Dosing guidelines for fluconazole in patients with renal failure

Lucile Cousin, Marie Le Berre, Vincent Launay-Vacher, Hassane Izzedine and Gilbert Deray

Department of Nephrology, Pitie-Salpetriere Hospital, Paris, France

Keywords: CAPD; CVVH; fluconazole; haemodialysis; renal insufficiency

Introduction

Fluconazole is a widely used drug that inhibits the synthesis of fungal cell membranes [1,2]. Its elimination is predominantly via renal excretion with most of the dose recovered in urine as an unchanged and active drug. As a result, drug pharmacokinetics are altered in patients with renal failure and it is essential to establish guidelines on how to handle this drug in those patients. Furthermore, in dialysis patients, the removal of the drug in the dialysate has to be elucidated to determine whether fluconazole should be administered after the session or not. A review of the literature was thus performed and analysis of the retrieved data permitted to establish dosage adjustment guidelines for fluconazole in patients with renal failure.

Pharmacokinetics

The oral bioavailability of fluconazole is >90%, which enables us to administer it with similar doses by i.v. and oral routes. Neither food nor gastric pH modifications have a significant effect on its oral absorption [3,4]. Fluconazole has low plasma protein binding (11%) and its apparent volume of distribution is 0.81/kg [5], which approximates total body water. The primary route of elimination is via renal excretion. Eighty per cent of an administered dose is recovered in urine as unchanged and active drug and 11% as the glucuronide and N-oxide metabolites, which are both inactive and probably come from metabolism in the liver by cytochrome P450 3A4 enzymes [6–8]. Over the range of 100–400 mg orally, the variation of fluconazole maximum plasma concentration (Cmax) and area under the concentration–time curve (AUC) are proportional to the administered dose, whereas the elimination half-life (30 h) and the time of maximal concentration remain constant (0.5–6 h). This indicates the linearity of the pharmacokinetics of fluconazole for oral doses ranging from 100 to 400 mg [3]. After doses of 200 and 400 mg, the plasma concentrations of fluconazole were, respectively, 4.6 and 9 mg/l at steady state, which is reached 4–5 days after administration of multiple doses and in ~2 days when given a loading dose representing the double of the maintenance dose: 400 or 800 mg, respectively. This pharmacokinetic profile enables us to obtain good results against sensitive or usually sensitive strains, as the minimum inhibitory concentrations (MICs) 90 of fluconazole are 1 mg/l for Candida albicans [9] and 16 mg/l for Candida glabrata [9,10] and Cryptococcus neoformans [11] (Table 1). In clinical practice, recommended efficient concentrations of fluconazole are 7–8 mg/l for Candida’s infections and 15–20 mg/l for severe infections [12].

Toxicity

Fluconazole is generally well tolerated. The main side effects are nausea, headache, skin rash, abdominal pain, vomiting and diarrhoea. The overall incidence of these adverse effects was 16% among 4000 patients treated by fluconazole [5]. Furthermore, fluconazole has been suggested to be potentially hepatotoxic. However, in comparative studies vs placebo, the pattern of abnormal aspartate amino transferase, alanine amino transferase, alkaline phosphatase, \( \gamma \)-glutamyl transferase and bilirubine values did not suggest that fluconazole treatment was associated with an increased risk for hepatotoxicity, although a marked elevation of some of these enzymes occurred in ~1% of patients [5]. It is thus important to adjust dosage in patients with renal insufficiency in order to avoid these side effects.

Patients with renal failure

Flulonazoles pharmacokinetics are altered in patients with renal insufficiency as its elimination is predominantly via the kidney. Indeed, studies showed that the elimination half-life may increase to up to 98 h in patients with a creatinine clearance of <20 ml/min
whereas it is ~30 h in patients with normal renal function [13]. Dosage reduction of fluconazole is thus mandatory in patients with renal impairment, i.e. patients with a creatinine clearance of <60 ml/min. In patients whose creatinine clearance is between 10 and 60 ml/min, it is recommended to reduce fluconazole maintenance doses by 50%, by halving the unitary dose or by doubling the dosing interval. The adaptation only concerns the maintenance dose and not the loading dose, which should be the same as for patients with normal renal function, as usually performed for most drugs. In the indication of vaginal or perineal candidiasis, a single oral dose of 150 mg is recommended. In this case, as the administration is not repeated and peak toxicity is only minor, there is no need to reduce the single dose in patients with renal failure (Tables 2–4).

**Haemodialysis patients**

Fluconazole is dialysable [14,15]. Moreover, data from the study of Oono et al. [15] evaluated the haemodialysis clearance (CL\textsubscript{HD}) of fluconazole. In this study on five haemodialysis patients, the authors determined the extraction ratio of fluconazole during a haemodialysis session of 3–4 h. The single-pass extraction ratio of the dialyser was 59% and the blood flow was 180 ml/min. Consequently, fluconazole’s CL\textsubscript{HD}, calculated with the formula: CL\textsubscript{HD} = extraction rate \times blood flow, was 106 ml/min. CL\textsubscript{HD} should then be compared with fluconazole’s extra-renal clearance (CL\textsubscript{ER}), which represents the total body clearance of the drug in the same patients on a non-haemodialysis day, in order to calculate the value of F\textsubscript{HD} (drug fractional clearance by haemodialysis) with the formula: F\textsubscript{HD} = CL\textsubscript{HD}/(CL\textsubscript{HD} + CL\textsubscript{ER}) [16,17]. If F\textsubscript{HD} is >25%, haemodialysis clearance should be considered as significant as compared with total body clearance of the drug and the administration should be performed after the session on haemodialysis days, as demonstrated previously [16,17]. The exact CL\textsubscript{ER} being unknown, it is thus not possible to calculate the exact value of F\textsubscript{HD}. However, the total body clearance of fluconazole in healthy volunteers with normal renal function is 17.9 ± 7.9 ml/min [13]. It can therefore be assumed that F\textsubscript{HD} will certainly be >25%. Indeed for a F\textsubscript{HD} value of <25%, fluconazole’s total body clearance should increase from 17.9 ml/min in patients with normal renal function to >318 ml/min in patients with end-stage renal disease, which is unlikely to occur. Subsequently, haemodialysis is likely to significantly impair the pharmacokinetics of fluconazole and it seems wise to administer the drug after the session on haemodialysis days to replenish depleted stores. Oono et al. [15] recommended that fluconazole should be given at the end of each haemodialysis session, thrice a week, at a dose of 100 mg intravenously or orally for oral or digestive candidiasis and 200 mg intravenously or orally in severe infection. Moreover, they indicated that fluconazole serum concentrations monitoring would be an interesting tool to assess efficacy. In another study concerning five patients with severe renal failure after kidney transplantation [18], the authors recommended the dose of 200 mg of fluconazole, intravenously or orally, after each haemodialysis session for the treatment of systemic mycoses. In these two studies, the authors did not discuss the loading dose. Finally, the most complete study of the pharmacokinetics of fluconazole in patients with renal impairment was performed by Berl et al. [19]. This study involved 40 patients with different degrees of renal insufficiency that were divided into four groups of 10 patients according to the level of their renal function, which was appreciated by the value of creatinine clearance (CL\textsubscript{CR}). The average values of CL\textsubscript{CR} were 107 (CL\textsubscript{CR} > 50 ml/min), 38 (CL\textsubscript{CR} between 21 and 50 ml/min), and 14.8 ml/min (CL\textsubscript{CR} between 11

### Table 1. Fluconazole MICs

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Candida albicans</th>
<th>Candida glabrata</th>
<th>Cryptococcus neoformans</th>
</tr>
</thead>
<tbody>
<tr>
<td>MICs (mg/l)</td>
<td>1</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

### Table 2. Dosage of fluconazole per os in patients with renal failure (Candidiasis)

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Fluconazole dosage</th>
<th>Oropharyngeal candidiasis</th>
<th>Maintenance doses</th>
<th>Vaginal candidiasis</th>
<th>Vaginal candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First dose</td>
<td>每48 h or 25 mg every 24 h</td>
<td></td>
<td>Amount</td>
<td>Amount</td>
</tr>
<tr>
<td>60–30</td>
<td>50 mg</td>
<td>50 mg every 48 h or 25 mg every 24 h</td>
<td></td>
<td>150 mg</td>
<td></td>
</tr>
<tr>
<td>30–10</td>
<td>50 mg</td>
<td>50 mg every 48 h or 25 mg every 24 h</td>
<td></td>
<td>150 mg</td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>50 mg after a</td>
<td>50 mg after a session</td>
<td></td>
<td>150 mg after a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>haemodialysis session</td>
<td>each haemodialysis session</td>
<td></td>
<td>haemodialysis session</td>
<td></td>
</tr>
<tr>
<td>CAPD</td>
<td>50 mg</td>
<td>50 mg every 24 h</td>
<td></td>
<td>150 mg</td>
<td></td>
</tr>
<tr>
<td>CVVHD</td>
<td>50 mg</td>
<td>50 mg every 24 h (depending on plasma concentrations)</td>
<td></td>
<td>150 mg</td>
<td></td>
</tr>
</tbody>
</table>

HD, haemodialysis; CAPD, continuous ambulatory peritoneal dialysis; CVVHD, continuous veno-venous haemodialysis.
and 20 ml/min) for groups 1, 2 and 3, respectively. Group 4 included subjects on chronic haemodialysis (three times per week). The authors concluded that there was no need for reducing the loading dose to the degree of renal impairment and that determination of the appropriate first dose should only be based on the therapeutic indication. On the other hand, the maintenance doses should be adjusted according to the creatinine clearance of the patient. In patients on chronic haemodialysis, fluconazole should be administered at doses ranging from 100 to 400 mg after each haemodialysis session, thrice a week, after a loading dose of 100 to 800 mg, administered after an haemodialysis session and depending on the indication (Tables 2–4).

### Patients on peritoneal dialysis

Most available studies of fluconazole in peritoneal dialysis or continuous ambulatory peritoneal dialysis (CAPD) focused on the treatment of fungal peritonitis. Two routes of administration were studied: orally or intraperitoneally. In this latter case, the drug was introduced into one of the exchange bags. In a prospective study concerning five patients on peritoneal dialysis and receiving a single 200 mg dose of i.p. fluconazole, the authors concluded that the dose of 200 mg every 48 h should be sufficient to obtain efficient serum concentrations of fluconazole. Indeed, they showed that fluconazole was well absorbed by this route with a bioavailability of 96%. A simulation of fluconazole serum concentrations, after repeated 200 mg doses every 48 h gave minimal and maximal serum concentrations of 6 and 9 mg/l, respectively.

Levine et al. [21] recommended only oral administrations consisting of a 200 mg loading dose and maintenance doses of 100 mg daily. This study concerned two patients on CAPD with a Candida’s peritonitis (Tables 1–3). The authors suggested that fluconazole should be considered as the treatment of choice in cases of fungal peritonitis in patients receiving CAPD and they reminded that fungal infections are frequent and account for between 1 and 15% of peritonitis episodes in CAPD patients.

Finally, in CAPD patients, as oral and peritoneal fluconazole bioavailabilities are similar (90 and 96%, respectively) the drug may be administered orally, intravenously or intraperitoneally depending on the indication and the clinical constraints.

### Patients on continuous renal replacement therapy

In three studies [22–24] and a subsequent analysis of two of them [25], the authors recommended to administer the usual dose of fluconazole in patients undergoing continuous renal replacement therapy, whatever the procedure used. Indeed, fluconazole is dialysable...
and the authors showed that during continuous renal replacement therapy in a patient with end-stage renal failure, the total body clearance of fluconazole was the same as the total body clearance observed in healthy subjects. Consequently, neither the loading dose nor the maintenance doses should theoretically be modified in patients undergoing continuous renal replacement therapy. However, the elimination rate of fluconazole varies considerably depending on the procedure used and on factors, which may influence the quality of drug extraction (type and size of the membrane, blood flow, dialysate flow rate, rate of ultrafiltration, etc.). In one study, the authors reported that it was necessary to increase the dose of fluconazole even above the usual doses of the patient with normal renal function due to the huge removal of fluconazole by haemodiafiltration [26]. Consequently, in patients undergoing continuous renal replacement therapy, whatever the procedure used, it is recommended to start treatment with usual doses of fluconazole and to control serum concentrations of the drug in order to further adjust the dose if fluconazole serum concentrations are too low [27] (Tables 2–4).

Conclusion

The pharmacokinetics of fluconazole is altered in patients with renal impairment and dosage adjustments are thus necessary in such patients. In all cases, there is no need to modify the loading dose of the drug but maintenance doses should be reduced according to the prescribing guidelines established from the literature.

Conflict of interest statement. None declared.

References


Table 4. Dosage of i.v. fluconazole in patients with renal failure (Cryptococcus)

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Fluconazole dosage</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction (6 to 8 weeks)</td>
<td>Maintenance</td>
<td></td>
</tr>
<tr>
<td>60–30 200 mg every 24 h</td>
<td>200 mg every 48 h or 100 mg every 24 h</td>
<td></td>
</tr>
<tr>
<td>30–60 200 mg every 24 h</td>
<td>200 mg every 48 h or 100 mg every 24 h</td>
<td></td>
</tr>
<tr>
<td>HD 200 mg thrice a week after each haemodialysis session</td>
<td>100 mg thrice a week after each haemodialysis session</td>
<td></td>
</tr>
<tr>
<td>CAPD 200 mg intraperitonally during a 12-h dwell or 200 mg orally</td>
<td>200 mg intraperitonally every 48 h during a 12-h dwell or 100 mg/day orally</td>
<td></td>
</tr>
<tr>
<td>CVVHD 400 mg every 24 h (depending on plasma concentrations)</td>
<td>200 mg every 24 h (depending on plasma concentrations)</td>
<td></td>
</tr>
</tbody>
</table>

HD, haemodialysis; CAPD, continuous ambulatory peritoneal dialysis; CVVHD, continuous veno-venous haemodialysis.