The pharmacokinetics of fluconazole after a single intravenous dose in AIDS patients

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The pharmacokinetics of fluconazole after a single 100 mg i.v. dose were studied in 10 healthy subjects (5 M; 5 F) and 10 HIV-positive patients (8 M; 2 F). The mean value of plasma clearance was 25% lower in the patient groups (17 ± 6 (s.d.) vs 23 ± 4 ml min⁻¹; 95% CI of difference −11 to −0.7; P < 0.05). This difference may have been related to slightly reduced kidney function in the patient group (mean creatinine clearance −18%) but is unlikely to be clinically significant. Therefore, no adjustment of the dose of intravenously administered fluconazole appears to be necessary in AIDS patients without clinical signs of enteropathy.

Keywords AIDS fluconazole triazole pharmacokinetics antimycotic drugs

Introduction

Fluconazole is an effective antimycotic triazole with high tissue penetration, low protein binding and almost exclusive renal excretion [1]. AIDS is often complicated by cryptococcal meningitis or oral candidiasis and fluconazole has been shown to be a useful drug in the treatment of these two conditions in AIDS patients [2–7]. We report a comparative study of the pharmacokinetics of fluconazole after a single intravenous dose in AIDS patients and in healthy subjects.

Methods

Subjects

The study was carried out in the Department of Internal Medicine of the Rudolf Virchow University Clinic, Charlottenburg, Berlin, Germany. The mean ages of the AIDS patients (n = 10) and healthy subjects (n = 10) were 35 ± 7 years and 27 ± 4 years, the mean heights were 176 ± 6 cm, and 175 ± 10 cm, and the mean weights were 61 ± 9 kg and 69 ± 12 kg, respectively (with s.d.s). The study was approved by the local Ethics Committee, and all subjects gave informed and written consent to participate.

A clinical examination, routine biochemical and haematological screening, and laboratory tests of kidney and liver function were performed before the study. Kidney and liver function was normal in members of both groups, although the AIDS patients had significantly lower creatinine clearance values than the healthy subjects (132 ± 24 vs 108 ± 20 ml min⁻¹, s.d. (P < 0.05, two-tailed t-test). All of the AIDS patients were positive for HIV antibodies. They were classified as stage CDC IV C/D with a mean CD4 count of 34/μl (range 5–99/μl). The AIDS patients were being treated with a variety of anti-infective, antitussive and analgesic drugs. They exhibited no signs of enteropathy.

Protocol

Fluconazole 100 mg was administered by intravenous infusion over 20 min to both patients and healthy subjects. Venous blood samples were taken at 5, 10, 15 and 30 min and at 1, 2, 4, 6, 8, 12, 24, 48, 72, 96 and 120 h after the end of infusion. Plasma was separated by centrifugation and stored at −70°C before analysis. Fluconazole is stable under these conditions.

Analytical methods

Fluconazole was extracted from the plasma samples with ethyl acetate and assayed by h.p.l.c. with u.v. detection [8].

The limit of determination of the assays (variance < 20%) was less than 10 ng ml⁻¹, which was well below the working range of the calibration curve (0.1 to 4.0 μg ml⁻¹). The accuracy of the measurements was within ± 9.1%, ± 2.0% and ± 0.7% at 0.5, 2.0 and 3.0 μg ml⁻¹ fluconazole, respectively.

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References


Table 1 Pharmacokinetic parameters of fluconazole following i.v. infusion of 100 mg over 20 min to healthy subjects and AIDS patients. Results are expressed as mean ± s.d., with 95% confidence interval for the difference between means of the two groups. *P < 0.05.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Volunteers (n = 10)</th>
<th>Patients (n = 10)</th>
<th>95% confidence interval (difference between means)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg m&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>2.8 ± 0.4</td>
<td>2.9 ± 0.9</td>
<td>-0.6 to +0.9</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2,z&lt;/sub&gt; (h)</td>
<td>35 ± 3</td>
<td>37 ± 3</td>
<td>-7 to +11</td>
</tr>
<tr>
<td>CL (ml min&lt;sup&gt;-1&lt;/sup&gt;)*</td>
<td>23 ± 4</td>
<td>17 ± 6</td>
<td>-11 to -0.7</td>
</tr>
<tr>
<td>V&lt;sub&gt;ss&lt;/sub&gt; (l kg&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.94 ± 0.05</td>
<td>0.84 ± 0.07</td>
<td>-0.27 to +0.07</td>
</tr>
</tbody>
</table>

Pharmacokinetic and statistical analyses

The plasma concentrations of fluconazole were subjected to non-compartmental analysis using the TOPFIT programme (Thomae Ltd, Biberach, Germany). Thus, values of λ<sub>2</sub>, t<sub>1/2,z</sub>, V<sub>ss</sub> and CL were estimated. The maximum plasma drug concentrations (C<sub>max</sub>) were noted directly from the experimental data.

The derived pharmacokinetic parameters were compared using Student's two-tailed t-test and 95% confidence limits were calculated for the differences between means.

Figure 1 Mean ± s.e. mean plasma concentrations of fluconazole after intravenous administration of 100 mg fluconazole to AIDS patients (●●●●…) (n = 10) and to healthy subjects (- - - - -) (n = 10).

Results

Mean plasma concentrations of fluconazole for the two groups of subjects are shown in Figure 1 and pharmacokinetic parameters summarized in Table 1. The mean plasma drug clearance was significantly lower (by 25%) in the AIDS patient group compared with that in the healthy subjects. Differences in other pharmacokinetic parameters were not detected.

Rifampicin can lower the AUC of fluconazole [9]. However, the single patient being treated with rifampicin in our study had an AUC value of 81.8 µg ml<sup>-1</sup> h, which was not a particularly low value.

Discussion

Lower plasma clearance of fluconazole in the AIDS patients may be related to the slightly decreased but still normal kidney function in the latter group. Decreased renal function is common in AIDS patients [10], although the degree of impairment in the present study was marginal.

We expect that the small decrease in the plasma clearance of fluconazole in AIDS patient relative to healthy controls is unlikely to be of clinical significance. There appears to be no basis for recommending dosage adjustment in the treatment of AIDS patients with intravenously administered fluconazole.

*(Received 5 August 1993, accepted 28 February 1994)*