CORRESPONDENCE

Itraconazole More Bioavailable in Solution

To the Editor:

In their review of antifungal prophylaxis,1 Uzun and Anaissie1 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/mL5 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 H2 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 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

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

<table>
<thead>
<tr>
<th>Drug Levels</th>
<th>1</th>
<th>8</th>
<th>16</th>
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<tbody>
<tr>
<td>AML</td>
<td>AUTO</td>
<td>AML</td>
<td>AUTO</td>
</tr>
<tr>
<td>Cmax*</td>
<td>149 ± 40</td>
<td>107 ± 48</td>
<td>593 ± 319</td>
</tr>
<tr>
<td>Cmin†</td>
<td>0</td>
<td>19 ± 33</td>
<td>409 ± 252</td>
</tr>
<tr>
<td>AUCt</td>
<td>1,479 ± 933</td>
<td>—</td>
<td>13,302 ± 6,016</td>
</tr>
</tbody>
</table>

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

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