Pharmacology of Ketoconazole Suspension in Infants and Children

CHARLES M. GINSBURG,* GEORGE H. MCCracken, JR., AND KURT OLSEN

Department of Pediatrics, The University of Texas Health Science Center at Dallas Southwestern Medical School, Dallas, Texas 75235

Received 2 December 1982/Accepted 2 March 1983

The pharmacokinetics of ketoconazole administered as either a commercially prepared suspension or as a crushed tablet in applesauce were studied in 12 children. The mean peak plasma concentration of ketoconazole and the area under the plasma time-concentration curve were approximately twofold greater with the suspension than with the crushed tablets.

Ketoconazole, a recently licensed synthetic dioxolane imidazole, has a wide spectrum of activity against Candida species, dermatophytes, and some fungi that cause invasive disease (2). Indications for its therapeutic use include superficial dermatophyte infections, onychomycosis, chronic mucocutaneous candidiasis, and systemic histoplasmosis and coccidiodomycosis.

Pharmacokinetic studies in adults have shown that absorption of ketoconazole after oral administration is affected by the presence of food in the gastrointestinal tract and by gastric acidity (1, 4, 6). There have been no comparable studies on the pharmacokinetics of ketoconazole in infants and children. Furthermore, the drug is not available in the United States as a liquid preparation but only as 200-mg tablets, which must be broken or crushed by parents or nurses and disguised in a suitable vehicle such as milk or applesauce to gain patient acceptance. This procedure makes administration of the drug difficult and inaccurate. Moreover, it is not known whether absorption of ketoconazole is altered by the various vehicles that are used to disguise the compound.

The purpose of the present study was to evaluate the bioavailability of ketoconazole as a suspension and as crushed tablets in infants and children.

The studies were conducted in the outpatient clinic of Children’s Medical Center, Dallas, Tex. Infants and children with oral candidiasis and superficial dermatophytoses were eligible to participate in the study. The decision to initiate antifungal therapy was made independently of the investigators. The parents of each patient were informed of the nature of the study and the possible benefits and liabilities of receiving ketoconazole. Informed, written consent was obtained before subjects were enrolled in the study.

Twelve patients were enrolled and studied in the fasting state on two separate occasions 5 to 7 days apart: once after receiving ketoconazole powder (crushed tablet) mixed with 2 tablespoons of applesauce, and once after receiving ketoconazole suspension (supplied by Janssen Pharmaceutica, New Brunswick, N.J., as a 20-mg/ml suspension, not yet commercially available). The tablets were all crushed and powdered by the same individual. A 5-mg/kg dose was used. Blood samples were obtained through a heparin-lock and a wing-tip needle inserted into a peripheral vein just before and at 0.5, 1, 2, 4, and 6 h after the dose.

Ketoconazole concentrations were measured on a Waters liquid chromatograph (Waters Associates, Milford, Mass.), equipped with a high-pressure delivery pump (M-45) and a variable-wave-length detector (H1450) set at 206 nm. Separation was achieved with a hypersil-ODS reverse-phase column (Chromanetics Corp., Kensington, Md.). The mobile phase was a mixture of 60% acetonitrile–40% 0.1 M Soren- sen buffer (pH 6.6). Standards were prepared by dissolving ketoconazole powder in acetonitrile, which was then added to pooled plasma in a final concentration of from 0.1 to 10 µg/ml. Ketoconazole had a retention time of 5.75 min, with no interfering peaks observed from structurally related analogs.

The intraassay precision of the method was tested by measuring spiked plasma specimens, containing 0.5 or 5.0 µg of ketoconazole per ml, 10 times in the same day. Concentrations averaged 0.48 ± 0.08 µg/ml (coefficient of variation, 16.7%) and 5.16 ± 0.23 µg/ml (coefficient of variation, 4.5%), respectively. The interassay reproducibility of the method was tested by determining plasma ketoconazole concentrations of 0.5- and 5.0-µg/ml doses 10 times over a 1-month period. Concentrations averaged 0.52 ± 0.1 µg/ml (coefficient of variation, 19.2%) and
TABLE 1. Pharmacokinetics of ketoconazole in infants and children

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Plasma concentration (µg/ml) at time (h) after dose:</th>
<th>AUC (µg·h/ml)</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Plasma concentration (µg/ml) at time (h) after dose:</td>
<td>AUC (µg·h/ml)</td>
<td>Half-life (h)</td>
</tr>
<tr>
<td>0.5</td>
<td>2.3 ± 0.2 (0.1-2.8)</td>
<td>2.6 ± 0.4 (0.4-6.5)</td>
<td>0.99 ± 0.1 (0.5-2.0)</td>
</tr>
<tr>
<td>1</td>
<td>2.6 ± 0.4 (0.4-4.1)</td>
<td>2.6 ± 0.4 (0.4-6.5)</td>
<td>0.99 ± 0.1 (0.5-2.0)</td>
</tr>
<tr>
<td>2</td>
<td>2.6 ± 0.4 (0.4-4.1)</td>
<td>2.6 ± 0.4 (0.4-6.5)</td>
<td>0.99 ± 0.1 (0.5-2.0)</td>
</tr>
<tr>
<td>4</td>
<td>2.6 ± 0.4 (0.4-4.1)</td>
<td>2.6 ± 0.4 (0.4-6.5)</td>
<td>0.99 ± 0.1 (0.5-2.0)</td>
</tr>
<tr>
<td>6</td>
<td>2.6 ± 0.4 (0.4-4.1)</td>
<td>2.6 ± 0.4 (0.4-6.5)</td>
<td>0.99 ± 0.1 (0.5-2.0)</td>
</tr>
</tbody>
</table>

Values given are the mean ± 1 standard error of the mean; the range is shown in parentheses.

4.9 ± 0.39 µg/ml (coefficient of variation, 7.9%), respectively. The linearity of the method was determined in the range of 0.1 to 10.0 µg/ml, with a linear regression coefficient of 0.998 in a regression line Y = 1.48 + 28.2X.

The equation for the regression line of the log plasma concentrations of ketoconazole against time was calculated by the method of least mean squares (5). The plasma half-life was determined by dividing the log₂ of the slope of the regression line. The area under the plasma concentration-time curve (AUC), expressed as micrograms per milliliter per hour, was formulated by successive trapezoidal approximation. Data were analyzed by single-factor analysis of variance (7). When significant differences between values were found, the two groups were compared by Newmala-Keuls multiple-comparison testing (7). Differences in values were considered significant at P ≤ 0.05.

Twenty-four pharmacokinetic studies were performed on 12 children from 2 to 12.5 years of age (mean age, 6 years). Seven were male and the ratio of boys to girls were similar. Their weights ranged from 13.5 to 64.9 kg (mean, 26.5 kg), and their heights ranged from 82 to 158 cm (mean, 114 cm). The average body surface area was 0.96 m². The pharmacokinetics of ketoconazole in these patients are shown in Table 1. Mean peak plasma concentrations were observed at 1 and 2 h after administration in patients who received the suspension and crushed tablets, respectively. Although there was considerable variation in plasma concentration, the mean values were from 1.6 to 4 times larger in children who received the ketoconazole suspension. Only 2 of 12 patients (16.7%) who received the crushed tablets had plasma concentrations of 4 µg/ml or higher, compared with 8 of 12 (67%) children who received the suspension. These differences are reflected in the significantly larger AUC values for patients who received the suspension compared with those for patients who ingested the crushed tablets. The plasma half-life tended to be longer after administration of crushed tablets than of the suspension; however, the difference between these values was not significant.

The indications from this study are that ketoconazole is more rapidly absorbed and produces higher concentrations in plasma when administered to infants and children as a suspension than as crushed tablets mixed with applesauce. Mean peak plasma concentrations of ketoconazole and AUC values were approximately twofold higher with the suspension that with the powder. Of the patients who received the suspension, 67% had peak plasma concentrations of 4 µg/ml or greater, a level that is 2- to 10-fold higher than the minimal inhibitory concentration.
for most dermatophytes, *Candida* species, and *Coccidioides immitis* (2). The significance of these findings to the clinical efficacy of the drug are unknown (3). Additional data are required before ketoconazole suspension can be routinely recommended for the therapy of fungal infections in infants and young children.

This study was funded by grants from Janssen Pharmaceutica and Eli Lilly Research Laboratories. Kent Dana and Nancy Wilson provided the statistical analysis.

**LITERATURE CITED**


