CORRESPONDENCE

Itraconazole More Bioavailable in Solution

To the Editor:

In their review of antifungal prophylaxis,[1] Uzun and Anaissie[1] omit to mention some aspects of the relative merits of the two oral agents, fluconazole and itraconazole. It is true that the bioavailability of itraconazole in capsule form is unpredictable between and within patients.[2] But we have now shown that the absorption of this drug is greatly enhanced and more consistent in a new cyclodextrin solution. Table 1 summarizes the pharmacokinetic data from patients undergoing remission induction chemotherapy for acute myeloblastic leukemia (AML)[3] and for patients undergoing autologous transplantation for a variety of hematological malignancies.[4]

Not only are these levels higher and more consistent than with the capsule form, but they were obtained in the presence of severe mucositis in some patients. Such patients tolerated a twice daily regimen of 2.5 mg/kg body weight better than a single daily dose of 5 mg/kg body weight. However, there was no significant difference in the overall bioavailability profiles between these two dosage regimens.

At day 8, coinciding usually with the onset of severe neutropenia, the mean Cmin was well above the recommended level of 250 ng/mL[5] in those patients given a total daily dose of 5 mg/kg body weight. A steady state appears to be achieved between days 8 and 15. The day 15 plus the wash-out levels indicate a saturated kinetic profile with mean serum levels still greater than 500 ng/mL at day 5 after stopping the drug in the AML study. This implies persistent protection for those patients with problems of compliance at times of severe mucositis. Overall compliance in our studies was good and adverse events attributable to itraconazole were low.

In 6 of 20 AML patients and in 7 of 8 autograft patients taking either cimetidine or ranitidine, bioavailability was not significantly different from the remainder who were not taking H_2 antagonists. The original observation of this allegedly clinically important interaction was made in normal volunteers in whom cimetidine produced a mean reduction of only 15% and ranitidine a mean reduction of only 20% in serum levels of itraconazole.[6] Such a reduction, if observed in such patients as ours, would not have had a significant impact on the pharmacokinetic profiles we obtained. Therefore, we believe that this interaction is probably not relevant when using this new solution in these patients.

Itraconazole is effective against *Aspergillus* but fluconazole is not.[7] *Candida krusei* resistance to fluconazole is well-recognized.[8] Therefore, on the basis of bioavailability and known spectrum of activity, itraconazole may be the superior prophylactic antifungal azole and reports of randomized controlled comparisons of the antifungal efficacy of these two drugs during the treatment of hematological malignancy will be available soon.

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REFERENCES

1. Uzun O, Anaissie EJ: Antifungal prophylaxis in patients with hematologic malignancies: A reappraisal. Blood 86:2063, 1995
2. Bradford CR, Prentice AG, Warnock DW, Copplestone JA: Comparison of multiple dose pharmacokinetics of two formations of itraconazole during remission induction for acute myeloblastic leukemia. J Antimicrob Chemother 28:555, 1991
3. Prentice AG, Warnock DW, Johnson SAN, Taylor PC, Oliver DA: Multiple dose pharmacokinetics of an oral solution of itraconazole in patients receiving chemotherapy for acute myeloid leukemia. J Antimicrob Chemother 36:657, 1995
4. Prentice AG, Warnock DW, Johnson SAN, Phillips MJ, Oliver DA: Multiple dose pharmacokinetics of an oral solution of itraconazole in autologous bone marrow transplant recipients. J Antimicrobial Chemother 34:247, 1994
5. Boogaerts MA, Verhoef GE, Zachee P, Demuynck H, Verbist L, De Beule K: Antifungal prophylaxis with itraconazole in prolonged neutropenia: Correlation with plasma levels. Mycoses 32:103, 1989 (suppl 1)
6. Stein A, Daneshmend TK, Warnock DW, Bhaskar N, Burke J, Hawkey CJ: The effects of H_2-Receptor antagonists on the pharmacokinetics of itraconazole, a new oral antifungal. Br J Clin Pharmacol 27:105, 1989
7. Anaissie EJ, Kontoyiannis DP, Huls C, Vartivarian SE, Karl C, Prince RA, Bosso J, Bodey GP: Safety, plasma concentrations, and efficacy of high-dose fluconazole in invasive mold infections. J Infect Dis 172:599, 1995

Table 1. Itraconazole Pharmacokinetic Data During Induction Therapy for Acute Myeloblastic Leukemia and Autologous Transplantation (AUTO)

	Drug Levels					
Day	1		8		15	
	AML	AUTO	AML	AUTO	AML	AUTO
C_{max}*	149 ± 40	107 ± 48	593 ± 319	723 ± 217	1,160 ± 594	1,292 ± 357
C_{min}†	0	19 ± 33	409 ± 252	394 ± 110	715 ± 385	845 ± 221
AUC‡	—	1,479 ± 933	—	13,302 ± 5,016	22,055 ± 9,775	25,143 ± 6,460

* C_{max}: Daily mean maximum concentration (ng/mL).
† C_{min}: Daily mean minimum concentration (ng/mL).
‡ AUC: Area under the curve for 0 to 24 hours calculated using the trapezoidal rule (ng/mL/h).

8. Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R: Increase in *Candida Krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N Engl J Med 325:1274, 1991