Pharmacokinetics of the Triazole Antifungal Agent Genaconazole in Healthy Men after Oral and Intravenous Administration

PARVIZ MOJAVERIAN,†* ELAINE RADWANSKI,† MELTON B. AFFRIME,‡ MITCHELL N. CAYEN,† and CHIN-CHUNG LIN†

Department of Drug Metabolism and Pharmacokinetics† and Department of Clinical Pharmacology,‡ Schering-Plough Research Institute, Kenilworth, New Jersey

Received 3 March 1994/Returned for modification 9 June 1994/Accepted 28 August 1994

The pharmacokinetics of genaconazole, a potent new difluorophenyl-triazole antifungal agent, was studied in 12 healthy male volunteers following a single oral or intravenous administration of the drug. In a randomized two-way crossover design, each volunteer received either two 50-mg genaconazole tablets orally or a parenteral preparation containing 100 mg of genaconazole given as a 30-min intravenous infusion. Both dosage regimens were well tolerated. Blood and urine samples were collected up to 10 days after drug administration. Concentrations of genaconazole in plasma and urine were determined by a specific high-performance liquid chromatography assay with a limit of quantitation of 0.1 µg/mL. Pharmacokinetic evaluation following oral and intravenous doses indicated that mean values for the area under the concentration-time curve from 0 h to infinity (137 and 136 µg · h/mL), half-life (50 and 49 h), volume of distribution (52 and 52 liters), and clearance (12 and 12 mL/min) were independent of the route of drug administration. The oral and intravenous administrations of genaconazole yielded virtually superimposable plasma concentration-time curves, resulting in an absolute bioavailability of 100%. Amounts of unchanged genaconazole found in urine samples from 0 to 240 h after oral and intravenous doses were comparable, and urinary excretion accounted for 76 and 78% of the administered dose, respectively. Renal clearances for the two routes of administration were also similar, and renal clearance accounted for over 80% of the total body clearance. The 100% absolute bioavailability of genaconazole regardless of the route of administration provides greater dosing flexibility in various clinical settings than currently exists.

Genaconazole, (±)-2(R)-2-(1,2,4-difluorophenyl)-3-methylsulfanyl-1-(1,2,4-triazol-1-yl)-butan-2-ol (SCH 39304) (Fig. 1), is a potent N-substituted triazole antifungal agent which is active parenterally, orally, and topically (2, 4, 19, 20, 22–24). It is active in vitro against Candida, Histoplasma, and Coccidioides (3, 17, 18) and ketoconazole-resistant Aspergillus and Cryptococcus species (21). The drug is superior to ketoconazole in an in vivo Candida infection model (19, 25) and superior to fluconazole in an immunocompromised Aspergillus animal model (4) and is also active against common dermatophytes, including Trichophyton rubrum (23). Genaconazole is a 50:50 racemic mixture of two enantiomers—SCH 42427 (RR, −), the active, and SCH 42426 (SS, +), the inactive—with similar pharmacokinetics in men (14).

Extended plasma elimination half-lives for genaconazole were observed with mice (6 h) (13), rats (13 h) (15), rabbits (22 to 25 h) (11, 13, 19), rhesus monkeys (46 h) (26), cynomolgus monkeys (52 to 61 h) (13, 15), and men (57 to 64 h) (9, 16). Following an oral dose (20 mg/kg of body weight) of the [14C]-labeled drug to rats (15), urinary excretion of total radioactivity accounted for 81% of the dose, with 65% of the dose excreted as unchanged genaconazole. With the cynomolgus monkey, 74% of the radiolabeled dose was excreted in the urine and the unchanged drug accounted for 65% of the dose (13, 15). These data indicate that genaconazole was well absorbed by both rats and cynomolgus monkeys and excreted in urine primarily as the unchanged drug.

Following a single oral dose of genaconazole to men, urinary excretion accounted for about 73 to 87% of the dose, primarily as the unchanged drug (9, 16). There were no detectable metabolites in either serum or urine samples, indicating negligible biotransformation of genaconazole in men (9, 14, 16).

The objective of this two-way crossover study was to determine the absolute bioavailability (F) and pharmacokinetic profile of genaconazole following a 100-mg oral dose or intravenous infusion of genaconazole to healthy volunteers.

This work was presented in part at the 30th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Ga., (1990).

MATERIALS AND METHODS

Dose form. Tablets of genaconazole (50 mg) were manufactured at Schering-Plough Corporation (Kenilworth, N.J.). The intravenous-dose form was prepared in a two-vial system. The first glass vial contained 54 mg of genaconazole in 90 ml of hydrochloric acid (0.6 mg/ml, 0.015 N), and the second plastic vial contained 23 ml of 1 N sodium hydroxide. The contents of the vials were mixed together prior to dosing to provide 105 ml of deliverable volume containing 50 mg of the drug. The two-vial mixing system was necessary to provide up to 4 h of stability for the final injectable solution when stored between 15 and 30°C.

Study design. Twelve healthy male volunteers ranging in age from 19 to 37 years (mean, 28 years) and weighing 54 to 76 kg (mean, 70 kg) participated in this randomized, two-way crossover study. Each subject in the study was enrolled on the basis of his medical history, a physical examination, an electrocardiogram, and clinical laboratory tests (hematology, blood chemistry, and urinalysis). All subjects signed a written informed-consent form prior to study participation.

* Corresponding author. Mailing address: Schering-Plough Research Institute, Department of Drug Metabolism and Pharmacokinetics, 2015 Galloping Hill Rd., Kenilworth, NJ 07033.

2758
ammonium hydroxide, mixed well, and extracted with 4.0 ml of 30% methylene chloride in n-hexane. Following extraction for 10 min by shaking and 5 min of centrifugation at (3,000 rpm), the organic layer was transferred into a clean tube and evaporated to dryness at 45 to 50°C. The residue was dissolved in 200 μl of mobile phase (15% acetonitrile and 1.6% tetrahydrofuran in 0.02 M monobasic potassium phosphate buffer); a 25- to 50-μl aliquot of this was injected onto the HPLC column (50 by 4.6 mm, C18), with the mobile-phase flow rate at 2.2 ml/min. Quantitation was performed with a calibration curve determined by the regression line defining the linear relationship between the peak-height ratio of the drug to the internal standard and the plasma standard concentrations (0.1 to 3.5 μg/ml). The interassay coefficients of variation (CV) at the LOQ (0.1 μg/ml) and the highest standard concentration (3.5 μg/ml) were 14.5 and 0.4%, respectively. Interassay variability for the four quality control samples (0.10 μg/ml, CV = 11.0%; 0.40 μg/ml, CV = 6.6%; 1.5 μg/ml, CV = 3.9%; and 3.26 μg/ml, CV = 2.0%) was within the acceptable range.

Drug concentrations in the urine samples were also determined by the HPLC method discussed above, and this entailed the direct injection of a suitable dilution (usually 1:5 in distilled water) of the sample onto the column. The CV at drug concentrations of 0.1 and 3.5 μg/ml were 9.1 and 1.7%, respectively, while the average interassay CV was 4.5%. Recently, a report on a slightly modified HPLC procedure for the determination of genaconazole concentrations in human serum (LOQ = 0.2 μg/ml) and urine (LOQ = 0.5 μg/ml) was published by our laboratories (7).

**Pharmacokinetic analysis.** Concentrations of genaconazole (racemate) in plasma above the LOQ (0.1 μg/ml) were used for pharmacokinetic analysis using model-independent methods (6). For all subjects, the maximum concentration in plasma and the time to maximum concentration were the observed values (following the oral dose only). The terminal-phase rate constant (k) was calculated by linear regression as the negative of the slope of the log-linear terminal portion of the serum concentration-time curve. The terminal-phase half-life, t1/2, was calculated as 0.693/k.

The area under the plasma concentration-time curve to the last determinable sample (AUC0∞) was calculated by the linear trapezoidal method, and the area under the concentration-time curve from 0 h to infinity (AUC0∞) was then estimated by the equation \( AUC_{0-\infty} = AUC_{0-t} + C_{t}/k \), where \( C_{t} \) is the drug concentration at the last determinable sampling time.

Total body clearance (CL) was calculated from the ratio of the dose to \( AUC_{0-\infty} \). The apparent volume of distribution (V) was calculated from the CL/k ratio. F was calculated from the ratio of \( AUC_{0-\infty} \) after oral and intravenous administrations.

The total amount (in milligrams) of unchanged genaconazole excreted in the urine to the final sampling time was calculated as the sum of the amounts excreted in each block collection period. The renal clearance (CLR) of genaconazole was calculated by the equation \( CLR = AE_{0-240}/AUC_{0-240} \), where \( AE_{0-240} \) is the amount excreted from 0 to 240 h.

**RESULTS**

Prestudy and poststudy physical examinations and electrocardiograms were unremarkable. Vital signs were within the ranges normally seen in healthy volunteers. Transient elevations in liver function tests were noted in four volunteers. No other clinically significant laboratory abnormalities were detected. Mild to moderate adverse experiences were reported by eight volunteers, three following oral administration and five following intravenous administration of genaconazole. Head-
ache was common, occurring in all eight volunteers reporting adverse experiences. Other adverse experiences included nausea and heartburn. Thus, genaconazole (100 mg) administered orally and intravenously was safe and generally well tolerated.

The mean plasma concentration-time curves obtained following a 100-mg dose of genaconazole administered either orally or intravenously to 12 healthy volunteers are presented in Fig. 2. There was no apparent difference between the two treatments at any time point except during the first 2-h interval, during which concentrations of genaconazole in plasma were lower following oral administration than after intravenous infusion.

The mean values for the pharmacokinetic parameters of genaconazole (AUC₁₀, AUC₀₋∞, Cₘₐₓ, t₁/₂, F, and CL) following oral and intravenous administration were similar (Table 1). The mean AUC₀₋∞ following oral dosing was almost identical to that following intravenous infusion (137 and 136 μg·h/ml, respectively), demonstrating an F of 100% (1.0) for genaconazole (Table 2).

The mean values for the urinary excretion of genaconazole after oral and intravenous administrations for each collection interval over the 10-day study period are also listed in Table 2. An average of 76 or 78% of the dose was excreted in the urine as unchanged drug following either an oral or intravenous dose, respectively (Table 2). Mean CL₁₂ values were also similar following both dosage regimens (~10 ml/min), with intersubject variabilities of 16 and 18% for the intravenous and oral routes, respectively.

**DISCUSSION**

The values for the pharmacokinetic parameters of genaconazole, a potent difluorophenyl-triazole antifungal agent, were shown to be similar for the oral and intravenous routes of administration. Mean plasma concentration-time profiles after oral and intravenous doses were superimposable. Mean values for the pharmacokinetic parameters (Table 1) were therefore shown to be independent of the route of administration.

Absorption of genaconazole after oral dosing was essentially complete, with an F value of 1.00 ± 0.08 (mean ± standard deviation) (Table 2). This represents a clinically relevant improvement in F after oral dosing over ketoconazole (75%) and miconazole (<50%) (1, 5). Other investigators have reported that gastric alkalization can significantly decrease the absorption of triazole antifungal agents administered via the oral route; the F of ketoconazole decreased almost 50% at a gastric pH of 6.0 compared with a pH of ≤3, and therapeutic failures resulted (10, 12).

In a separate clinical study with nine healthy male volunteers (8), concomitant administration of antacid (60 ml of Mylanta) or cimetidine (300 mg four times daily for 3 days followed by a single 300-mg dose on the fourth day) did not alter the F of

![Graph](http://aac.asm.org/)

**FIG. 2.** Mean plasma concentration-time curves for genaconazole following oral (solid squares) and intravenous (open diamonds) administrations of 100-mg doses to 12 healthy male volunteers. The oral dose consisted of two 50-mg tablets; the intravenous dose was a 100-mg infusion.

| Route of administration | Cₘₐₓ (μg/ml) | Tₘₐₓ (h) | AUC₀₋₁₀ (μg·h/ml) | AUC₀₋∞ (μg·h/ml) | t₁/₂ (h) | V (liters) | F | CL (ml/min) |
|-------------------------|-------------|---------|-------------------|-------------------|---------|------------|---|------------|
| Oral                    | 1.8 (11)    | 3.9 (38)| 128 (15)          | 137 (15)          | 49.7 (18)| 52.4 (11) | 1.0 (8) | 12.4 (14)  |
| Intravenous             | 1.7 (10)    |         | 127 (9)           | 136 (9)           | 49.1 (14)| 52.2 (14) | 12.3 (10) |             |

* Values in parentheses are CV (percent). Cₘₐₓ, maximum concentration; Tₘₐₓ, time to maximum concentration.
genaconazole. This is clinically significant because of the increased gastric pH often observed in immunocompromised (AIDS) subjects, patients with relative achlorhydria, and those who may be receiving antacid and/or H2-antagonist treatment.

The apparent V of genaconazole was approximately 0.75 liter/kg (Table 1), which indicated that the drug was moderately distributed throughout the body. This V value is comparable to the reported value for fluconazole of 0.7 ± 0.6 liter/kg (mean ± standard deviation) but in contrast to those for ketoconazole (0.1 to 0.3 liter/kg) and miconazole (2 to 3 liters/kg) (1, 5).

Peak concentrations of genaconazole in plasma were achieved within 4 h of oral dosing; this was followed by a very slow terminal phase (t1/2 = 50 h), and as a result, concentrations of the drug in plasma could be detected 10 days after the administration of a single 100-mg dose. These values are consistent with the time to maximum concentration (3.3 h) and t1/2 (57 h) values obtained in our previous studies involving a single 100-mg oral dose of genaconazole in healthy male volunteers (9, 16). The prolonged t1/2 of genaconazole gives it an advantage for once-daily or alternate-day dosing over ketoconazole and fluconazole, which have relatively short and intermediate terminal-phase t1/2 values of 8 h (1) and 22 to 36 h (5), respectively.

Urinary excretion of unchanged genaconazole accounted for 76 and 78% of the administered doses after oral and intravenous administrations, respectively, which was consistent with our previous finding in men (9, 16). In addition, CLR following oral and intravenous dosing (10 ml/min [Table 2]) accounted for more than 80% of the total body CL (12 ml/min [Table 1]). Therefore, urinary excretion of the unchanged drug and not systemic biotransformation was responsible for most of the elimination of genaconazole in humans. Since renal excretion of the unchanged drug is the main elimination pathway for this compound, dosage adjustment may be needed in patients with renal insufficiency. This was also the case for fluconazole (5) but not for ketoconazole or miconazole (1) because of their shorter elimination t1/2.

In comparison with other antifungal agents such as ketoconazole and miconazole which undergo 95 and 50% biotransformation (1), respectively, genaconazole undergoes negligible biotransformation in men (11, 13, 16). Therefore, drug-drug interactions of concurrently prescribed medications are expected to be minimal.

Genaconazole is a potent new N-substituted difluorophenyltriazole, broad-spectrum antifungal agent which exhibits complete absorption after oral administration, a prolonged terminal-phase elimination t1/2, and negligible biotransformation in humans. The compound represents a therapeutic advantage over other available antifungal agents for the treatment of fungal infections because of its superior clinical efficacy and pharmacokinetic profile. Oral and intravenous administrations of the drug result in nearly identical concentration profiles of the drug in plasma, providing greater dosing flexibility in various clinical situations.

**ACKNOWLEDGMENT**

We thank J. A. F. de Silva for his critical technical and editorial review of the manuscript.

**REFERENCES**

1. Barriere, S. L. 1990. Pharmacology and pharmacokinetics of traditional systemic antifungal agents. Pharmacotherapy 10:1348–1405.
2. Clemons, K. V., L. H. Hanson, A. M. Perlman, and D. A. Stevens. 1990. Efficacy of SCH39304 and fluconazole in a murine model of disseminated coccidioidomycosis. Antimicrob. Agents Chemother. 34:928–930.
3. Cook, R. A., K. A. McIntyre, and J. N. Galgiani. 1990. Effects of incubation temperature, inoculum size, and medium on agreement of macro- and microdilution broth susceptibility test results for yeasts. Antimicrob. Agents Chemother. 34:1542–1545.
4. Delavert, J., S. H. Sun, and J. R. Graybill. 1990. Treatment of murine coccidioidal meningitis with SCH39304. Antimicrob. Agents Chemother. 34:663–664.
5. Dudley, M. N. 1990. Clinical pharmacology of fluconazole. Pharmacotherapy 10:1415–1455.
6. Gibaldi, M., and D. Perrier. 1982. Pharmacokinetics, 2nd ed., p. 409–417. Marcel Dekker, Inc., New York.
7. Kim, H., A. Lapigueria, and C.-C. Lin. 1994. Gas chromatograph and high-performance liquid chromatographic methods for the determination of genaconazole in biological fluids. J. Chromatogr. B65:21–26.
8. Kosoglou, T., G. P. Perentesis, M. B. Affrine, C.-C. Lin, P. Mojaverian, E. Radwanski, and P. H. Vlasses. 1990. The effect of...
antacid and cimetidine on the oral absorption of the antifungal agent SCH 39304. J. Clin. Pharm. 30:638-642.

9. Kramer, W., H. Kim, S. Synchowicz, G. Perentesis, M. Affrime, and C.-C. Lin. 1988. Pharmacokinetics of Sch 39304 in man, abstr. 165, p. 139. Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother.

10. Lake-Bakaar, G., W. Tom, D. Lake-Bakaar, N. Gypter, S. Beidas, M. Elsakr, and E. Strauss. 1988. Gastropathy and ketoconazole malabsorption in AIDS. Ann. Intern. Med. 109:471-473.

11. Lee, J. W., C. Lin, D. Loebenberg, M. Rubin, P. A. Pizzo, and T. J. Walsh. 1989. Pharmacokinetics and tissue penetration of Sch 39304 in granulocytopenic and nongranulocytopenic rabbits. Antimicrob. Agents Chemother. 33:1932-1935.

12. Lelawongs, P., J. A. Barone, J. L. Calaizzi, A. T. M. Hsuan, W. Mechlinski, R. Legendre, and J. Guarnieri. 1988. Effect of food and gastric acidity on absorption of orally administered ketoconazole. Clin. Pharm. 7:228-235.

13. Lin, C.-C., H. Kim, A. Lapiguera, D. Loebenberg, G. H. Miller, and S. Synchowicz. 1988. Comparative pharmacokinetics of Sch 39304 and fluconazole in mice, rabbits, S. monkeys and c. monkeys, abstr. 163, p. 138. Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother.

14. Lin, C.-C., H. Kim, M. B. Affrime, E. Radwanski, R. Guerciolini, S. Synchowicz, and M. N. Cayen. 1991. SCH 39304, a potent antifungal drug, in man, abstr. 446. Abstr. Proc. 17th Int. Congr. Chemother.

15. Lin, C.-C., H. Kim, A. Lapiguera, and S. Synchowicz. 1989. Pharmacokinetics and metabolism of a new oral antifungal agent, SCH 39304, in rats and cynomolgus monkeys, abstr. 543.1. Abstr. Proc. 16th Int. Congr. Chemother.

16. Lin, C.-C., W. Kramer, H. Kim, G. P. Perentesis, M. B. Affrime, and S. Synchowicz. 1989. Pharmacokinetics of a new oral antifungal agent, SCH 39304, in man, abstr. 544.1. Abstr. Proc. 16th Int. Congr. Chemother.

17. McIntyre, K. A., and J. N. Galgiani. 1989. In vitro susceptibilities of yeasts to a new antifungal triazole, SCH 39304: effects of test conditions and relation to in vivo efficacy. Antimicrob. Agents Chemother. 33:1095-1100.

18. Meunier, F., C. Lambert, and P. Van der Auwera. 1990. In vitro activity of SCH 39304 in comparison with amphotericin B and fluconazole. J. Antimicrob. Chemother. 25:227-236.

19. Perfect, J. R., K. A. Wright, M. M. Hobbs, and D. T. Durack. 1989. Treatment of experimental cryptococcal meningitis and disseminated candidiasis with SCH39304. Antimicrob. Agents. Chemother. 33:1735-1740.

20. Restrepo, B. L., J. Ahrens, and J. R. Graybill. 1989. Efficacy of SCH39304 in murine cryptococcosis. Antimicrob. Agents Chemother. 33:1242-1246.

21. Schmitt, H. J., E. M. Bernard, M. Hauser, and D. Armstrong. 1988. Comparison of antifungal agents in a rat model of pulmonary aspergillosis, abstr. 171, p. 140. Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother.

22. Sugar, A. M., M. Picard, and L. Noble. 1990. Treatment of murine pulmonary blastomycosis with SCH 39304, a new triazole antifungal agent. Antimicrob. Agents Chemother. 34:896-898.

23. Tanio, T., K. Ichise, T. Nakajima, and T. Okuda. 1990. In vivo efficacy of SM-8668 (SCH 39304), a new oral triazole antifungal agent. Antimicrob. Agents Chemother. 34:980-984.

24. Walsh, T. J., J. W. Lee, J. Lecciones, P. Kelly, J. Peter, V. Thomas, J. Bacher, and P. A. Pizzo. 1990. SCH-39304 in prevention and treatment of disseminated candidiasis in persistently granulocytopenic rabbits. Antimicrob. Agents Chemother. 34:1560-1564.

25. Walsh, T. J., J. W. Lee, J. Peter, R. Schaufele, M. Rubin, and P. A. Pizzo. 1988. SCH-39304 in the treatment of disseminated candidiasis in persistently granulocytopenic and non-granulocytopenic rabbits, abstr. 169, p. 139. Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother.

26. Walsh, T. J., C. Lester-McCully, M. G. Rinaldi, J. E. Wallace, F. M. Balis, J. W. Lee, P. A. Pizzo, and D. G. Poplack. 1990. Penetration of SCH-39304, a new antifungal triazole, into cerebrospinal fluid of primates. Antimicrob. Agents Chemother. 34:1281-1284.