Pharmacokinetics of Ketoconazole in Patients with Neoplastic Diseases

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Twenty-seven patients with advanced malignancies were given 200 mg of ketoconazole orally every 6 or 12 h. Blood samples were collected during these intervals and after the last dose to determine plasma concentrations and half-lives. The mean plasma concentrations measured after the initial dose were 1.7 ± 1.1 μg/ml at 2 h, 0.9 ± 0.2 μg/ml at 6 h, and 0.7 ± 0.4 μg/ml at 8 h. Plasma concentrations rose significantly in patients on the every-6-h schedule. Concentrations were more variable in patients on the every-12-h schedule, and changes in mean plasma concentrations after 7 and 14 days were not significant. Half-lives ranged from 1.3 to 11.6 h in individual patients. The mean half-life for all patients studied was 3.7 ± 0.6 h on day 1. The calculated area under the curve was 12.0 ± 4.7 μg·h/ml on day 1; it increased after 7 and 14 days of administration (every-6-h schedule), suggesting plasma binding or wide drug distribution or both. Saturation of storage compartments is also suggested. Less than 1% of the administered dose was recoverable as active drug from the urine over 6 h.

Ketoconazole, an imidazole absorbed when administered orally, inhibits the growth of Coccioides immitis (4, 6), Candida albicans (4, 12), and Candida parapsilosis (4) at concentrations of <1 μg/ml and Aspergillus spp. and Torulopsis glabrata at concentrations of 2 to 10 μg/ml or more. Fungal infections due to Candida spp., particularly C. albicans, and Aspergillus sp. are a common cause of mortality and morbidity in patients with acute leukemia and other advanced malignancies (3). Because these patients are at high risk of fungal infection, we conducted a study to evaluate the potential of ketoconazole as a prophylactic and therapeutic antifungal agent. Studies of plasma concentrations and urinary elimination were performed to guide dosage and schedule of administration in these patients.

MATERIALS AND METHODS

The plasma concentrations of ketoconazole were measured in 26 patients with acute leukemia and 1 patient with thyroid carcinoma. Nineteen males and eight females, ranging in age from 18 to 76 years (median, 45 years), participated in the study. All patients had been assigned to receive ketoconazole as therapy or prophylaxis of fungal infection and were requested to participate in the pharmacological study. Informed consent was obtained from all patients according to institutional policy. Renal and hepatic functions were assessed before treatment and at least weekly thereafter by the measurement of serum glutamic oxaloacetic transaminase and alkaline phosphatase. All parameters were normal throughout the study in 16 patients. Eleven patients had slight elevations of alkaline phosphatase or serum glutamic oxaloacetic transaminase initially; however, as their plasma ketoconazole concentrations did not differ significantly from those of other patients, all results were combined in the analysis.

Ketoconazole was administered orally at least 1 h before or after food ingestion. Antacids were avoided except when considered mandatory for patient management; they were administered at least 2 h from the time of ketoconazole administration.

Twenty-three patients were given 200 mg of ketoconazole every 6 h for 4 to 35 days. Blood samples were drawn before and 2, 4, and 6 h after the administration of the drug. Serial studies were performed on six patients on days 1, 8, and 15 of drug administration. Four patients were studied on day 1 only, and eight patients were studied on day 3 or 4 only. Five patients were studied up to 18 h after drug administration after 7 days of treatment.

Four patients were given 200 mg of ketoconazole every 12 h for 8 to 122 days. Blood samples were drawn before and 2, 4, and 8 h after administration. Serial studies were done on three patients on days 1, 8, and 15; the other patient was studied on day 1 only.

Urine samples were collected from 12 patients on the every-6-h schedule before and for 6 h after the administration of the initial dose. These samples were assayed to determine the amount of active ketoconazole excreted.

Ketoconazole concentrations were analyzed by two techniques. For all except the 18-h studies, plasma and
urine samples were assayed by a microbiological technique at the Naval Biosciences Laboratory, Oakland, Calif. Inhibition of the growth of endospores of *C. immitis* by equal-volume portions of test sample and standard dilutions of ketoconazole hydrochloride was compared as previously described (10). Plasma samples from the 18-h studies were analyzed at Pittman-Moore Laboratories, New Brunswick, N.J., by high-pressure liquid chromatography (1). Thirty samples were analyzed by both techniques, and parallel results were obtained. The results obtained with high-pressure liquid chromatography averaged 7% below those obtained with the microbiological technique. The lower limit of resolution was 0.4 μg/ml for the microbiological technique and 0.1 μg/ml for high-pressure liquid chromatography.

The standard error of the mean was calculated, and 95% confidence limits were taken as twice the standard error of the mean. The terminal half-life ($t_{1/2}$) of ketoconazole was determined by exponential curve fitting. Values for the area under the curve (AUC) were calculated according to the methods of Ritschel (13) with an open single-compartment model.

**RESULTS**

After the initial dose of ketoconazole, the mean peak plasma concentration in six patients on the every-6-h schedule was $1.6 \pm 0.4 \mu g/ml$ 2 h after drug administration (Table 1). After 6 h, the mean plasma concentration was $0.6 \pm 0.1 \mu g/ml$. The mean peak concentration on day 8 rose to $3.1 \pm 0.6 \mu g/ml$, significantly higher than that on day 1 ($P < 0.05$). The mean concentration at 2 h on day 15 was $3.6 \pm 0.4 \mu g/ml$ ($P > 0.05$). The mean concentrations before the administration of the drug on days 8 and 15 were 2.6 and 2.4 μg/ml, respectively. The data from four patients studied on day 3 or 4 only (every-6-h schedule) were similar to those from patients studied sequentially on days 8 and 15.

For patients on the every-12-h schedule, the mean peak plasma concentration of ketoconazole was $1.8 \pm 0.6 \mu g/ml$ on day 1, $2.7 \pm 1.1 \mu g/ml$ on day 8, and $3.6 \pm 2.1 \mu g/ml$ on day 15. These values are not significantly different at the $P = 0.05$ level because of variability. In two patients, concentrations were <1 μg/ml before drug administration on day 15.

The highest plasma concentration of ketoconazole measured on day 1 in all patients occurred 2 h after administration in 10 patients and 4 h after administration in the other 4 patients. The highest concentration measured at 2 h was 3.5 μg/ml, and the lowest was 0.2 μg/ml.

Samples were drawn for 18 h after the last dose from five patients who had received ketoconazole every 6 h for 7 days (Fig. 1). The peak serum concentration was $3.8 \pm 0.8 \mu g/ml$ at 2 h; the mean concentration at 18 h was $0.2 \pm 0.1 \mu g/ml$. The mean plasma $t_{1/2}$ in this group was 3.5 ± 1.3 h.

The AUC and the plasma $t_{1/2}$ of ketoconazole in sequentially studied patients are given in Table 2. The AUC values increased for patients on the every-6-h schedule from 12.0 μg h/ml on day 1 to 27.0 μg h/ml on day 8. No difference was noted between values on days 8 and 15. The $t_{1/2}$ was $5.1 \pm 1.5$ h on day 1 and $3.9 \pm 0.8$ h on day 15. The change in AUC was not as great for patients on the every-12-h schedule from days 1 to 15. The mean $t_{1/2}$ was $3.0$ h on days 1 and 15 and $2.4$ h on day 8. The mean $t_{1/2}$ for all patients studied on day 1 was $3.7 \pm 0.6$ h.

In 7 of 12 patients from whom urine samples were collected, no drug was detectable in urine for 6 h after the administration of the initial dose of ketoconazole. In five other patients, a mean amount of 0.5 mg was excreted over the 6-h collection period (0.02 to 1.38 mg).

No patient on either schedule developed severe toxicity attributable to ketoconazole. The

**TABLE 1. Plasma ketoconazole concentrations**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Concn (μg/ml ± SEM)</th>
<th>Preadministration</th>
<th>Postadministration*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 h</td>
<td>4 h</td>
</tr>
<tr>
<td>Every 6 h (six patients)</td>
<td></td>
<td>2 h</td>
<td>4 h</td>
</tr>
<tr>
<td>Day 1</td>
<td>0</td>
<td>1.6 ± 0.4</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Day 8</td>
<td>2.6 ± 0.5</td>
<td>3.1 ± 0.6</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>Day 15</td>
<td>2.4 ± 0.5</td>
<td>3.6 ± 0.4</td>
<td>2.7 ± 0.5</td>
</tr>
<tr>
<td>Every 6 h (four patients; days 3 and 4)</td>
<td>2.5 ± 0.6</td>
<td>3.2 ± 0.6</td>
<td>2.9 ± 0.6</td>
</tr>
<tr>
<td>Every 12 h (three patients)</td>
<td></td>
<td>2 h</td>
<td>4 h</td>
</tr>
<tr>
<td>Day 1</td>
<td>0</td>
<td>1.8 ± 0.6</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Day 8</td>
<td>1.3 ± 0.7</td>
<td>2.7 ± 1.1</td>
<td>1.5 ± 0.6</td>
</tr>
<tr>
<td>Day 15</td>
<td>0.4 ± 0.4</td>
<td>3.6 ± 2.1</td>
<td>2.1 ± 1.5</td>
</tr>
</tbody>
</table>

* Dose, 200 mg of ketoconazole orally.
most common side effect was nausea (1 of 4 patients on the every-12-h schedule and 6 of 23 patients on the every-6-h schedule). The drug was discontinued for this reason in one patient on the every-6-h schedule. Other side effects noted were somnolence (two patients) and anorexia (two patients). No alterations in renal or hepatic function were attributable to the administration of ketoconazole.

**DISCUSSION**

Imidazoles provide an alternative to amphotericin B for the management of certain fungal infections. The frequency of toxicity with miconazole is low; toxic effects include hyperlipidemia (2), nausea and tremors (8), and cardiac and anaphylactic reactions (9) due in part to solubilizing compounds rather than the drug itself. Ketoconazole is an interesting imidazole, as it is administered orally and is as active as miconazole in vitro against most fungal species at the concentrations achieved in the patients in this study.

Plasma ketoconazole concentrations were variable, particularly after the initial dose. The mean plasma concentrations at all sample times were higher after 7 days in patients on the every-6-h schedule. This is not surprising since the plasma $t_{1/2}$ of ketoconazole was 3.7 h; thus, drug accumulation would be expected in patients on an every-6-h schedule. On this schedule, equilibrium with ketoconazole appears to have been achieved within 3 to 4 days since the plasma concentrations observed at that time were similar to those observed on day 8. Plasma concentrations also increased in patients given the drug every 12 h, but the differences did not reach statistical significance even after 14 days of therapy. In addition, there were two to three plasma $t_{1/2}$s between doses; hence, the plasma concentration was only 0.4 µg/ml before the second dose.

The mean peak plasma concentration of ketoconazole on day 1 for the patients on the every-6-h schedule was 1.6 µg/ml, lower than that reported by Brass et al. for 10 patients given single doses of ketoconazole (2.75 µg/ml) (5). The difference could be related to the effect of chemotherapy on the absorption of the drug or to the underlying malignancies in our patients. The mean peak concentration on day 8 was 3.1 µg/ml, similar to that reported for miconazole 20 min after the infusion of 9 mg/kg (3.1 µg/ml) (14). Lewi et al. have reported a triphasic drug disappearance curve for miconazole, with a second $t_{1/2}$ of 2.1 h, somewhat shorter than that reported here for ketoconazole (11). We were unable to detect a prolonged terminal phase in the elimination of ketoconazole because of the design of the study and the limitation on the quantitation of plasma concentrations of <0.1 µg/ml with the techniques employed.

Plasma concentrations of ketoconazole were usually less than 1 µg/ml in patients on the every-12-h schedule before the administration of the drug on days 8 and 15. Concentrations remained consistently above 1 µg/ml in patients on the every-6-h schedule. Since in vitro susceptibility to ketoconazole varies among fungal species and because the presence of neutrophils may be of particular importance for the effectiveness of this drug (7), the every-6-h schedule may be preferable, especially for patients who have prolonged periods of profound neutropenia.

The progressive rise in the calculated AUC in the every-6-h group suggests penetration of the drug into deep peripheral tissues and storage or extensive binding of the drug to biological materials (plasma protein), as reported by Stevens et al.
al. for miconazole (14). The overall amount of drug excreted in active form from the kidneys was <1%, suggesting that other mechanisms such as hepatic metabolism are more important, as is the case with other imidazoles.

No severe or unexpected toxicities were recognized in the patients in this study. The most common toxic effects were nausea and anorexia, more prevalent in patients on the every-6-h schedule. No evidence of hepatic or renal toxicity was noted. Two patients experienced drowsiness, which resolved when the drug was discontinued.

Conclusions. Ketoconazole (200 mg orally every 6 h) was absorbed to potentially therapeutic concentrations in a group of patients with advanced malignancies, most of whom were being actively treated for acute leukemia. Plasma concentrations of ketoconazole were lower and more variable when the drug was given every 12 h. The t\textsubscript{1/2} ranged from 1.3 to 11.6 h, suggesting that many patients require frequent dose administration to maintain therapeutic concentrations of ketoconazole. The drug appears to be highly bound in plasma and widely distributed throughout the body.

Renal excretion accounts for a very small proportion of drug elimination, suggesting the importance of other routes of excretion or metabolism.

Ketoconazole was well tolerated by patients on both administration schedules, and no significant toxicity was encountered in any patient studied. Nausea and anorexia were the most common side effects, particularly in patients on the every-6-h schedule.

Studies to evaluate the prophylactic and therapeutic potential of this drug in patients with advanced malignancies appear to be warranted.

LITERATURE CITED