Comparison of Fluconazole and Itraconazole in a Rabbit Model of Coccidioidal Meningitis

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Coccidioidal meningitis is a devastating disease that requires long-term therapy with little hope of cure. A rabbit model of coccidioidal meningitis was used to compare the therapeutic efficacies of fluconazole (FCZ) and itraconazole (ITZ). Hydrocortisone-treated male New Zealand white rabbits were infected intracisternally with 5.0 ± 10^5 to 5.4 × 10^6 arthroconidia of Coccidioides immitis. Oral treatment with polyethylene glycol 200 (PEG) (n = 9), FCZ (n = 8; 80 mg/kg of body weight/day), or ITZ (n = 8; 80 mg/kg/day) began 5 days after infection and continued for 28 consecutive days. Both FCZ and ITZ reduced the number of CFU of C. immitis organisms in the spinal cord and brain compared with the number in PEG-treated animals (P ≤ 0.003), but the results for FCZ and ITZ were not different from each other. Both treatments resulted in lower cerebrospinal fluid (CSF) protein concentrations and leukocyte counts and faster clearing of C. immitis from CSF compared with the results for PEG-treated controls. Neither drug affected CSF glucose levels. Both compounds were effective at reducing neurological and systemic signs and extending survival (P ≤ 0.014). FCZ was more effective at reducing head and body shakes, posture changes, and incontinence; ITZ was more effective at reducing continuous fever. Mean levels of FCZ and ITZ in the serum and CSF were determined by bioassay; at 17 to 26 h postdosing, levels were 28.1 to 40.0 and 22.4 to 29.9 µg/ml, respectively, for FCZ and 0.77 to 2.51 and 0 µg/ml, respectively, for ITZ. The sera of most animals developed antibody to C. immitis, but azole treatment attenuated antibody development in CSF and its titer. In conclusion, both FCZ and ITZ were efficacious, but neither was curative in a rabbit model of coccidioidal meningitis.

Coccidioidomyces is caused by the fungus Coccidioides immitis. It usually enters the body by inhalation of arthroconidia. Dissemination of the parasitic form of the fungus from the lungs to other parts of the body including the meninges may occur. Coccidioidal meningitis is one of the most severe and devastating fungal diseases, with over 200 new cases occurring annually (7). If left untreated, 90% of the patients with this disease die within 1 year and 100% die within 2 years (6, 24). Complications of coccidioidal meningitis include vasculitis and stroke (25) and hydrocephalus. Treatment for coccidioidal meningitis has been limited to intrathecal amphotericin B (10) or oral ketoconazole (4), fluconazole (FCZ) (8, 15, 21), or itraconazole (ITZ) (20). Although these treatments may produce improvements and relieve some symptoms, cure is unusual. Currently, treatment of coccidioidal meningitis with an oral azole is considered a life-long therapy (5).

Finding of a curative treatment for coccidioidal meningitis has been hampered to some degree by the lack of a suitable animal model with which one can study the disease. Recently, we developed a rabbit model of coccidioidal meningitis whose clinical signs and laboratory findings closely mimic those of the disease in humans (26). This model permits repeated sampling of the cerebrospinal fluid (CSF), and investigational drugs can be administered by a number of routes, including the intracisternal route. Furthermore, clinical parameters during treatment, survival, fungal tissue burden, and histological examination can be assessed.

FCZ has been used extensively against many fungal diseases and has excellent penetration into tissue and CSF (1, 2, 13, 21, 27). On the other hand, ITZ does not penetrate into the CSF to any great degree (16, 23). Despite these differences, both drugs appear to offer some means of control of coccidioidal meningitis (19). However, there have been no comparative studies of FCZ and ITZ for the treatment of coccidioidal meningitis. We report on the first comparative study of the efficacies of FCZ and ITZ against coccidioidal meningitis in a rabbit model.

MATERIALS AND METHODS

Animals and study design. New Zealand White male rabbits (weight, 3 to 4 kg) obtained from Kraleck Farms (Turlock, Calif.) were used in the study. The study was done in two parts. Each part used 12 to 13 rabbits, with 4 or 5 rabbits per treatment group.

Immune suppression. At 1 day prior to infection, on the day of infection, and on 3 consecutive days following infection, all rabbits received an intramuscular
injection of hydrocortisone acetate (Steris Laboratory, Inc., Subsidiary of Schein Pharmaceutical, Inc., Florham Park, N.J.) at 2 mg/kg of body weight.

**Test organism.** *C. immitis* strain Silveira (ATCC 26868) was used in the study. A suspension of the arthroconidia of *C. immitis* was prepared as described previously (26). The suspension was stored at 4°C.

**Infection.** Prior to infection, the stock suspension of arthroconidia was quantitated by serial plating on Mycosel agar plates (Becton Dickinson and Co., Cockeysville, Md.). The stock suspension was further diluted to make an inoculum that contained 2.5 × 10⁵ CFU/ml. Each rabbit was sedated and was infected intracisternally as described previously (26). Up to 0.6 ml of CSF was removed by gentle aspiration, and then 0.2 ml of the inoculum was injected and flushed with 0.6 ml of sterile saline. Blood was collected from either the marginal ear vein or the central ear artery. Each rabbit was given yohimbine at 0.2 mg/kg intravenously to aid with recovery from anesthesia.

**Postinoculation monitoring.** Rabbits were monitored twice daily for evidence of systemic, neurological, or discomfort sequelae. Evaluations consisted of food and water consumption, coat appearance, respiration, vocalization, head and body shaking, head and body cants, mobility, paresis or paralysis, awareness, reflex, pain sensation, convulsion, agitation, lethargy, other behavior changes, weight, and temperature. In addition, the posture of each animal was graded according to the following criteria: 0, normal posture; 1, slightly abnormal weight distribution to the hind legs; 2, abnormal weight distribution to the hind legs; 3, abnormal weight distribution to the hind legs and slightly opisthotonoid posture; 4, opisthotonoid posture. Animals that exhibited signs of discomfort were given buprenorphine subcutaneously at 0.008 mg/kg twice daily. A high-calorie dietary supplement (Vitacal; Burns Veterinary Supply, Inc., Rockville Centre, N.Y.) and fluids (Lactated Ringer’s Injection, USP; McGaw, Inc. Irvine, Calif.) were given as needed to stimulate appetite and prevent dehydration. Rabbits were euthanized if they exhibited undue discomfort, paralysis, convulsions, stupor, or prolonged anoxia or dehydration.

**Treatment.** Starting 5 days postinfection, the animals were divided into three groups and were given one of these oral treatments with a 3-ml syringe with an attached animal feeding needle (18 gauge by 3 in.): (i) placebo, polyethylene glycol 200 (PEG), (ii) FCZ at 80 mg/kg/day, or (iii) ITZ at 80 mg/kg/day. The animals were treated once daily for 5 days. Drug dosage was adjusted daily on the basis of the rabbit’s weight. The drugs were suspended in PEG at a concentration of 120 mg/ml. FCZ and ITZ were provided as gifts from Pfizer (Groton, Conn.) and Janssen Pharmaceutica (Titusville, N.J.), respectively.

**Collection of CSF and serum.** Every 7 to 12 days, the rabbits were anesthetized with isoflurane. CSF and serum were collected as described previously (26). Euthanasia and tissue collection. Rabbits that required euthanasia prior to the end of the study or those that survived 7 or 8 days after the last treatment (39 or 40 days postinfection) were anesthetized, CSF and serum were collected, and the rabbits were euthanized by an intravenous injection of a concentrated pentobarbital solution (Euthasol; Delmarva Laboratories, Inc., Bristol, Tenn.). After euthanasia, brains and proximal spinal cords were collected. The left half of the brain including the cerebellum and upper cervical cord was transected and was placed into 10% buffered formalin for histopathologic study. The right half of the specimen was transected into brain (cerebrum, cerebellum, pons, and medulla) and proximal spinal cord (approximately 1.5 cm), and these were processed separately for quantitative fungal culture as described previously (26).

**Histopathology scoring.** The central nervous system (CNS) was sectioned into two blocks containing either the cerebrum or the brain stem, midbrain, cerebellum, and upper cervical cord. Each section was scored by using the following semiquantitative system: 0 (0.5), one to two foci of chronic inflammation; 1+, more diffuse chronic inflammation in meninges with a few giant cells and few organisms; 2+, more prominent meningeal inflammation, possibly some focal invasion of the infiltrate into the brain or cord parenchyma; 3+, more marked inflammation in the meninges with infiltration, encephalitis, usually meningeal endarteritis, and possibly some microinfarcts; 4+, the most extensive, i.e., greatest volume of inflammation in subarachnoid space, extensive invasion, encephalitis, multiple foci of infarcts, and endarteritis in the meninges. Histopathologic evaluation was performed by an observer blinded to both the treatment and the clinical status of the animals.

**CSF protein and glucose concentrations, fungal culture, and antibody titers.** CSF protein and glucose concentrations were determined with a Syncron CX system with the microprotein (M-TP) and glucose (GLU3) analysis kits (Beckman Instruments, Inc., Brea, Calif.), respectively. Total leukocyte (WBC) counts in the CSF were determined by counting cells in the freshly obtained CSF with a hemacytometer. Quantitative CSF fungal cultures were performed by plating 0.2 ml of freshly obtained CSF on Mycosel agar. The titers of immunoglobulin G against coccidioidal antigen in CSF and serum were determined by quantitative immunodiffusion (14).

**CSF and serum drug levels.** Drug concentrations in the CSF and serum of FCZ- and ITZ-treated animals were determined by bioassay as described previously (9, 18, 22). Lower detection limits for FCZ were 2.0 μg/ml for both serum and CSF. Lower detection limits for ITZ were 0.63 and 0.31 μg/ml for serum and CSF, respectively.

**Statistical analyses.** Data are presented as means ± standard deviations. GB-STAT for MS Windows (version 6.0, Dynamic Microsystems, Inc., Silver Spring, Md.) was used for all statistical analyses with the exception of survival analysis. Survival data were analyzed by using Statview for Macintosh (version 5; SAS Institute, Inc., Cary, N.C.). Confidence (95%) intervals of the log odds of the means for the culture data were compared, and a Kruskal-Wallis one-way analysis of variance was used to detect differences among the groups. In addition, a Mann-Whitney U test was used to compare each group. Mann-Whitney U tests were used to compare mean WBC counts and protein and glucose concentrations in the CSF.

A Fisher exact test was used to compare survival between treatment groups at day 39 and the incidence of vasculitis. A Kaplan-Meier survival analysis followed by a treatment group comparison by the Breslow-Gehan-Wilcoxon test was used to compare prolongation of survival. A P value of ≤0.05 was considered significant for all tests.

**RESULTS**

**Survival.** Figure 1 shows that treatment with either FCZ or ITZ increased survival through day 39 compared with the survival of the PEG-treated animals (*P* ≤ 0.003). The FCZ-treated group had eight of eight survivors and the ITZ-treated group had seven of eight survivors, whereas one of nine of the PEG-treated animals survived. Both FCZ and ITZ treatments prolonged survival compared with that after PEG treatment (*P* ≤ 0.014). Mean survival times were 24.0, 39.0, and 35.1 days for PEG-, FCZ-, and ITZ-treated animals, respectively.

**CUF of *C. immitis* in Ringer’s solution.** *C. immitis* was recovered from the CSF of 50% of the PEG-treated animals 11 or 12 days after infection (Table 1), and the proportion decreased to 17% by 20 or 21 days after infection. Treatment with either FCZ or ITZ cleared *C. immitis* from the CSF faster, as none was detected in animals treated with these drugs throughout the study. Data for one ITZ-treated animal that died early in the study, on day...
8, are not included in Table 1. CSF collected postmortem from this animal was culture positive for *C. immitis*.

**CFU of *C. immitis* in tissue.** Treatment with either FCZ or ITZ caused a reduction in the numbers of *C. immitis* in the CNS tissues compared with the numbers in PEG-treated animals (Fig. 2). FCZ produced 2,000-fold (*P* = 0.0004) and 500-fold (*P* = 0.0004) reductions and ITZ produced 600-fold (*P* = 0.0004) and 200-fold (*P* = 0.003) reductions in the numbers of CFU in the spinal cord and brain, respectively. Neither drug produced a superior reduction in the number of CFU over the other. Only one FCZ-treated animal had a spinal cord and brain that appeared to be sterilized of *C. immitis* (below the detectable limits of about 15 and 5 CFU/g of spinal cord and brain, respectively). Likewise, one ITZ-treated animal had sterilization of the brain but not of the spinal cord.

**Histopathology.** FCZ or ITZ treatment equally attenuated histopathological severity compared with that for the controls (*P* ≤ 0.0004). In general, semiquantitative scores for the brain stem, midbrain, cerebellum, and upper cervical cord area were slightly higher than the scores for the cerebrum. Mean and standard deviation scores for the brain stem, midbrain, cerebellum, and upper cerebral cord area were 3.8 ± 0.4, 1.3 ± 0.7, and 1.8 ± 1.2, for PEG-, FCZ-, and ITZ-treated animals, respectively. Scores for the cerebrum were 3.3 ± 0.8, 1.0 ± 0.5, and 1.3 ± 0.9 for PEG-, FCZ-, and ITZ-treated animals, respectively. One FCZ-treated animal had a pathological score of 0 for both areas. This was the same animal that had no detectable *C. immitis* in the brain and spinal cord tissues.

Vasculitis was observed in 100% of the PEG-treated animals, while a 25% (*P* = 0.002; PEG versus ITZ) incidence of vasculitis was observed in ITZ-treated animals. No vasculitis was observed in FCZ-treated rabbits (*P* < 0.0001; PEG versus FCZ). Infarcts were observed in 78% of the PEG-treated rabbits, whereas they were observed in 0% (*P* = 0.002) and 13% (*P* = 0.02) of the FCZ- and ITZ-treated rabbits, respectively.

**Clinical signs.** Most of the animals showed clinical signs of coccidioidal meningitis such as weight loss and reduced activity and appetite before treatments began on day 5. Both FCZ and ITZ were more effective than PEG at preventing many of the systemic and neurological signs. During the study nearly all animals showed agitation (Fig. 3) that was most likely a result of stiffness of the neck and back associated with the coccidioidal meningitis. Overall, FCZ-treated animals had fewer posture changes, incontinence, head and body shaking, head and body cant, ataxia, seizures, and paresis or paralysis than PEG- or ITZ-treated animals. A faster response to therapy was seen in FCZ-treated animals and was evident by lower mean posture scores from day 15 throughout the remainder of the study (Fig. 4). ITZ was more effective than either PEG or FCZ at reducing the occurrence of continuous fever (Fig. 3). Although ITZ-treated animals showed a slower response to therapy, the response was more consistent in that all animals responded to the same degree with gradual increases in appetite and weight and a decreased severity of the signs mentioned previously. On PEG treatment, one animal became moribund on day 8, another became moribund on day 14, and the majority became moribund between days 20 and 30 (Fig. 1). All these animals showed posture changes, as a result of coccidioidal meningitis, starting between days 5 and 8 (Fig. 4). Eight of nine animals became ataxic between days 6 and 13, with the one surviving animal not showing ataxia until day 37. They all developed paresis in at least one limb, with seven of nine animals showing paresis between days 6 and 15 and the other two animals showing paresis on days 23 and 34. As the disease progressed and the animals became moribund, paresis in all limbs was evident in some of the animals and two animals had seizures.

Only three of eight FCZ-treated animals showed posture changes and ataxia. The onset of posture changes was between days 7 and 14, which was delayed 2 to 6 days from that for PEG-treated animals. The onset of ataxia was also delayed and started between days 11 and 13.

Among the ITZ-treated animals, one animal became moribund and had seizures early in the study, on day 8. All of the ITZ-treated animals displayed posture changes as a result of coccidioidal meningitis between days 6 and 19, which was delayed 1 to 11 days from the time that PEG-treated animals displayed posture changes. Three of eight animals showed ataxia between days 5 and 7, and one showed paresis on day 13.

**CSF glucose concentrations.** By 11 or 12 days after infection, the mean CSF glucose concentrations for all treatment groups decreased markedly (Table 2). After this initial decrease, CSF glucose levels slowly increased for all treatment groups, but they still never attained the baseline levels measured before infection.
TABLE 2. CSF WBC, protein, and glucose levels during the course of infection and treatment

| CSF component and treatment | Levels on the following days after infection:<br> | | | | | 0 | 11–12 | 20–21 | 32–33 | 39–40 |
|----------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Glucose (mg/dl)            | PEG                                             | 116.6 (5; 102–137)                               | 59.3 (4; 56–63)                                 | 67.0 (2; 29–105)                                 | 76 (1; 76)                                       | 87 (1; 87)                                      |
|                            | FCZ                                             | 119.5 (8; 102–137)                               | 64.9 (7; 57–73)                                 | 76.9 (8; 69–85)                                 | 79.1 (8; 72–87)                                 | 93.5 (8; 82–105)                               |
|                            | ITZ                                             | 119.9 (8; 110–130)                               | 61.2 (5; 40–82)                                 | 70.7 (6; 64–77)                                 | 76.8 (6; 72–82)                                 | 91.7 (7; 75–109)                               |
| Protein (mg/dl)            | PEG                                             | 24.8 (5; 21–29)                                  | 256.0 (4; 132–380)                              | 347.5 (2; 0–2,133)                              | 492 (1; 492)                                    | 317 (1; 317)                                   |
|                            | FCZ                                             | 31.9 (7; 12–52)                                  | 133.0 (8; 63–203)                               | 109.0 (7; 54–164)                               | 87.6 (8; 18–157)                                | 85.1 (8; 29–141)                               |
|                            | ITZ                                             | 25.1 (8; 20–30)                                  | 140.2 (5; 81–200)                               | 172.3 (6; 72–273)                               | 73.8 (6; 57–91)                                 | 104.3 (7; 38–171)                              |
| WBC (no. of cells/mm³)     | PEG                                             | 46.9 (8; 0–101)                                  | 1,900.0 (5; 742–3,058)                          | 675.0 (5; 242–1,109)                            | 750 (1; 750)                                    | 1,125 (1; 1,125)                               |
|                            | FCZ                                             | 31.3 (8; 0–105)                                  | 1,218.8 (8; 64–2,374)                           | 500.0 (8; 130–871)                              | 171.9 (8; 0–348)                                | 515.6 (8; 111–920)                             |
|                            | ITZ                                             | 62.5 (8; 0–210)                                  | 982.1 (7; 106–1,859)                            | 604.2 (6; 97–1,112)                            | 232.1 (7; 92–373)                               | 500.0 (7; 202–799)                             |

*Means, followed in parentheses by number of animals and the 95% confidence interval, are shown.

**P < 0.05 versus day 0.
***P < 0.001 versus day 0.
****P < 0.005 versus day 0.
*****P < 0.05 versus PEG on day 11.
******P < 0.05 versus day 0.

infection. Treatment with FCZ or ITZ had no effect on the glucose concentrations, as there were no significant differences in CSF glucose concentrations between any of the groups at any sampling period.

**CSF protein concentrations.** Mean protein concentrations markedly increased for all treatment groups 11 or 12 days after infection (Table 2). Treatment with FCZ or ITZ attenuated this increase compared to the increase in PEG-treated controls. Animals given FCZ or ITZ equally maintained lower mean CSF protein concentrations than PEG-treated controls throughout the rest of the study. CSF protein levels for FCZ- or ITZ-treated animals never fully returned to the baseline levels measured before the infection.

**CSF WBC counts.** By 11 or 12 days after infection, mean CSF WBC counts were markedly higher than those on day 0 (Table 2). Treatment with FCZ or ITZ then lowered the CSF WBC counts; however, these counts were not significantly different from those for PEG-treated animals until days 32 to 33 and 39 to 40. One week after treatment stopped, on day 39 or 40, the WBC counts within the CSF increased for the FCZ or ITZ treatment groups compared with those on day 0.

**Drug levels.** The levels of both FCZ and ITZ in serum and CSF were measured after 17 to 26 h postdosing (Table 3). Mean levels of FCZ were 28.1 to 40.0 and 22.4 to 29.9 μg/ml for serum and CSF, respectively. Overall, the levels of FCZ in the CSF were about 19 to 25% lower than the levels in serum during treatment. Mean levels of ITZ were 0.77 to 2.51 and 0 μg/ml for serum and CSF, respectively. After 7 or 8 days without treatment, neither FCZ nor ITZ was detected in either the serum or the CSF. In all rabbits in which drug levels were measured, the level of drug in both the serum and the CSF decreased as treatment continued. This suggests some induction of increased metabolism or a decrease in the level of absorption of the drugs.

**Antibody titers.** Many of the rabbits developed antibody to *C. immitis* (determined by quantitative immunodiffusion) in the serum and CSF. For PEG-treated animals, all eight of the animals sampled (one animal died on day 8 and was not sampled) developed antibody in serum within 14 to 32 days after cisternal infection. The titers ranged from positive undiluted to 1:32. Five of seven rabbits had antibody in CSF, and the titers ranged from undiluted to 1:16. Antibody in CSF was detected at the same time or one sampling period (7 to 12 days) after antibody in serum was detected.

For FCZ-treated animals, seven of eight animals developed antibodies in serum that were first detected on day 21. Titers ranged from undiluted to 1:4. Only one of eight animals had detectable antibody in CSF; this was first detected at day 21, and the titer peaked on day 33 at 1:4. That particular animal took longer to respond to therapy, as evidenced by reduced appetite, posture changes, and body weight.

Six of seven surviving ITZ-treated animals had antibodies in serum that were detected as early as day 11. Two of seven rabbits had detectable antibody in CSF, with titers of undiluted and 1:2, respectively.

**DISCUSSION**

This study compared two azoles at equal milligram-per-kilogram-of-body-weight doses in a rabbit model of progressively acute coccidioidal meningitis. One azole, FCZ, is known to penetrate the blood-brain barrier and CSF. The rapid penetration into the CSF may explain the lower posturing scores and the lack of vasculitis and infarcts within the FCZ treatment group. In contrast, ITZ penetrates CSF poorly (16), but ITZ may penetrate CNS tissues. Perfect and Durack (16) measured detectable levels (0.078 and 0.156 μg/ml) of ITZ in the CSF of rabbits 1 to 3 h after oral administration and reported a higher level of ITZ in CSF at 1 to 2 h after oral administration.

**TABLE 3.** Mean drug levels in CSF and serum measured between 17 and 26 h postdosing by bioassay

<table>
<thead>
<tr>
<th>Drug</th>
<th>Body fluid</th>
<th>Mean ± SD drug concn (μg/ml) on the following days postinfection (no. of doses):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>11–12 (6 or 7)</td>
</tr>
<tr>
<td>FCZ Serum</td>
<td>40.0 ± 7.17 (8)</td>
<td>31.9 ± 7.88 (8)</td>
</tr>
<tr>
<td>CSF</td>
<td>29.9 ± 7.12 (6)</td>
<td>25.8 ± 4.98 (6)</td>
</tr>
<tr>
<td>ITZ Serum</td>
<td>2.51 ± 1.02 (6)</td>
<td>2.22 ± 1.22 (7)</td>
</tr>
<tr>
<td>CSF</td>
<td>0 (7)</td>
<td>0 (6)</td>
</tr>
</tbody>
</table>

*After a 7- or 8-day washout period.

Values in parentheses in table body are number of rabbits.
ratio of the level in CSF/level in serum in rabbits with experimentally induced meningitis. The rabbits in their study were given dosages of ITZ similar to those used in our study. However, in another study with these same dosages of ITZ, no ITZ was detected in the CSF at 1 and 24 h postdosing (17). Although ITZ was not detected in the CSF at 17 to 26 h postdosing in our study, it is possible that peak concentrations of ITZ, which should occur at 6 h postdosing (23), were high enough to inhibit or clear C. immitis from the CSF or that reduction of infection in the meninges and brain by ITZ subsequently rendered the CSF sterile. Possible evidence for this was seen after 6 to 7 days of treatment, when 100% of the ITZ-treated animals, as well as 100% of the FCZ-treated animals, had sterile CSF. It is conceivable that considerably less ITZ would be needed to inhibit C. immitis because ITZ is about eight times more active in vitro against C. immitis strain Silveira, for which the ITZ MIC is 0.78 g/ml, whereas the FCZ is 6.3 g/ml (3, 12). Whatever the sequence of events, it does appear that ITZ, like FCZ, is reaching the site of infection and reducing the fungal burden.

Coccidioidal meningitis is difficult to treat, with little hope of cure with current azole therapies, and patients with this disease may require lifelong treatment (5). Similarly, in the present study neither FCZ nor ITZ was able to eliminate C. immitis from the majority of CNS tissue samples cultured, even after 4 weeks of treatment with 80 mg/kg/day. A recent comparative study of FCZ dosages in rabbits and humans showed that between 48 and 87 mg/kg/day given to rabbits by infusion was approximately equal in terms of the peak level in serum and the area under the concentration-time curve to a high oral dose of 1,600 mg of FCZ per day given to humans (11). However, no related comparisons have been done for ITZ. The use of 80 mg of ITZ per kg greatly exceeds the normal doses used for humans, but this high dose was chosen since others have also found that high doses of ITZ are required to achieve efficacy in this animal host (17). In addition, we wanted to achieve levels in serum similar to those seen after oral administration of ITZ to humans. The ITZ levels seen in the rabbits were approximately equal to those seen in humans after administration of a 200- to 400-mg/day dose. The lack of sterilization at these high dose levels clearly demonstrates the need for new drug formulations and antifungal agents that can be used to cure coccidioidal infections.

Although azole treatment reduced the fungal burden and eliminated many of the signs associated with coccidioidal meningitis, inflammation was seen on histological examination in nearly all of the animals. Azole treatment did reduce the incidence of vasculitic complications that are major causes of morbidity and mortality in the human disease (25). No FCZ-treated and only 25% of the ITZ-treated animals showed vasculitic complications, whereas 100% of the PEG-treated animals showed vasculitic complications. The more prompt response to therapy seen in the FCZ-treated animals suggests that a rapid response to therapy prevented the development of vasculitis, at least for the duration of this study. In addition, the animals that responded best or early to ITZ treatment also had no vasculitic complications.

In conclusion, FCZ and ITZ had equivalent efficacies, considering the quantitative data. However, FCZ appeared to give an overall faster response to therapy. Both azoles were effective at controlling coccidioidal meningitis, but neither drug was able to eliminate C. immitis from the CNS tissues. It appears that drug penetration into the CSF is not necessary for control of coccidioidal meningitis.

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