ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2004, p. 4063–4066 Vol. 48, No. 10
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.10.4063–4066.2004

Efficacy of Posaconazole in a Murine Model of Central Nervous System Aspergillosis

Jackie K. Imai,[1] Gaurav Singh,[1] Karl V. Clemons,[1,2,3]* and David A. Stevens[1,2,3]

California Institute for Medical Research[1] and Department of Medicine, Division of Infectious Diseases, Santa Clara Valley Medical Center,[2] San Jose, and Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University, Stanford,[3] California

Received 15 March 2004/Returned for modification 13 May 2004/Accepted 1 July 2004

Human central nervous system (CNS) aspergillosis has >90% mortality. We compared posaconazole with other antifungals for efficacy against murine CNS aspergillosis. All tested regimens of posaconazole were equivalent to those of amphotericin B and superior in prolonging survival and reducing CFU to those of itraconazole and caspofungin and to vehicle controls. No antifungal regimen effected cure. No toxicity was noted. Overall, posaconazole shows potential for treating CNS aspergillosis.

Aspergillus fumigatus causes increasingly frequent opportunistic fungal diseases in immunocompromised or immunodeficient patients (21). Dissemination to the central nervous system (CNS) from pulmonary tissues is most common (11). CNS infections are highly lethal, with greater than 90% mortality (22). With the development of a murine model of CNS aspergillosis, current and new antifungal drugs can be examined for efficacy specifically against CNS infection (7). Traditionally, deoxycholate amphotericin B (AmB) has been the treatment for aspergillosis, although dose-associated toxicities limit optimal treatment (34). Other therapies are lipid AmB formulations, itraconazole (ICZ), and caspofungin (CAS) (1, 5, 30, 32). Recently, voriconazole has shown advantages in therapy of aspergillosis (15, 18), but metabolism issues make this drug difficult to study in rodents (B. Patterson and P. Coates, Abstr. 36th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F78, 1995). Each has been used for the treatment of CNS disease and has been anecdotally reported to be effective (11, 31, 34). However, cure is elusive, and potential problems, such as the emergence of ICZ-resistant strains of *A. fumigatus*, make treatment more difficult (8, 9, 16). Thus, it is critical to continue the search for better antifungals that exhibit minimal toxicity and high fungicidal activity.

In this study, we sought to determine the efficacy of posaconazole (POS) against CNS aspergillosis. POS is a triazole currently undergoing clinical trials. In vitro, POS demonstrates good activity against *A. fumigatus*, with lower MICs (<1 μg/ml) than either AmB or ICZ (27, 29, 35). In other studies, POS has reduced CFU in the brains of mice infected with *Cryptococcus neoformans* and was successfully used as salvage therapy to resolve human brain abscesses caused by *Scedosporium apiospermum* (3, 24). Additionally, POS has demonstrated efficacy in murine and rabbit models of aspergillosis (4, 13, 19, 25, 28). We compared various regimens of POS with those of AmB, CAS, and ICZ in a murine model of CNS aspergillosis to define curative potential against CNS aspergillosis infection.

* Corresponding author. Mailing address: Division of Infectious Diseases, Santa Clara Valley Medical Center, 751 South Bascom Ave., San Jose, CA 95128-2699. Phone: (408) 998-4557. Fax: (408) 998-2723. E-mail: clemons@cimr.org.

The method for MIC determination used for testing the in vitro susceptibility of *A. fumigatus* strain 10AF to CAS and POS followed a broth macrodilution method using yeast nitrogen broth previously described (33). MICs were read after 48 h as the first clear tube; the minimum effective concentration (MEC) of CAS was read as the first tube with 2+ (50% of control growth) or less growth. Vehicles used were as follows: CAS, sterile water; POS, dimethyl sulfoxide.

For the animal studies, 5-week-old male CD-1 mice (average weight, 27.2 g) were purchased from Charles River Laboratories. Animals were kept under standard conditions, and experiments were performed with the approval of the Institutional Animal Care and Use Committee of the California Institute for Medical Research. Immunosuppression and infection of all mice were performed as described previously, with cyclophosphamide at 200 mg/kg of body weight given intraperitoneally (i.p.) 2 days prior to infection and every 5 days thereafter (6). On day 0, mice were infected intracerebrally with 7.1×10^6 conidia of *A. fumigatus* strain 10AF/mouse.

Drugs were prepared in accordance with the manufacturer's instructions, with CAS and POS prepared daily. AmB (Bristol Myers Squibb, Princeton, N.J.) was diluted in sterile 5% dextrose water (D5W). CAS (Cancidas; Merck, Whitehouse Station, N.J.) was diluted in sterile saline. POS (Schering-Plough, Kenilworth, N.J.) doses were prepared by diluting the oral suspension of POS (40 mg/kg) with sterile water to the desired concentration. ICZ was prepared by diluting the oral formulation (10 mg/kg in 40% cyclodextrin [HPβCD]; Sporanox oral solution; Ortho Biotech, Raritan, N.J.) with sterile water. HPβCD was used as the vehicle control and was prepared by diluting 40% stock HPβCD with sterile water to 34%, which equaled the percentage used in the ICZ dosing. CAS and POS were prepared daily.

Therapy began 1 day after infection for 10 consecutive days. Mice were randomized into eight groups ($n \geq 10$) and were given AmB at 3 mg/kg i.p.; POS at 5, 25, or 100 mg/kg orally; CAS at 5 mg/kg i.p.; or ICZ at 50 mg/kg orally. Two groups of mice served as controls and were given D5W i.p. or HPβCD orally. ICZ and HPβCD were administered in a volume of 0.15 ml, and POS was administered in 0.1 ml. HPβCD and ICZ

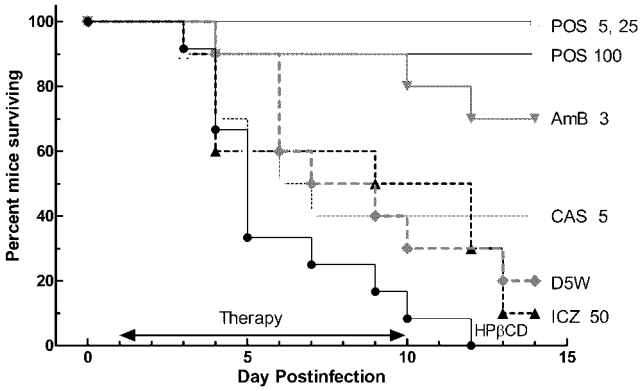

FIG. 1. Kaplan-Meier plot of the cumulative mortality of male CD-1 mice challenged with 7.1×10^6 conidia of *A. fumigatus* (strain 10AF)/mouse through intracerebral inoculation. Groups of mice serving as controls were treated with HPβCD ($n = 11$) or D5W ($n = 10$). Six other groups (all $n = 10$) were treated with AmB at 3 mg/kg; POS at 5, 25, or 100 mg/kg; CAS at 5 mg/kg; or ICZ at 50 mg/kg (twice daily).

were given twice daily, and all other regimens involved once-daily dosing.

Survival was tallied through day 14 postinfection, at which time all surviving mice were euthanatized by CO_2 asphyxia. The brains and kidneys were removed aseptically, and fungal burdens were determined by quantitative plating of organ homogenates (14). Kaplan-Meier survival plots were analyzed by a log rank test (Prism, version 3.02; GraphPad Software, San Diego, Calif.). Fungal burdens were converted to $\log_{10}$ CFU per entire organ and analyzed by the Mann-Whitney U test (Prism; GraphPad Software). *P* values were considered significant at the 0.05 level.

The AmB MIC and minimal fungicidal concentration (MFC) of 2 μg/ml and the ICZ MIC of 3.13 μg/ml against *A. fumigatus* 10AF were as reported previously (7). These were determined by the same methodology as that used for CAS and POS in the present study. The MIC of CAS was >50 μg/ml, whereas the MEC was ≤ 0.39 μg/ml. The POS MIC and MFC were 0.39 μg/ml. Equivalent results were obtained with the M38-A (26) method of testing filamentous fungi.

Daily observations of animals noted that control mice and those treated with ICZ or CAS appeared more ill. These animals were less active and had ruffled fur and notable weight loss. Mice treated with POS appeared healthiest.

The Kaplan-Meier plot in Fig. 1 illustrates the survival curves for the different treatment groups. Mice treated with HPβCD showed rapid mortality, with <50% survival noted by day 5 and 0% survival by day 12. Mice receiving D5W or ICZ had ≤20% survival by day 13. Mice given CAS had 40% survival. In contrast, mice given AmB had 70% survival and those given POS at 5, 25, or 100 mg/kg had ≥90% survival. Treatment with D5W, AmB, or POS at 5, 25, or 100 mg/kg significantly prolonged survival over treatment with HPβCD ($P \leq 0.04$). Mice treated with AmB, or POS at 5, 25, or 100 mg/kg, had significantly prolonged survival over mice given D5W ($P \leq 0.02$) or ICZ ($P \leq 0.01$). There was a trend toward significant prolongation of survival following ICZ treatment in comparison with HPβCD treatment ($P = 0.06$). AmB and POS at 5, 25,

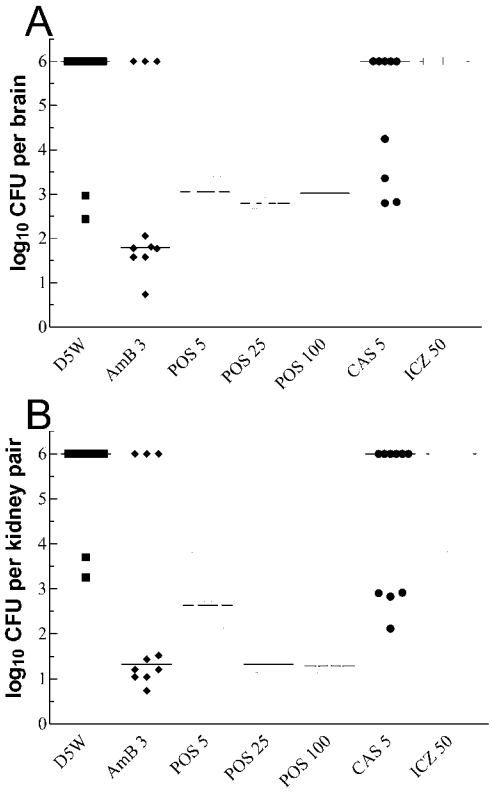

FIG. 2. Scattergrams reflecting the $\log_{10}$ CFU per indicated organ recovered from the surviving untreated (diluent controls) and treated mice infected with *A. fumigatus*. Bars, median $\log_{10}$ CFU per organ for each therapy group. A value of 6 represented mice that died of infection (20).

or 100 mg/kg were equivalent in prolonging survival ($P > 0.05$). All regimens of POS were superior to CAS in prolonging survival ($P \leq 0.02$).

All surviving mice had detectable CFU in both the brain and the kidneys (Fig. 2). CFU for mice treated with HPβCD were not evaluated, as there was 100% mortality before the end of the study. All other mice that did not survive to the conclusion of the experiment were assigned an arbitrary $\log_{10}$ CFU of 6.0 to ensure that the assumed fungal burden at death was worse than any fungal burden found in the sacrificed mice (20). Mice treated with AmB had the lowest median fungal burden for the brain, with median $\log_{10}$ CFU of 1.80 per brain (Fig. 2A). Those given POS at 25 mg/kg showed a slightly lower median burden ($\log_{10}$ CFU of 2.79) than those given POS at 5 or 100 mg/kg (median $\log_{10}$ CFU/brain of 3.05 and 3.02, respectively).

For the kidneys (Fig. 2B), the median $\log_{10}$ CFU was lower than that seen in the brains, since kidney infection represents only some secondary spread from the primary site of infection in this model. Mice given AmB and those given POS at 25 or 100 mg/kg had similar medians of $\log_{10}$ CFU/kidney pair of 1.33, 1.33 and 1.29, respectively. Mice treated with POS at 5 mg/kg had a higher median than the three aforementioned groups, with a median $\log_{10}$ CFU/kidneys of 2.64. Treatment with AmB, or POS at 5, 25, or 100 mg/kg, was superior to D5W (all $P \leq 0.02$), CAS (all $P \leq 0.04$), and ICZ (all $P \leq 0.009$) in reducing CFU from recovered organs. AmB and (POS at 5, 25,

or 100 mg/kg) were equivalent in reducing CFU from either brain or kidneys.

In this study, we examined the comparative efficacies of various regimens of POS against those involving AmB, CAS, and ICZ in murine CNS aspergillosis. CAS, the first of the echinocandins to be licensed for use as salvage therapy in invasive aspergillosis, inhibits the synthesis of 1,3-β-D-glucan, a component of the fungal cell wall (10, 36). MICs and MECs obtained in our study for CAS were in accordance with those found in other studies (2). In a previous study, CAS showed a flat dose response and a similar dosage was maximally effective in treating CNS aspergillosis where the inoculum was 5.4×10^6 conidia/mouse (J. G. Singh, J. Imai, K. V. Clemons, and D. A. Stevens, Abstr. XVth Congr. Int. Soc. Hum. Anim. Mycol., abstr. 144, 2003). The reduced efficacy of CAS in the present study of CNS aspergillosis may be due to the challenge of 7.1×10^6 conidia/mouse administered to the mice in this study, higher than that used in the referenced study. We have reported a similar reduction in CAS efficacy in this model with increasing inoculum size in studies comparing Abelcet and CAS given alone or in combination (J. Imai, G. Singh, B. Fernandez, K. V. Clemons, and D. A. Stevens, Abstr. 103rd Gen. Meet. Am. Soc. Microbiol., abstr. F087, 2003).

Despite the fact that several clinical trials have demonstrated efficacy of ICZ in cases of severe invasive aspergillosis (5, 11, 22, 32, 34), mice treated with ICZ had high overall mortality, with ≤20% survival. However, this mortality was delayed in comparison to that for the group of mice given HPβCD, and the delay approached significance ($P = 0.06$); most deaths of ICZ-treated animals occurred between days 6 and 12, as opposed to day 5 for HPβCD-treated mice. These results are similar to those reported previously (7) and are indicative of partial efficacy of ICZ against CNS infection with *A. fumigatus*, even when given at a high dose in HPβCD to maximize oral absorption (17). Similar to the results with CAS, when lower challenge inocula are used, ICZ shows better efficacy.

This study clearly demonstrated that POS at 5, 25, or 100 mg/kg was efficacious in prolonging survival and reducing fungal burdens in the brain and kidney compared to controls, CAS, or ICZ. However, POS at the tested regimens did not show dose responsiveness in reducing CFU from the brain and showed dose responsiveness only between the 5- and 25-mg/kg doses in the kidneys. We have previously shown that assessment of fungal burden by determining CFU gives results equivalent to those obtained by a quantitative PCR method and have demonstrated a lack of dose responsiveness by CAS over the range studied in this model (G. Singh, J. Imai, K. V. Clemons, and D. A. Stevens, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. M-363, 2003). Thus, we believe that the results reported here for POS are an accurate reflection of activity.

In addition, no regimen completely cleared the pathogen from the host. These results are similar to those published previously, where POS significantly prolonged survival and was more effective than ICZ (13, 19, 28). In contrast to the efficacy of POS in systemic and pulmonary models of aspergillosis, where it was more efficacious than AmB (13, 19, 28), we found that POS was equivalent to AmB in the CNS model of aspergillosis. Thus, comparative POS efficacy may also depend on the site of infection.

In vitro results for POS were consistent with results from other published studies (4, 12, 23). In vivo, POS given orally demonstrated efficacy equivalent to that of AmB, the "gold standard," given parenterally, in prolonging survival, as well as equivalence in reducing CFU from the brain and the kidneys. In addition, no overt toxicity was seen, and clinical observations noted that mice treated with POS appeared healthier than those in other therapy groups. Overall, in our murine model, POS shows promise in treating CNS aspergillosis. Subsequent studies are warranted to clearly define its complete therapeutic potential.

These studies were funded in part by a grant from Schering-Plough.

REFERENCES

1. **Abruzzo, G. K., C. J. Gill, A. M. Flattery, L. Kong, C. Leighton, J. G. Smith, V. B. Pikounis, K. Bartizal, and H. Rosen.** 2000. Efficacy of the echinocandin caspofungin against disseminated aspergillosis and candidiasis in cyclophosphamide-induced immunosuppressed mice. Antimicrob. Agents Chemother. **44:**2310–2318.
2. **Arikan, S., M. Lozano-Chiu, V. Paetznick, and J. H. Rex.** 2001. In vitro susceptibility testing methods for caspofungin against *Aspergillus* and *Fusarium* isolates. Antimicrob. Agents Chemother. **45:**327–330.
3. **Barchiesi, F., A. M. Schimizzi, F. Caselli, D. Giannini, V. Camiletti, B. Fileni, A. Giacometti, L. F. Di Francesco, and G. Scalise.** 2001. Activity of the new antifungal triazole, posaconazole, against *Cryptococcus neoformans*. J. Antimicrob. Chemother. **48:**769–773.
4. **Cacciapuoti, A., D. Loebenberg, E. Corcoran, F. Menzel, Jr., E. L. Moss, Jr., C. Norris, M. Michalski, K. Raynor, J. Halpern, C. Mendrick, B. Arnold, B. Antonacci, R. Parmegiani, T. Yarosh-Tomaine, G. H. Miller, and R. S. Hare.** 2000. In vitro and in vivo activities of SCH 56592 (posaconazole), a new triazole antifungal agent, against *Aspergillus* and *Candida*. Antimicrob. Agents Chemother. **44:**2017–2022.
5. **Caillot, D., H. Bassaris, A. McGeer, C. Arthur, H. G. Prentice, W. Seifert, and K. De Beule.** 2001. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or AIDS. Clin. Infect. Dis. **33:**e83–e90. [Online.]
6. **Chiller, T. M., J. Capilla Luque, R. A. Sobel, K. Farrokhshad, K. V. Clemons, and D. A. Stevens.** 2002. Development of a murine model of cerebral aspergillosis. J. Infect. Dis. **186:**574–577.
7. **Chiller, T. M., R. A. Sobel, J. Capilla Luque, K. V. Clemons, and D. A. Stevens.** 2003. Efficacy of amphotericin B or itraconazole in a murine model of central nervous system *Aspergillus* infection. Antimicrob. Agents Chemother. **47:**813–815.
8. **Dannaoui, E., E. Borel, M. F. Monier, M. A. Piens, S. Picot, and F. Persat.** 2001. Acquired itraconazole resistance in *Aspergillus fumigatus*. J. Antimicrob. Chemother. **47:**333–340.
9. **Dannaoui, E., E. Borel, F. Persat, M. F. Monier, and M. A. Piens.** 1999. In-vivo itraconazole resistance of *Aspergillus fumigatus* in systemic murine aspergillosis. EBGA network. European Research Group on Biotypes and Genotypes of *Aspergillus fumigatus*. J. Med. Microbiol. **48:**1087–1093.
10. **Denning, D. W.** 1997. Echinocandins and pneumocandins—a new antifungal class with a novel mode of action. J. Antimicrob. Chemother. **40:**611–614.
11. **Denning, D. W., and D. A. Stevens.** 1990. Antifungal and surgical treatment of invasive aspergillosis: review of 2,121 published cases. Rev. Infect. Dis. **12:**1147–1201.
12. **Espinel-Ingroff, A.** 1998. Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J. Clin. Microbiol. **36:**2950–2956.
13. **Graybill, J. R., R. Bocanegra, L. K. Najvar, M. F. Luther, and D. Loebenberg.** 1998. SCH56592 treatment of murine invasive aspergillosis. J. Antimicrob. Chemother. **42:**539–542.
14. **Hanson, L. H., K. V. Clemons, D. W. Denning, and D. A. Stevens.** 1995. Efficacy of oral saperconazole in systemic murine aspergillosis. J. Med. Vet. Mycol. **33:**311–317.
15. **Herbrecht, R., D. W. Denning, T. F. Patterson, J. E. Bennett, R. E. Greene, J. W. Oestmann, W. V. Kern, K. A. Marr, P. Ribaud, O. Lortholary, R. Sylvester, R. H. Rubin, J. R. Wingard, P. Stark, C. Durand, D. Caillot, E. Thiel, P. H. Chandrasekar, M. R. Hodges, H. T. Schlamm, P. F. Troke, and B. de Pauw.** 2002. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N. Engl. J. Med. **347:**408–415.
16. **Hossain, M. A., and M. A. Ghannoum.** 2000. New investigational antifungal

agents for treating invasive fungal infections. Expert Opin. Investig. Drugs **9:**1797–1813.
17. **Hostetler, J. S., L. H. Hanson, and D. A. Stevens.** 1992. Effect of cyclodextrin on the pharmacology of antifungal oral azoles. Antimicrob. Agents Chemother. **36:**477–480.
18. **Johnson, L. B., and C. A. Kauffman.** 2003. Voriconazole: a new triazole antifungal agent. Clin. Infect. Dis. **36:**630–637.
19. **Kirkpatrick, W. R., R. K. McAtee, A. W. Fothergill, D. Loebenberg, M. G. Rinaldi, and T. F. Patterson.** 2000. Efficacy of SCH56592 in a rabbit model of invasive aspergillosis. Antimicrob. Agents Chemother. **44:**780–782.
20. **Lachin, J. M.** 1999. Worst-rank score analysis with informatively missing observations in clinical trials. Controlled Clin. Trials **20:**408–422.
21. **Latge, J. P.** 1999. *Aspergillus fumigatus* and aspergillosis. Clin. Microbiol. Rev. **12:**310–350.
22. **Lutz, J. E., and D. A. Stevens.** 1995. Treatment of invasive aspergillosis. Intern. Med. **16:**25–31.
23. **Marco, F., M. A. Pfaller, S. A. Messer, and R. N. Jones.** 1998. In vitro activity of a new triazole antifungal agent, SCH 56592, against clinical isolates of filamentous fungi. Mycopathologia **141:**73–77.
24. **Mellinghoff, I. K., D. J. Winston, G. Mukwaya, and G. J. Schiller.** 2002. Treatment of *Scedosporium apiospermum* brain abscesses with posaconazole. Clin. Infect. Dis. **34:**1648–1650.
25. **Najvar, L. K., A. Cacciapuoti, S. Hernandez, J. Halpern, R. Bocanegra, M. Gurnani, F. Menzel, D. Loebenberg, and J. R. Graybill.** 2004. Activity of posaconazole combined with amphotericin B against *Aspergillus flavus* infection in mice: comparative studies in two laboratories. Antimicrob. Agents Chemother. **48:**758–764.
26. **National Committee for Clinical Laboratory Standards.** 1998. Reference method for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi. Proposed standard M38-A. National Committee for Clinical Laboratory Standards, Wayne, Pa.
27. **Oakley, K. L., C. B. Moore, and D. W. Denning.** 1997. In vitro activity of SCH-56592 and comparison with activities of amphotericin B and itraconazole against *Aspergillus* spp. Antimicrob. Agents Chemother. **41:**1124–1126.
28. **Oakley, K. L., G. Morrissey, and D. W. Denning.** 1997. Efficacy of SCH-56592 in a temporarily neutropenic murine model of invasive aspergillosis with an itraconazole-susceptible and an itraconazole-resistant isolate of *Aspergillus fumigatus*. Antimicrob. Agents Chemother. **41:**1504–1507.
29. **Pfaller, M. A., S. A. Messer, R. J. Hollis, and R. N. Jones.** 2002. Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of *Aspergillus* spp. and other filamentous fungi: report from SENTRY antimicrobial surveillance program, 2000. Antimicrob. Agents Chemother. **46:**1032–1037.
30. **Sable, C. A., B. Y. Nguyen, J. A. Chodakewitz, and M. J. DiNubile.** 2002. Safety and tolerability of caspofungin acetate in the treatment of fungal infections. Transplant. Infect. Dis. **4:**25–30.
31. **Schwartz, S., and E. Thiel.** 2004. Update on the treatment of cerebral aspergillosis. Ann. Hematol. **83**(Suppl. 1)**:**S42–S44.
32. **Stevens, D. A.** 2001. Challenges and new approaches to managing aspergillosis. J. Crit. Illn. **16:**s43–s49.
33. **Stevens, D. A., and B. H. Aristizabal.** 1997. In vitro antifungal activity of novel azole derivatives with a morpholine ring, UR-9746 and UR-9751, and comparison with fluconazole. Diagn. Microbiol. Infect. Dis. **29:**103–106.
34. **Stevens, D. A., V. L. Kan, M. A. Judson, V. A. Morrison, S. Dummer, D. W. Denning, J. E. Bennett, T. J. Walsh, T. F. Patterson, and G. A. Pankey.** 2000. Practice guidelines for diseases caused by *Aspergillus.* Infectious Diseases Society of America. Clin. Infect. Dis. **30:**696–709.
35. **Uchida, K., N. Yokota, and H. Yamaguchi.** 2001. In vitro antifungal activity of posaconazole against various pathogenic fungi. Int. J. Antimicrob. Agents **18:**167–172.
36. **Walsh, T. J., M. A. Viviani, E. Arathoon, C. Chiou, M. Ghannoum, A. H. Groll, and F. C. Odds.** 2000. New targets and delivery systems for antifungal therapy. Med. Mycol. **38**(Suppl. 1)**:**335–347.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2004, p. 4931 Vol. 48, No. 12
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.12.4931.2004

ERRATUM

Efficacy of Posaconazole in a Murine Model of Central Nervous System Aspergillosis

Jackie K. Imai, Gaurav Singh, Karl V. Clemons, and David A. Stevens

California Institute for Medical Research and Department of Medicine, Division of Infectious Diseases, Santa Clara Valley Medical Center, San Jose, and Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University, Stanford, California

Volume 48, no. 10, p. 4063–4066, 2004. Page 4064, column 2: The last sentence should read "AmB and POS (POS was used at 5, 25, or 100 mg/kg) were equivalent in reducing CFU from either brain or kidneys."

Page 4065, column 1: The second sentence of the first full paragraph should read "CAS, the first of the echinocandins to be licensed, for use as salvage therapy in invasive aspergillosis, inhibits the synthesis of 1,3-β-D-glucan, a component of the fungal cell wall (10, 36)."