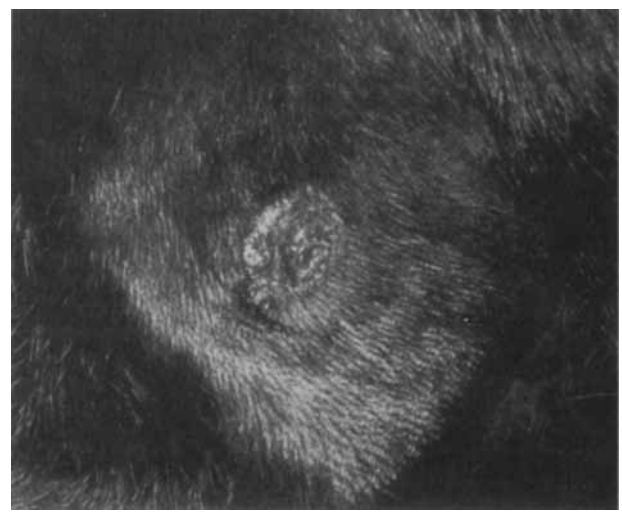

Fig 3. Focal ulcerative skin lesions associated with itraconazole treatment.

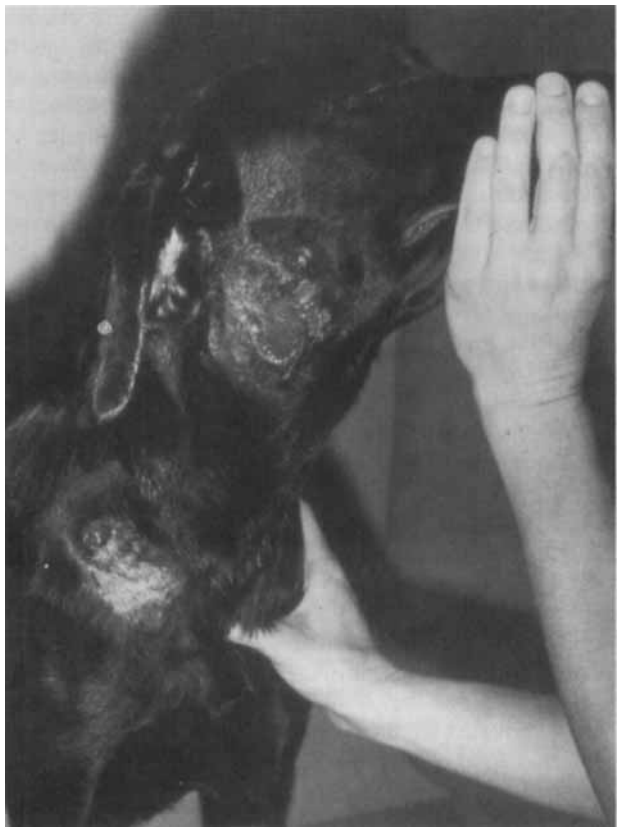

Fig 4. Extensive skin lesions associated with itraconazole treatment.

Liver Enzyme Activities Changes

The relationship between itraconazole and serum liver enzyme activities after 30 days of treatment is shown in Table 5. The median serum activities of ALT after 30 days of treatment in dogs in group 1 was 84 IU/L (range, 7 to 5,000 IU/L) compared with 35 IU/L (range, 13 to 423 IU/L) in dogs in group 2 ($P < .002$). The median SAP activity after 30 days of treatment was 62 IU/L (range, 25 to 334 IU/L) for dogs in group 1, and 62 IU/L (range, 18 to 273 IU/L) for dogs in group 2 ($P = .30$). The differences in serum liver enzyme activities between the 2 groups were marked only for the ALT.

Table 5. Serum Alkaline Phosphatase and Alanine Aminotransferase Activities in Dogs After Receiving Itraconazole 10 mg/kg/d or 5 mg/kg/d for 30 Days

	Group 1		Group 2	
Enzyme Activity	SAP (n = 28)	ALT (n = 40)	SAP (n = 24)	ALT (n = 24)
Normal	15 (54%)	16 (40%)	15 (63%)	21 (88%)
Mild	9 (32%)	17 (43%)	8 (33%)	2 (8%)
Moderate	2 (7%)	4 (10%)	1 (4%)	—
Severe	2 (7%)	3 (8%)	—	1 (4%)

Serum alkaline phosphatase (SAP) activity was categorized as: normal, 12 to 72 IU/L; mild, 73 to 200 IU/L; moderate, 201 to 400 IU/L; and severe, >400 IU/L. Serum alanine aminotransferase (ALT) activity was categorized as: normal, 20 to 75 IU/L; mild, 76 to 200 IU/L; moderate, 201 to 400 IU/L; and severe, >400 IU/L.

Group 1 received itraconazole 10 mg/kg/d and group 2 received 5 mg/kg/d.

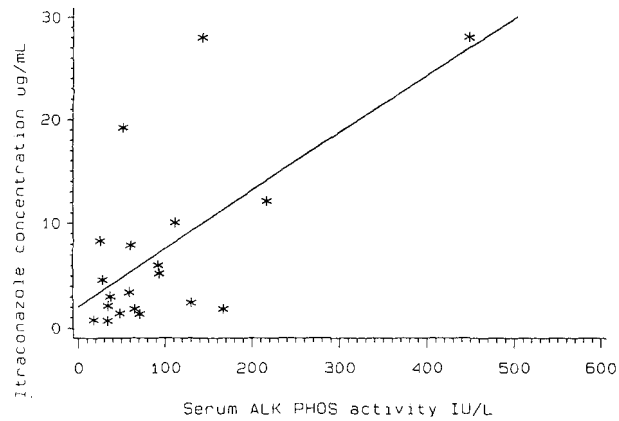

Fig 5. Correlation of serum itraconazole concentration with serum SAP activity at 30 days after beginning of treatment ($r^2 = .42$, $P \leq .002$, n = 20).

After 30 days of treatment, serum concentrations of itraconazole were correlated with serum activities of SAP and ALT. Itraconazole concentration was correlated with both SAP ($r = .45$, $P < .05$) and ALT ($r = .45$, $P < .03$) (Figs 5 and 6).

Discussion

The treatment of blastomycosis with itraconazole was as effective as was treatment with amphotericin B in an earlier study.[10] More than half of the dogs were cured with a single course of itraconazole therapy. Mortality and relapse rates in the present study were similar between the 2 dose groups and to those dogs treated with amphotericin B.[10] When com-

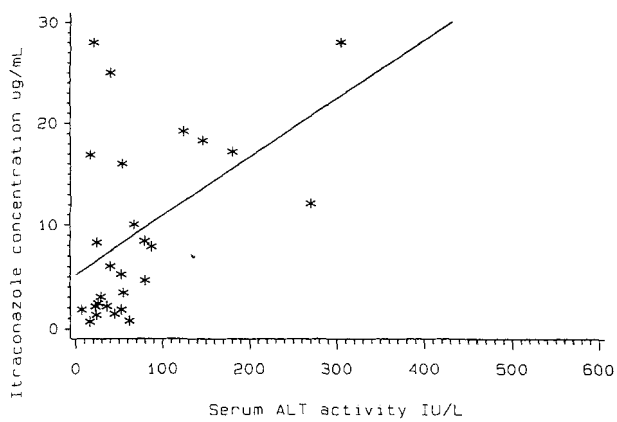

Fig 6. Correlation of serum itraconazole concentration with serum ALT activity at 30 days after beginning treatment ($r^2 = .24$, $P \leq .009$, n = 27).

pared with amphotericin B, itraconazole is easier to administer and has fewer adverse effects. Because itraconazole is administered PO, dogs can be treated at home. Although expensive ($5.00 a day for a 20-kg dog), the cost of itraconazole treatment is similar to that of amphotericin B when the cost of IV administration of amphotericin B and the frequent monitoring of renal function are included. We recommend itraconazole at 5 mg/kg/d to clients as the best treatment for dogs with blastomycosis.

Although dogs were not randomized to dose-groups in this study, the groups were similar based on characteristics that may be expected to affect the outcome. All dogs with blastomycosis treated from January 1987 to June 1990 were included. Patients treated with amphotericin B and used as the control group were treated from April 1977 to January 1982.[10] The characteristics of the latter groups were similar to those treated with amphotericin B.

Overall, effectiveness of itraconazole treatment may be better than shown in Table 2 because there were 21 dogs lost to follow-up that were excluded from the calculations. Only 3 of the 21 dogs that were lost to follow-up were lost during the first 60 days of treatment. Most deaths from blastomycosis occur in the first week of treatment, so dogs alive and well at 60 days would be expected to survive. Exclusion of the dogs lost to follow-up was done to compare these data with those obtained in the previous study of treatment with amphotericin B. The survival chart (Fig 1) provides the most accurate estimate of prognosis because all dogs were included and given credit for the total amount of time that they were under observation.

Recurrence of disease occurred in approximately 20% of the dogs with blastomycosis treated with either dose of itraconazole. The number of relapses may have been overestimated because some dogs were euthanized by referring veterinarians because of suspicion of recurrence of blastomycosis without a definitive diagnosis. Dogs that died after having signs consistent with blastomycosis were considered to have had a relapse even though they were not examined by a veterinarian. Only 4 of the 19 dogs with relapse had cytological or necropsy evidence of blastomycosis. The mortality and relapse data represent the worse case scenario in which all possible blastomycosis-related deaths or relapses were included.

The severity of lung disease significantly affected survival in dogs with blastomycosis (Fig 2). Dogs with severe lung disease (grades 3 and 4) were more likely to die than dogs without lung lesions or those with mild to moderate disease (grades 0, 1, and 2) ($P \leq .05$). Seventeen of 23 deaths occurred during the first week of antifungal treatment before therapy had time to suppress the infection. Most early deaths were attributed to respiratory failure. Reducing the high early mortality rate in dogs with severe pulmonary blastomycosis requires earlier diagnosis and treatment, rather than a better antifungal drug.

The rate of recurrence was approximately 20%, regardless of the therapy. Treatment for longer than 60 days may reduce the rate of recurrence of blastomycosis. People with blastomycosis in whom treatment was considered a success were treated for a median time of 6.2 months.[18] The benefit of treatment times longer than 60 days in reducing recurrence of blastomycosis is currently being evaluated.

The outcome of treatment was not related to the site of disease involvement, except for the brain ($P = .042$); all 4 dogs with brain involvement died of the disease. Blastomycosis of the brain carries a guarded prognosis regardless of treatment. Although the response in these dogs was poor, itraconazole is probably an effective drug in blastomycosis of the central nervous system. Itraconazole has been effective in the treatment of cats and rabbits with experimentally induced cryptococcal meningitis,[19,20] even though measurable amounts of itraconazole are rarely found in the cerebrospinal fluid because the drug is highly lipophilic. Itraconazole is also effective in treatment of ocular blastomycosis in dogs, where a barrier to drug penetration exists.[21]

The presence of lung involvement as a site that influences outcome approached significance ($P = .06$), so dogs with mild or no lung disease may have a better prognosis (Fig 2). No other sites of involvement significantly affected survival.

Dogs receiving 5 mg/kg/d of itraconazole responded as well as those receiving 10 mg/kg/d. This was attributed to the 5 mg/kg/d dose producing mean serum itraconazole concentrations of 3.55 μg/mL (range, 0.67 to 10.8 μg/mL) that greatly exceeded the minimum inhibitory concentrations (MICs) reported for *Blastomyces dermatitidis* (0.001 to 0.1 μg/mL).[22] Further increases in drug dose to 10 mg/kg/d increased serum itraconazole concentration, as well as drug toxicity (Figs 5 and 6 and Table 4) without increasing the cure rate.

There was a marked difference in the number and severity of adverse effects between the 2 groups (Table 4). Anorexia was the most common adverse effect, and it was usually associated with an increase in ALT. At the 5 mg/kg/d dose, 92.5% of dogs had no adverse effects. Even at the 10 mg/kg/d dose, 70% had no adverse effects (Table 4). Anorexia usually resolved in 3 or 4 days after discontinuation of itraconazole therapy. More dogs in group 1 had moderate and severe increases in liver enzyme activity than did those in group 2 (Table 5). There was a marked positive correlation between serum itraconazole concentrations and increases in serum ALT and SAP activities (Figs 5 and 6). The 5 mg/kg/d dose is clearly superior for dogs with blastomycosis because it minimizes the adverse effects without compromising drug effectiveness.

Ulcerative dermatitis was an unexpected adverse effect associated with itraconazole treatment (Figs 3 and 4). Ulcerative dermatitis occurred in 5 (7.5%) of the dogs in group 1 but was not seen in dogs in group 2. We also have seen ulcerative dermatitis in dogs with other fungal infections treated with itraconazole (data not shown). Biopsy specimens from 2 dogs revealed vasculitis in the periphery of the skin ulcers, but the etiology of these lesions was not determined. Many dogs with blastomycosis have greatly increased serum gamma globulin concentrations[23] due to the chronic disease process. Vasculitis may be caused by immune complex deposition, but drug eruption is a more likely explanation because the lesions resolved quickly after itraconazole therapy was discontinued (data not shown). Vasculitis

did not recur in those dogs restarted on itraconazole at the 5 mg/kg/d dose.

Some of the adverse effects (Table 4) may not have been caused by the itraconazole therapy. Pollakiuria was seen in only 1 dog. One of the 2 dogs with an increased BUN concentration had previously had amphotericin B therapy.

The 5 mg/kg/d dose, while producing fewer adverse effects, may not be the best dose for all fungal infections in dogs. Organisms such as *Aspergillus fumigatus* have MICs of 0.01 to 1 μg/mL[22] and, therefore, they may require the 10 mg/kg/d dose of itraconazole in spite of the greater potential for toxicity.

Resistance to itraconazole by *Blastomyces* organisms was not seen when dogs that relapsed were retreated with the drug. Dogs that had recurrence of disease responded to a second course of itraconazole (data not shown).

Serum itraconazole concentrations varied among dogs receiving the same dose of drug. In humans, administering itraconazole with food results in higher serum concentrations.[24] Owners were advised to give itraconazole with food to maximize absorption, but it was not determined if they followed feeding instructions. In dogs in group 1, serum concentrations at 30 days had a range of 1.8 to 28 μg/mL. Similar variations were seen in dogs in group 2, with serum concentrations at 30 days that ranged from 0.67 to 10.8 μg/mL. Higher serum drug concentrations are associated with more toxicity. Dogs given 10 mg/kg/d (group 1) had more adverse effects and higher ALT and SAP activities. There was a positive correlation between serum itraconazole concentrations and serum ALT and SAP activities. Based on these results, when toxicity occurs, it is justified to continue treatment at a reduced dose of itraconazole after signs of toxicity have resolved. Affected dogs probably will have an adequate serum concentration at the reduced dose because they absorb the drug well. Therapy should not be resumed until the appetite is normal and serum ALT activity is decreasing. To verify that serum itraconazole concentrations are adequate, measurement of serum itraconazole concentration 2 weeks after resuming therapy at the lower dose is recommended.

Itraconazole therapy at 5 mg/kg/d with food is as effective as amphotericin B in dogs with blastomycosis. Amphotericin B is more toxic, requires frequent monitoring, and has to be administered IV. Itraconazole is the treatment of choice for blastomycosis in dogs because it produces fewer adverse effects, it is easier to administer, and its cost is similar to that of amphotericin B treatment.

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