Effect of Oral Antacid Administration on the Pharmacokinetics of Oral Fluconazole

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Absorption and elimination of fluconazole after oral administration of a 100-mg capsule were unaffected by concomitant administration of an antacid containing aluminum and magnesium hydroxides.

Fluconazole is a new bis-triazole which has shown good antifungal activity in animal models of fungal infection (4) and in clinical studies of vaginal candidiasis (1, 9), oropharyngeal candidiasis in patients with acquired immunodeficiency syndrome and malignancies (3), and dermatophyte infections (10).

As well as having good absorption after oral administration (>95% bioavailability), fluconazole has a long half-life (25 to 30 h) in plasma and exhibits low protein binding (12%). Fluconazole is excreted mainly unchanged in the urine (2).

Optimal absorption of ketoconazole after oral administration has been shown to require normal gastric acidity. It has been postulated that the low aqueous solubility of ketoconazole in mildly acidic or neutral conditions is the reason for this impaired absorption in patients with hypochlorhydria, and this was later verified with volunteers (12). Fluconazole, a less lipophilic, more weakly basic bis-triazole derivative, is water soluble in both neutral and acidic conditions and may, therefore, be subject to the same limitations in gastrointestinal absorption. However, a significant proportion of patients who suffer from fungal infections do have impaired gastric acidity, whether it be from gastric secretory failure in patients with acquired immunodeficiency syndrome (6) or gastrointestinal disorders brought about by chemotherapy for treatment of malignancies and requiring antacid treatment. The purpose of the present work was to look at the effect of an antacid on the absorption and, hence, bioavailability of fluconazole following oral administration.

Fourteen healthy male subjects 21 to 29 (mean, 25.2) years old entered an open two-way crossover study. Subjects could enter the study only if they had no abnormality on medical examination or from prestudy laboratory testing and gave informed written consent. Subjects were not allowed to enter the study if they had a history of gastrointestinal disease, had taken any drugs during the previous 8 weeks, or had a known dependence on drugs or alcohol. In addition, subjects with a history of intolerance to imidazole or triazole drugs or antacids were not allowed to enter.

Each subject received a single oral 100-mg capsule of fluconazole after an overnight fast on two occasions 14 days apart, once immediately following a dose of an antacid (20 ml of Maalox forte containing aluminum hydroxide [1,800 mg] and magnesium hydroxide [1,200 mg]). The order of treatment was established by a predetermined randomization schedule. Each fluconazole capsule was administered with 150 ml of water, and food was not allowed until 4 h postadministration. Blood samples (8 ml) were withdrawn immediately before and 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 h after administration of each fluconazole dose. Plasma from each sample was separated, frozen at −20°C, and stored until assay at Biosciences by a gas chromatographic method for which the limit of detection was 0.1 μg/ml (13). Standard calibration curves established with samples with concentrations of 0.1 to 5 μg/ml during the study to control the linearity and accuracy of the method had relative standard deviations which varied from 2.4 to 5.4%. Replicate assays (n = 6) on samples with concentrations of 0.25 and 4 μg/ml had relative standard deviations of 5.9 and 2.6%, respectively.

For determination of pharmacokinetic parameters, the maximum fluconazole concentration (Cmax) and the time to the first maximum concentration (Tmax) were determined by inspection of the concentrations in plasma from each phase

Without Antacid

With Antacid

FIG. 1. Mean concentrations of fluconazole in plasma following a single 100-mg dose, alone or after antacid administration (n = 14).

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for each subject. Nonhomoscedastic variance modelization was used for the plasma concentration-time curve, which was fitted by using a peeling algorithm (SIFPAR [SIMED, Creteil, France] run on a Compaq Deskpro 80/20). The area under the plasma concentration-time curve extrapolated to infinity (AUC sub(inf)) was determined by summing the AUC from 0 to 144 h (AUC sub(0-144)), determined by the trapezoidal rule, and the terminal area integrated from 144 h onwards. The elimination rate constant (k sub(e)) was calculated by loga-

### TABLE 1. Pharmacokinetic parameters for fluconazole with and without an antacid

<table>
<thead>
<tr>
<th>Regimen</th>
<th>C max (μg/ml)</th>
<th>T max (h)</th>
<th>AUC sub(0-144) (μg h/ml)</th>
<th>k e (1/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole without antacid</td>
<td>1.70 ± 0.26</td>
<td>4.29 ± 2.59</td>
<td>93.00 ± 13.82</td>
<td>0.01957 ± 0.0025</td>
</tr>
<tr>
<td>Fluconazole with antacid</td>
<td>1.71 ± 0.22</td>
<td>5.14 ± 1.88</td>
<td>92.43 ± 14.57</td>
<td>0.01964 ± 0.0027</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± standard deviations. Differences between parameters were not statistically significant (see text). Ranges for individual subjects are shown in parentheses (n = 14).

The maximum contributions due to extrapolation from 144 h to infinity were 8.2 and 9.0% for fluconazole without and with the antacid, respectively.

These properties of fluconazole are particularly relevant, since it has recently been shown that the bioavailability of oral ketoconazole is reduced in patients with acquired immunodeficiency syndrome, largely as a result of gastric hypochlorhydria. Therefore, it has been suggested that ketoconazole tablets be given with acid to such patients (7). With fluconazole, this procedure should not be necessary.

### LITERATURE CITED