Pharmacokinetics of Fluconazole in Renal Failure

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ABSTRACT

Fluconazole (FLU) is a widely used antifungal agent. The multiple-dose pharmacokinetics of FLU in renal impairment have not been previously investigated. The following groups were studied: volunteers with creatinine clearances (CLcr, >50 mL/min) of 107 mL/min, given a loading dose of 400 mg and a daily dose of 200 mg/day for 9 days (Group 1); subjects with CLcr between 21 and 50 mL/min with a mean of 38 mL/min, given a loading dose of 200 mg and a maintenance dose of 100 mg/day for 9 days (Group 2); subjects with CLcr between 11 and 20 mL/min with a mean of 14.8 mL/min, given a loading dose of 100 mg and a maintenance dose of 50 mg/day for 9 days (Group 3); and subjects on hemodialysis (three times per week) receiving a loading dose of 200 mg and then 100 mg after each of four dialysis sessions (Group 4) (N = 10 per group). After the administration of the loading dose on Day 1, the mean area under the curve (AUC) (0–24) measurements were approximately proportional to the dose of FLU and independent of renal function. After 10 days of FLU dosing, the mean renal clearance of FLU decreased as CLcr decreased for Groups 1 to 3, and the Day 10 mean half-lives were inversely related to mean CLcr (36.7 h in Group 1, 84.5 h in Group 2, and 101.9 h in Group 3). The mean AUC (0–24) on Day 10 was similar for Group 1 compared with Group 2, despite a reduction in the maintenance dose by 50%. The mean AUC (0–24) for Group 3, for which the maintenance dose was 25% of that for Group 1, decreased by approximately 50% as compared with Group 1. For subjects in Group 4, for which the maintenance dose was 50% of that for Group 1, hemodialysis resulted in a decrease in peak dose serum concentrations of approximately 50% compared with Group 1. It was concluded that the loading dose for FLU need not be adjusted for the degree of renal impairment. The maintenance dose should be reduced by 50% for subjects with CLcr ≤50 mL/min, with no further reductions for subjects with CLcr <20 mL/min. Subjects on hemodialysis should receive the recommended maintenance dose after each hemodialysis session.

Key Words: Antifungals, creatinine clearance, dosage modification

Since its approval by the Food and Drug Administration in 1990, the bis trifluoromethylazole (FLU) has been found to be an effective oral antifungal agent (1). As such, it is widely used in the treatment of a variety of fungal infections. It was soon recognized that unlike ketoconazole and itraconazole, FLU is metabolically stable and the major proportion (∼70 to 80%) of the administered drug is excreted unchanged in the urine of humans (2). The renal clearance (CLR) of FLU in humans ranges from 15 to 19 mL/min (3,4). Alterations in renal function would therefore be expected to influence the pharmacokinetics of the drug. In this regard, only one study using a single 50-mg dose of the drug noted a direct relationship between the GFR (measured by creatinine clearance [CLcr]) and the CLR, of the drug (5), leading to a commensurate increase in FLU halflife (t1/2). On the basis of these data, modification of maintenance dosing or dosing interval has been advocated (4). In view of its 30-h t1/2, approximately 6 days of daily dosing is required before steady state is reached. It is not known whether the recommended doses yield comparable drug levels in subjects with renal insufficiency compared with subjects with normal renal function, or what the pharmacokinetics are under steady-state conditions that are akin to the use of the drug in clinical practice. This study was therefore undertaken to compare the pharmacokinetics of FLU in subjects with normal renal function with that of subjects with renal insufficiency, including those requiring intermittent hemodialysis.

METHODS

Oral FLU was administered to a total of 40 volunteers who provided written informed consent. As noted in Table 1, they were divided into four groups of 10 subjects each in accordance with the following levels of renal function: Group 1 included subjects with CLcr >50 mL/min; Group 2 included subjects with CLcr between 21 and 50 mL/min, inclusive; Group 3 included subjects with a CLcr between 11 and 20 mL/min, inclusive; and Group 4 included subjects requiring hemodialysis three times per week. In Groups 1, 2, and 3, FLU was administered orally as a single loading dose for 1
TABLE 1. Renal function and FLU dosing in the four study groups

<table>
<thead>
<tr>
<th>Group</th>
<th>CLcr (mL/min)</th>
<th>Loading Dose (mg) (Day 1)</th>
<th>Maintenance Dose (mg) (Days 2 to 10)</th>
<th>Screening CLcr (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;50</td>
<td>400</td>
<td>200</td>
<td>107 (79-174)</td>
</tr>
<tr>
<td>2</td>
<td>21-50</td>
<td>200</td>
<td>100</td>
<td>38 (22-49)</td>
</tr>
<tr>
<td>3</td>
<td>11-20</td>
<td>100</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>Hemodialysis</td>
<td>200 postdialysis</td>
<td>100 postdialysis (Days 3, 6, 8, and 10)</td>
<td>15 (11-22)</td>
</tr>
</tbody>
</table>

day, followed by 9 days of maintenance dosing in the manner described in Table 1, which follows currently recommended doses. The subjects in Group 4 received the loading and maintenance doses immediately after hemodialysis. The latter group was given doses only on Days 3, 6, 8, and 10, coincident with the days on which hemodialysis was performed. Approval of this investigation was granted by the Colorado Multiple Institutional Review Board at the University of Colorado Health Sciences Center, the Institutional Review Board at the University of Texas, Southwestern Medical Center at Dallas, and the Human Studies Subcommittee at the Dallas Veterans Affairs Medical Center.

For Groups 1, 2, and 3, two CLcr were determined on separate occasions on the basis of 24-h urine collections and serum creatinine. The mean of the two CLcr was used as the basis for inclusion into the study.

For Groups 1, 2, and 3, blood samples were collected at 0 (predose), 1, 1.5, 2, 4, 6, 8, 12, 18, and 24 h postdose on Day 1; just before morning dosing on Days 3 to 9; and at 0 (predose), 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, and 144 h postdose on Day 10. For Groups 2 and 3 only, additional blood samples were collected at 168, 192, 216, and 240 h after Day 10 dosing. For those subjects in Group 4, blood samples were collected at 0 (predose), 1, 2, 4, 8, 12, 18, and 24 h postdose on Day 1; before drug administration (posthemodialysis) on Days 3, 6, and 8; approximately the same time as Day 3 on nondosing Days 4, 5, 7, and 9; and at 0 (predose), 1, 2, 4, 8, 12, 18, 24, 36, 48, and 72 h postdose on Day 10. The 72-h postdose sample was collected after the completion of hemodialysis on this day (i.e., Day 13). All samples were collected in red-top specimen tubes (no anticoagulant or preservative) and allowed to clot at room temperature. The harvested serum samples were stored at -20°C until analyzed. Urinary concentrations of FLU were determined by HPLC-UV (7). The linear dynamic range of the urine assay was from 10.0 to 300 g/mL.

Urine samples were collected from subjects in Groups 1, 2, and 3 on Day 1 before dosing and from 0 to 24 h postdose. On Day 10, urine samples were collected over the following postdose intervals: 0 to 24 h, 24 to 48 h, 48 to 72 h, and 72 to 96 h after dosing. There were no urine samples collected from subjects in Group 4. Urine samples were stored at -20°C until analyzed. The concentrations of FLU in serum were determined by a validated HPLC-UV method (6). The linear dynamic of the assay was from 0.05 to 20.0 μg/mL.

The terminal phase rate constant (Kel) was estimated by the use of linear least squares regression analysis of the serum FLU concentration-time data obtained during the terminal natural log-linear phase. The t_{max} was determined as 0.693/Kel, and the mean t_{max} was determined as 0.693/mean Kel. The area under the serum concentration-time curve from 0 to 24 h postdose ([AUC(0-24)]) was determined by linear trapezoidal approximation. The maximum serum FLU concentration (C_{max}) was determined directly from the concentration data, with t_{max} defined as the first occurrence of C_{max}. CLcr was estimated for subjects in Groups 1, 2, and 3 after dosing on Days 1 and 10 as: X(U(0-24))/AUC(0-24) where X(U(0-24)) is the amount of unmetabolized FLU excreted in the urine over the 0- to 24-h collection interval. Data are shown as mean ± standard deviation.

Because the loading and maintenance doses given to Groups 2, 3, and 4 were lower than those for Group 1, the AUC(0-24) and the C_{max} data were also statistically analyzed when normalized by dividing the AUC(0-24) and C_{max} by the respective doses for Groups 1, 2, 3, and 4. Then, natural log-transformed AUC(0-24) and C_{max} and untransformed t_{max} and Kel were analyzed by the use of Fisher's least significant difference procedure to examine differences between groups for both the normalized and the nonnormalized data. A one-way analysis of variance was used to test for a renal group effect on the basis of a 5% level of significance.

RESULTS

The screening creatinine clearances of the groups is noted in Table 1. There was a predominance of men in all groups. The mean age was 51 in Group 1, 56 in Group 2, 64 in Group 3, and 47 in Group 4.

Pharmacokinetics of FLU After Loading Dose Administration

Figure 1 depicts the mean serum levels of FLU after the loading dose of Day 1, and Table 2 summarizes the pharmacokinetics and resulting statistical analyses, respectively. The AUC as well as the C_{max} in Groups 2,
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TABLE 2. Mean ± SD FLU pharmacokinetic parameter estimates resulting from the administration of the loading dose on Day 1 to subjects with varying degrees of renal function

<table>
<thead>
<tr>
<th>Group (N = 10)</th>
<th>Loading Dose (mg)</th>
<th>AUC(0-24) (µg·h/mL)</th>
<th>C_{max} (µg/mL)</th>
<th>CL_{r} (mL/min)</th>
<th>In AUC(0-24)</th>
<th>In C_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>145.2 ± 19.7</td>
<td>8.53 ± 1.56</td>
<td>14.0 ± 4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>81.2 ± 15.7</td>
<td>4.36 ± 0.66</td>
<td>6.8 ± 1.2^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>42.7 ± 8.6</td>
<td>2.42 ± 0.78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>200</td>
<td>102.5 ± 11.7</td>
<td>5.48 ± 0.91</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nonnormalized Data Comparison^b

| 1 vs. 2        | 0.0001           | 0.0001              |
| 1 vs. 3        | 0.0001           | 0.0001              |
| 2 vs. 3        | 0.0001           | 0.0001              |
| 1 vs. 4        | 0.0001           | 0.0001              |

Normalized Data Comparison^b

| 1 vs. 2        | 0.1700           | 0.7839              |
| 1 vs. 3        | 0.0417           | 0.3007              |
| 2 vs. 3        | 0.4811           | 0.4441              |
| 1 vs. 4        | 0.0001           | 0.0097              |

^a N = 6.
^b Summary of analysis of variance results; difference between renal function groups on Day 1 (loading dose). Values are P values.

3, and 4 was significantly lower than those in Group 1. As summarized in Table 2, when the data were normalized for the given doses, there was no statistically significant difference in the AUC(0–24) data between Groups 1 and 2 or Groups 2 and 3. Even though there was a statistically significant difference between Groups 1 and 3 (P = 0.0417), the difference between the two groups was <20% and is not considered to be clinically meaningful. Likewise, when normalized for the dose, there was no significant difference in C_{max} between Groups 1, 2, and 3. A comparison of Groups 1 and 4 with normalized data reflects a significantly higher AUC and C_{max} in Group 4 when compared with Group 1, suggesting that were such patients to get the full recommended loading dose of 400 mg, the failure of renal excretion would lead to a larger drug exposure and drug level than in control subjects. The mean time to maximal drug level (T_{max}) for Groups 1 to 4 were 2.2, 2.5, 3.2, and 3.9 h, respectively. There was no significant difference in T_{max} among the four groups. As is shown in Table 2, the mean CL_{r} of the drug was 14.0 mL/min for subjects in Group 1, with 31% of the dose excreted in the urine over the first 24 h. The determination of CL_{r} could be assessed in only six subjects in Group 2 and in none of the subjects in Group 3 because the urine concentration over the 24-h collection interval was below the limit of assay quantification. In the six subjects in Group 2, the CL_{r} of FLU averaged 6.8 mL/min, with only 8% of the dose excreted in the urine over the ensuing 24-h period.

Trough FLU Concentrations After Maintenance Dose Administration

Figure 2 depicts trough FLU concentrations obtained over Days 2 to 11 (i.e., 24 h after last administered dose on Day 10) for Groups 1, 2, and 3. Subjects with normal renal function on 200 mg/day achieved steady-state trough levels on Day 10 of 7 to 8 µg/mL. Similar steady-state levels were achieved by subjects with moderate renal insufficiency (Group 2) on 100 mg/day by Day 10. However, the further decrease in dosage to 50 mg/day in subjects with more advanced impairment (Group 3) was associated with the attainment of steady-state trough levels of 4 to 5 µg/mL by Day 10. The trough levels in dialysis subjects are shown in Figure 3. The administration of 100 mg of FLU postdialysis led to concentrations of approximately 4 µg/mL, 24 and 48 h after each procedure. Dialysis decreased FLU concentrations by approximately 50%.

Pharmacokinetics of FLU at Steady State After Maintenance Dose Administration

Figure 4 shows the mean FLU concentrations after the last administered dose of Day 10, and Table 3...
summarize the pharmacokinetics and resulting statistical analyses. On Day 10, the mean AUC(0-24) for Groups 1 and 2 were 217.7 and 211.7 μg·h/mL, respectively. The nonnormalized difference between the two groups was not statistically significantly different despite the lower maintenance dose administered to Group 2 (100 mg to Group 2 versus 200 mg to Group 1). In fact, the normalized data that corrects for this difference in dose reveal a highly significant difference (P < 0.001). In contrast, the subjects in Group 3, who received a maintenance dose of 50 mg, had a mean AUC(0-24) of only 117.9 μg·h/mL, which was statistically different from that of Groups 1 or 2. The mean AUC(0-24) for Group 4 was 107.5 μg·hr/mL after the 100-mg dose (P < 0.001 versus Group 1). When normalized for dose, the AUC(0-24) between Groups 2 and 3 and between Groups 1 and 4 was not different. The Cmax in Groups 1 and 2 was also similar, 12.6 and 10.4 μg/mL, respectively, but because of the small variability of the data, this small difference achieved statistically significance. In contrast, subjects in Groups 3 and 4 achieved levels of only 6.0 and 5.27 μg/mL, both the fact significantly lower than controls. Even when normalized, the comparisons between Groups 2 and 3 and Groups 1 and 4 (P < 0.03) were statistically significant despite differences of <20% that are probably not clinically significant. The mean Tmax for Groups 1 to 3 was similar to their Day 1 values, whereas the mean Tmax in Group 4 was prolonged (7.6 h). The mean CLr of the drug in Groups 1 (13.2 mL/min) and 2 (5.3 mL/min) were similar to those values obtained on Day 1. In eight subjects in Group 2 whose CLr could be estimated, mean CLr was 3.3 mL/min. These decreases in FLU CLr in subjects with renal insufficiency were associated with a statistically significant decrease in the drug’s terminal elimination constant. Specifically, this corresponded to a t1/2 of 36.7 h in controls (Group 1), 84.5 h in Group 2, and 101.9 h in Group 3.

DISCUSSION

The bistriazole antifungal agent FLU is widely used in the treatment of a variety of fungal infections (1). The pharmacokinetics of FLU have been extensively investigated in normal volunteers (7,8) and summarized by Debruyne and Ryckelynck (4). These studies reported a t1/2 ranging from 22 to 42 h and CLr, ranging from 7.3 to 17.3 mL/min after multiple dosing. Thus, these data are in agreement with measurements of a t1/2 of 36.7 h and CLr of 14 mL/min in our control subjects (Group 1) after the administration of multiple doses of FLU. Likewise, a study using a loading dose of 400 mg found a maximal concentration of 9.1 μg/mL (4), comparable to the 8.53 μg/mL in our control Group 1. In contrast to the abundant information available in normal subjects (8,9), data in subjects with renal insufficiency are limited, despite the established observation that the drug is primarily eliminated by the kidney, with approximately 70 to 80% of the drug excreted unchanged in the urine (4). The single-dose pharmacokinetic study by Toon et al. (5) has provided the primary guidelines for the modification of FLU use in renal impairment. However, there were several limitations to that study: (1) the AUC data generated from that study were not under clinical practice conditions, i.e., steady state, where an accurate characterization of the terminal elimination is not required; (2) data were collected from only five subjects per group; and (3) data generated from that study used a fixed dose of 50 mg. In our study, we evaluated the pharmacokinetics of FLU under steady state with 10 subjects per study group. In addition, the doses used in this study are those currently recommended for a number of therapeutic indications.

The results of our study, with respect to the effect of renal dysfunction on FLU CLr and t1/2, are in agreement with those of Toon et al. (5). Specifically, in the latter study, subjects with a mean CLcr of 35 mL/min (range, 20 to 70 mL/min) had an average CLr of 6.8...
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TABLE 3. Mean ± SD FLU pharmacokinetic parameter estimates resulting from the administration of the oral maintenance dose on Day 10 to subjects with varying degrees of renal function

<table>
<thead>
<tr>
<th>Group (N = 10)</th>
<th>Loading Dose (mg)</th>
<th>AUC(0-24) (μg·h/mL)</th>
<th>Cmax (μg/mL)</th>
<th>CLr (mL/min)</th>
<th>In AUC (0-24)</th>
<th>In Cmax</th>
<th>In Kel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
<td>217.7 ± 38.6</td>
<td>12.60 ± 2.00</td>
<td>36.7</td>
<td>13.2 ± 3.9</td>
<td>0.5617</td>
<td>0.0087</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>211.7 ± 59.4</td>
<td>10.24 ± 2.51</td>
<td>84.5</td>
<td>5.3 ± 5.3</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>117.9 ± 12.9</td>
<td>6.01 ± 1.00</td>
<td>101.9</td>
<td>3.3 ± 0.7</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>107.5 ± 12.8</td>
<td>5.27 ± 0.82</td>
<td></td>
<td></td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Nonnormalized Data Comparison

1 vs. 2        | 0.5617           | 0.0087               | 0.0001       |
1 vs. 3        | 0.0001           | 0.0001               | 0.0001       |
2 vs. 3        | 0.0001           | 0.0001               | 0.0001       |
1 vs. 4        | 0.0001           |                      |              |

Normalized Data Comparison

1 vs. 2        | 0.0001           | 0.0001               | 0.0001       |
1 vs. 3        | 0.0001           | 0.0001               | 0.0001       |
2 vs. 3        | 0.0991           | 0.0370               |              |
1 vs. 4        | 0.9588           | 0.0320               |              |

a Q 0.693/mean Kel.
b N = 7.
c N = 8.
d Summary of analysis of variance results: difference between renal function groups on Day 10 (maintenance dosing). Values are P values.

mL/min and a t½ of 59 h. In our study, a similar group of subjects with a mean CLcr of 38 mL/min (Group 2) had a mean CLr of 5.4 mL/min, leading to a prolonged t½ of 84.5 h after 10 days of dosing. The difference in t½ values is most likely the result of the large range of CLcr for that particular group of subjects studied by Toon et al. Likewise, their subjects with advanced renal impairment (mean CLcr of 14.0 mL/min) had a mean CLr of 3.2 mL/min and a t½ of 98 h. These data are similar to data from our Group 3 subjects (mean CLcr of 15 mL/min), in whom the mean CLr was 3.1 mL/min and the t½ was 101.9 h.

Our study reveals a number of important facts about the pharmacokinetics of the drug in renal failure. After the administration of a loading dose, the mean AUC(0–24) and Cmax of FLU were successively reduced by approximately one-half from Groups 1 to 3 (Table 2). This reduction paralleled the decrease in the loading dose (i.e., 400 to 200 to 100 mg for Groups 1, 2, and 3, respectively). These results indicate that renal insufficiency does not alter FLU concentrations over the first 24 h after the administration of the loading dose. The loading dose does not need to be adjusted for renal impairment, as reflected by the nonsignificant differences with data normalized for dose (Table 2). The significant differences for the dialysis subjects would suggest a level of drug exposure and Cmax that are higher if the dose given is the same as that given to controls. Nonetheless, the 200-mg dose gives undesirably low levels, whereas the full dose would exceed controls only marginally. Thus, dialysis patients should receive the same loading dose as controls.

After maintenance dosing, the predose drug concentration (Figure 2), as well as the AUC and Cmax of FLU, was similar between Groups 1 and 2, even though the dose of Group 2 was one-half that of Group 1 (Table 3). This indicates that the maintenance dose should be reduced by 50% for subjects whose CLcr are <50 mL/min. However, predose drug levels, as well as the AUC and Cmax for Group 3, were lower than in Groups 1 and 2 but similar to Group 2 when the data are normalized, suggesting that such patients should receive a dose similar to that of Group 2 patients. On the basis of these data, no further reductions should be required for subjects with CLcr equal to or <20 mL/min. The importance of this dose adjustment with FLU has clinical implications because most Candida species are inhibited by FLU concentrations ≥6 μg/mL (9,10), whereas even higher concentrations (≥10 μg/mL) may be needed to effectively treat organisms such as Candida neoformans or Candida immitis or aspergillosis (11,12). Thus, dose adjustments based on the single-dose pharmacokinetic study may leave subjects with CLcr equal to or <20 mL/min with trough and peak blood concentrations that could be subtherapeutic.

We also studied the pharmacokinetics of FLU in subjects undergoing intermittent hemodialysis (Group 4). We confirmed the previously reported removal of the drug by hemodialysis (5,13) as drug concentrations were decreased by ~40 to 50% by the procedure with minimal decline in the interdialytic period. A maintenance dose of 200 mg, one-half that of group 1, resulted in a corresponding decrease in AUC(0–24) to approximately one-half that of Group 1 (Table 3). The analysis of normalized AUC data comparing Groups 1 versus 4, in fact, reveals that dialysis patients should get a maintenance dose similar to that of controls after hemodialysis. These data indicate that subjects receiving intermittent hemodialysis should receive the recommended maintenance dose...
on the basis of the indication after each hemodialysis session.

In this study, we did not investigate the pharmacokinetics of the drug in subjects undergoing peritoneal dialysis. However, an analysis has been carefully undertaken by Debruyne et al. (14). They propose the administration of 150 mg in a 2-L dialysate bag every 2 days (4, 14). The blood levels achieved are only ~2 µg/mL but may be adequate to treat most Candida species that cause peritonitis in such subjects.

In summary, our study is the first to examine steady state pharmacokinetics of the widely used antifungal agent FLU in subjects with varying degrees of renal dysfunction. Our findings indicate that the loading dose of FLU should be based only on indication. The maintenance dose should then be reduced by 50% for subjects with CLcr equal to or <50 mL/min. Additional adjustments for subjects with CLcr equal to or <20 mL/min could result in trough and peak concentrations that could be subtherapeutic. Finally, dialysis subjects should receive the recommended maintenance dose after each hemodialysis treatment.

REFERENCES