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A three-phase animal model system has been used in efficacy comparisons of orally-administered imidazole and triazole drugs for deep mycotic disease.

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SEPARATUM
A three-phase animal model system has been used in efficacy comparisons of orally-administered imidazole and triazole drugs for deep mycotic disease (1). The test organism was 30-80 arthrospores of Coccidioides immitis introduced intranasally into mice (LD90-LO95). In Phase-I studies, treatment was initiated on the 4th day after infection with an LD90 dose of arthrospores, after the onset of pulmonary disease but prior to the development of extensive extrathoracic disease. In Phase-II studies, treatment was withheld until the onset of moribundity or pre-moribundity, at which time massive disseminated fungal involvement of the organs of the peritoneal cavity was demonstrated. Finally, in Phase-III, treatment for 120 days was given to survivors of an acute LD30 dose of arthrospores. Indices of efficacy were based upon survival rates, pathologic sequelae and the frequency and extent of continuing infection during and after treatment. Ketoconazole (12-3), among eightazole derivatives, was markedly therapeutic; mortality was prevented completely in Phase-I studies, reduced significantly in Phase-II evaluations, and the infection was well-controlled in a chronic disease syndrome, which occurs in Phase-III studies, and which ordinarily leads to death. Other drugs, active in Phase-I, were ineffective in Phases II or III.

Tests for anticoxycidoidal activity in vitro (4) have not given a reliable indication of efficacy in infected animals. Thus, for

Table 1. Tioconazole and ketoconazole in vitro and in Phase-I studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tioconazole</th>
<th>Ketoconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC (agar diff.)</td>
<td>0.05 mcg/ml</td>
<td>0.3 mcg/ml</td>
</tr>
<tr>
<td>MIC (tube dil.)</td>
<td>0.05 mcg/ml</td>
<td>0.4 mcg/ml</td>
</tr>
<tr>
<td>Phase-I mortality</td>
<td>28%</td>
<td>0%</td>
</tr>
<tr>
<td>40 mg/kg b.i.d.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase-I mortality</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

example, in a direct comparison of activities of ketoconazole and tioconazole, the latter drug was more active than the former in vitro. However, as outlined in Table 1, tioconazole was
without therapeutic effect in the Phase-I therapy model, whereas ketoconazole protected all of the animals.

The major value of the Phase-I model lies in its utility for in-vivo screening of potentially efficacious drugs for a deep mycotic infection. The model, however, varies markedly from the requirements the drug is likely to face in actual use for clinical coccidioidomycosis. In the Phase-I model, treatment is initiated when the lesions are young and still well-vascularized. The animals' lungs are almost fully functional and there is not yet a syndrome of debilitation. Patients, however, frequently have relatively long-standing disease with destructive pulmonary lesions, often with a poor blood supply. The Phase-II and Phase-III models attempt to evaluate the likely role of the drug in the situations of advancing and advanced disease.

The Phase-II animals receive their initial treatment on the 13th day of the infection, one-to-two days before the initial deaths occur. The objective is to determine if aggressive treatment at this time offers the possibility of salvaging any or all of them. The Phase-II studies can distinguish therapeutic advantages between drugs that Phase-I studies cannot. We found that Bay-L-9139 and ketoconazole were therapeutically comparable in Phase-I studies, but, as shown in Table 2, markedly divergent in the Phase-II evaluation, where only ketoconazole was with therapeutic effect.

Table 2. Bay-L-9139 and ketoconazole in Phase-II studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dead/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 16</td>
</tr>
<tr>
<td>Bay-L-9139, 50 mcg/kg b.i.d.</td>
<td>0/20</td>
</tr>
<tr>
<td>Ketoconazole, 50 mcg/kg b.i.d.</td>
<td>1/19</td>
</tr>
<tr>
<td>Control</td>
<td>0/20</td>
</tr>
</tbody>
</table>

The Phase-III studies measure the capacity of the drug to keep infected animals with chronic, deep-seated disease alive during a prolonged course of treatment. Here again, the model can distinguish different drugs: Bay-N-7133 did not sustain life whereas ketoconazole did. (Recently Plempel has reported that the failure of Bay-N-7133 may be attributed to enzyme induction in mice which may not occur in man). The Phase-III comparison of Bay-N-7133 and ketoconazole is summarized in Table 3.
Table 3. Bay-N-7133 and ketoconazole in Phase-III studies of survivors of an acute LD30 dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dead/Total</th>
<th>Day 40</th>
<th>Day 80</th>
<th>Day 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bay-N-7133, 35 mcg/kg b.i.d.</td>
<td>0/23</td>
<td>0/23</td>
<td>5/23</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole, 35 mcg/kg b.i.d.</td>
<td>0/25</td>
<td>0/25</td>
<td>0/25</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0/24</td>
<td>0/24</td>
<td>7/24</td>
<td></td>
</tr>
</tbody>
</table>

Thus a meaningful experimental pre-clinical index of antifungal activity, in our experience, requires evaluation of efficacy under the varying conditions of disease mentioned above. In all cases the drugs were administered orally and the infecting dose was given intranasally. We believe it is important to avoid treatment initiated at the time of infection or given by the route of infection which, in certain circumstances, artificially maximizes the possibility for interaction between the drug and the organism.

REFERENCES


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