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Use of fluconazole in daily practice: still room for improvement

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One hundred courses of fluconazole treatment in a university hospital and 81 courses in a non-university teaching hospital have been analysed in a prospective audit to evaluate prescribing practices. The quality of treatments was assessed by an infectious disease specialist and a pharmacist according to standard guidelines. In the non-university hospital, prescribed dosages were lower than in the university hospital, and often below the recommended dose. Mean duration of treatment for oesophageal candidosis and disseminated infections was considerably shorter in the non-university hospital compared with the university hospital, and often judged too short. Microbiological samples were examined in 75% of the cases in both hospitals. The expert reviewers agreed with the indication to use fluconazole in 58–100% of cases in the university hospital and 42–80% in the non-university hospital, depending on the type of infection. There did not appear to be a major problem with inappropriate use of fluconazole. However, important issues for improvement could be identified, such as increasing the dosage and duration of treatment in cases of serious infections, and withholding treatment from patients with colonization rather than infection.

Introduction

Worldwide, there is an increasing incidence of fungal infections.[1] This may be owing to a growing number of immunocompromised hosts, such as granulocytopenic cancer patients,[2] organ transplant recipients and AIDS patients, as well as to the escalating use of broad-spectrum antibiotics in patients in haematology wards and intensive care units.[3] Fluconazole is one of the best tolerated antifungal drugs available, with good activity against most yeast species. It has favourable pharmacokinetic properties with an oral bioavailability of >90%, a half-life of approximately 30 h and good penetration into tissues.[4] Furthermore, the drug has a wide therapeutic range, with little toxicity.[5] These properties inherently lead to a low threshold of prescribing, which gives rise to concerns about the quality of use. It has been suggested that the increasing use of fluconazole has concurred with a rising incidence of *Candida* non-*albicans* strains that have a reduced susceptibility to fluconazole.[6–12] Although the proof of a causative role has been lacking, fluconazole should be prescribed with caution and on strict indications to reduce the potential development of resistance. In addition, administration may induce drug interactions, thereby influencing the effect of other prescribed drugs. The aim of this study was to perform a comprehensive evaluation of the use of fluconazole, in order to assess the prescribing practices in daily clinical practice. A prospective audit of the use of fluconazole was undertaken in two different hospitals, a university and a non-university hospital in The Netherlands.

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Materials and methods

The study was performed in two hospitals, a 980-bed university hospital (hospital A) and an 820-bed non-university teaching hospital (hospital B), for 9 and 12 month periods, respectively. Consecutive adult patients receiving a prescription for fluconazole were included in the study. Patients in the haematology department receiving fluconazole as part of a standard prophylaxis protocol were excluded. The clinical notes and drug charts were reviewed. The reason for initiation of fluconazole, the underlying disease, the dosage, means of administration and duration of therapy, previous and concomitant treatment with antibiotics or other antifungals, and outcome of the treatment were recorded on data collection sheets. Results of microbiological tests were obtained from the computer databases of the microbiology departments.

Assessment of therapy

Each course of fluconazole treatment was assessed by B. J. K. (infectious diseases specialist) and S. N. (pharmacist) on the basis of current guidelines employed in the hospitals and national and international recommendations. Recently published comprehensive guidelines were in press at the time of the evaluation,[13,14] but there was agreement among experts on principles of antifungal treatment and several recommendations and reviews on the subject had been published in The Netherlands.[9,15,16] Table I is a compilation of these and represents the guidelines applied to this evaluation.

The percentage agreement with indication, dosage and duration of treatment was determined using a standardized method for antimicrobial drug use evaluation, developed by Gyssens *et al.*[17] The indications were subdivided into superficial infections (oral and vaginal candidosis and skin infections), oesophageal candidosis, disseminated infections (catheter-related infections, bloodstream infections, presumed systemic fungal infection), deep localized infections (pneumonia, urinary tract infections, peritonitis, meningitis) and prophylactic treatments.

Laboratory investigations

Blood (at least 15 mL) was cultured aerobically using the Bactec 9240 (Becton-Dickinson, Woerden, The Netherlands) in hospital A and the BacT/Alert (Organon Teknika, Boxtel, The Netherlands) automated system in hospital B. In hospital A, *Candida* isolates were processed in the local specialist mycology laboratory. In hospital B, they were processed in the general microbiology laboratory.

Candida albicans was identified by germ tube and chlamydospore formation. Suspected *Candida dubliniensis* or germ tube negative isolates were further identified with the Auxacolor commercial yeast identification system (Bio-Rad, Marnes-La-Coquette, France). Yeast susceptibility testing was performed by broth dilution according to the NCCLS.[18] Interpretative breakpoints for fluconazole were applied as proposed by Rex *et al.*[19]

Results

One hundred consecutive courses of fluconazole in 88 patients in hospital A and 81 courses in 81 patients in hospital B were included in the study. The distribution of the various indications is shown in Table II. For the two hospitals, expert reviewers agreed with the indications in 72 and 63% of cases, respectively.

Prescribed dosages

On average, higher dosages were prescribed in hospital A compared with hospital B (Figure 1). The evaluation revealed least agreement with the dosage in cases of oesophageal candidosis, because of rather low dosages prescribed in both hospitals, contravening the guidelines. In hospital B in particular, prescribed dosages for all indications often tended to be lower than those recommended.

Duration of treatment

Patients who died during treatment, or who were switched to another antifungal treatment, were excluded from the evaluation of duration of treatment (Figure 2). The mean duration of treatment for oesophageal candidosis and disseminated infection was considerably longer in hospital A than in hospital B ($P = 0.03$ and $P = 0.006$, respectively). The reviewers agreed with the duration of treatment in only 40–50% of cases of oesophageal candidosis, mainly because the prescribed courses of treatment were considered to be too short. Also, for disseminated infections, duration of treatment was considered too short in 60% of cases in hospital B.

Microbiological results

Culture results were available in 75% of the cases. In 84 and 87% of these cases from hospitals A and B, respectively, the isolate was identified. In hospital A, *C. albicans* was found in 73% of the cases and *Candida glabrata* in 17%. In hospital B, *C. albicans* was isolated in 87% and *C. glabrata* in only 8% (Table II).

Susceptibility to antifungal agents was determined for 18 *Candida* isolates in hospital A and six isolates in hospital B. All isolates of *C. albicans* tested were susceptible to fluconazole (MIC $\leqslant$ 4 mg/L). Four of the 15 isolates of *C. glabrata* were resistant (MIC $\geqslant$ 64 mg/L), one isolate was susceptible dose dependent (MIC 16 mg/L), six were susceptible (MIC $\leqslant$ 8 mg/L) and for four isolates, susceptibility was not determined. In three patients with resistant *C. glabrata* isolates, treatment was changed to itraconazole

Table I. Treatment recommendations for *Candida* infection (modified according to refs 9, 13–16)

Indication	Recommended therapy	Dosage of fluconazole
Superficial infection		
oropharyngeal infection	oral azoles[a], oral polyenes[b], iv amphotericin B if refractory	100 mg/day for 7–14 days
vaginal infection	topical[c] or oral azoles	150 mg single dose
skin infection	topical or oral azoles	100 mg/day
Oesophageal candidosis	oral azoles, iv amphotericin B if refractory	100–200 mg/day for 14–21 days
Disseminated infection	iv amphotericin B, oral or iv fluconazole, combination with flucytosine may be considered	400 mg/day until 2–4 weeks after last positive blood culture
Deep localized infections		
pneumonia	iv amphotericin B or fluconazole	400 mg/day
intra-abdominal infection	iv amphotericin B, oral or iv fluconazole	400 mg/day for 2–3 weeks
meningitis	iv amphotericin B, flucytosine may be added, iv fluconazole	until 4 weeks after resolution of all symptoms
urinary tract infection	oral or iv fluconazole, iv amphotericin B, oral flucytosine	200 mg/day for 7–14 days
Prophylaxis		
AIDS and cancer patients	oral fluconazole or itraconazole	100 mg/day
neutropenic patients and solid-organ transplantation	oral or iv fluconazole, iv amphotericin B, oral itraconazole	150–400 mg/day

[a]Oral azoles: fluconazole, ketoconazole, itraconazole.
[b]Oral polyenes: nystatin, amphotericin B suspension.
[c]Topical azoles: clotrimazole, miconazole and others.

Table II. Indications for which fluconazole was prescribed and the microorganisms isolated

Indication	Hospital A	Hospital B
Total	100	81
Superficial infections	33	23
oropharyngeal	31	19
vaginal	2	3
skin	–	1
Oesophageal candidosis	13	18
Disseminated infection	28	21
with positive blood cultures	15	2
positive cultures from other sites	13	19
Deep localized infections	15	12
pneumonia	–	6
intra-abdominal infection	4	1
meningitis	4	–
urinary tract infection	5	4
parotitis	1	–
pleural infection	1	–
Dysbacteriosis of the gut	–	1
Prophylaxis	11	5
Not documented	–	2
Microorganism isolated	63	53
C. albicans	46 (73%)	46 (87%)
C. glabrata	11 (17%)	4 (7.5%)
Candida tropicalis	2	1
Candida krusei	1	1
Candida parapsilosis	–	1
Cryptococcus neoformans	2	–
Sporobolomyces spp.	1	–

after obtaining the *in vitro* susceptibility results, and in one patient, the dose of fluconazole was increased to 800 mg/day. The patient with the susceptible dose-dependent isolate first received higher doses of fluconazole and was later switched to amphotericin B. Of the four patients in whom the susceptibility of the isolate was not known, one was switched to itraconazole, one suffered from a urinary tract infection, which was successfully treated with a single dose of 400 mg fluconazole and two died as a result of other medical complications of their underlying disease within 2 and 40 days, respectively, after initiation of fluconazole treatment.

Superficial infections

The reviewers disagreed with the indication in 40% of the cases of presumed superficial candidosis in both hospitals. Reasons for disagreement were lack of culture results after failure of another antifungal treatment, or negative culture results. Seventeen patients in hospital A and six patients in hospital B had received prior antifungal therapy. Agreement with the prescribed dosage was 82% in hospital A and 56% in hospital B. In hospital A, disagreement was due to the administration of higher than recommended dosages, while in hospital B the prescribed dosages were too low. There was agreement with the duration of treatment for 82% of cases in both hospitals.

Oesophageal candidosis

Endoscopy was performed in 61% of patients with oesophageal candidosis in both hospitals. In hospital A, culture samples were taken in 75% of these, while in hospital B this was the case in only one patient.

There was agreement with the indication to use fluconazole in 77% of the cases of oesophageal candidosis in both hospitals. Agreement with dosage was 62% in hospital A but only 39% in hospital B, largely because of low prescribed dosages. Also, the duration of treatment was judged too short in 46% of cases in hospital A and 61% in hospital B.

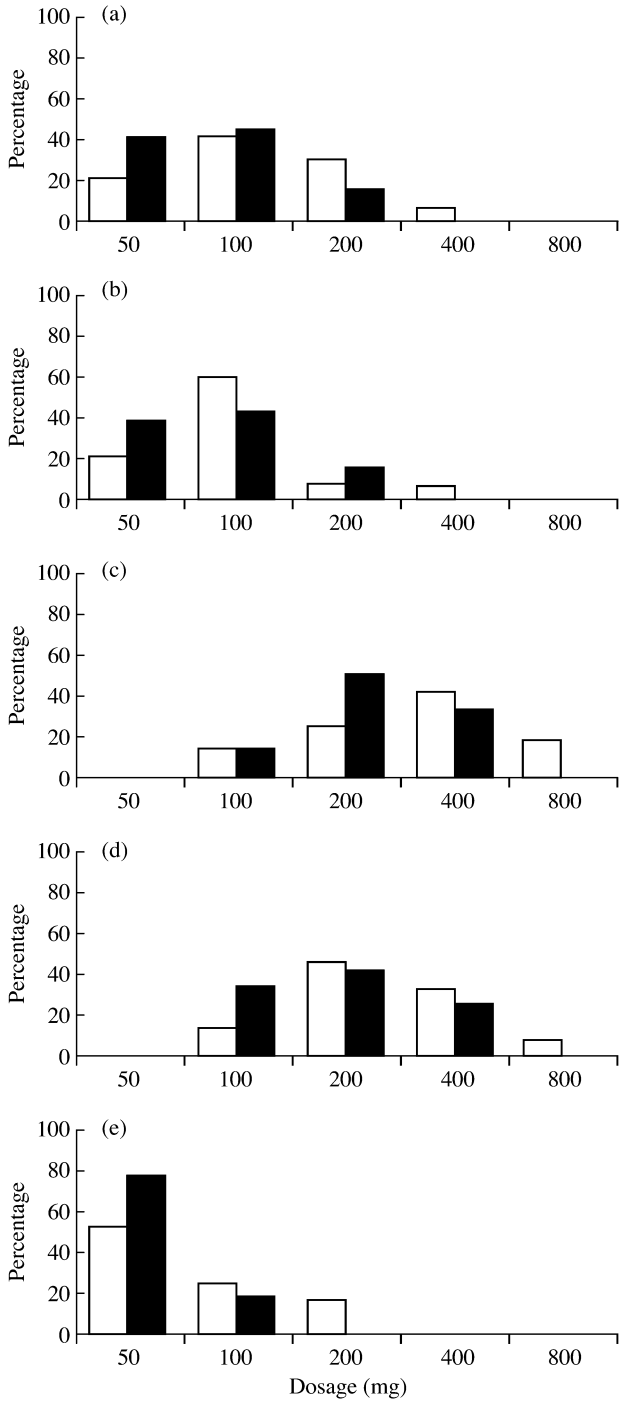

Figure 1. Percentage of patients receiving each dosage of fluconazole for different indications: (a) superficial infections; (b) oesophagitis; (c) disseminated infections; (d) deep localized infections; and (e) prophylaxis, in hospital A (□) and hospital B (■).

Disseminated infections

Of the 28 patients with disseminated candidosis in hospital A, 15 had positive blood cultures and 13 had negative blood cultures but were presumed to have disseminated infection on the basis of positive cultures from multiple, normally sterile, sites. Treatment of all cases with positive blood cultures was judged adequate, whereas of the cases with negative blood cultures, only six treatments were judged as definitely justified and three as probably justified. In the remaining four cases the indication was not justified, as the culture results were felt to reflect colonization rather than disseminated infection. The prescribed dosage was adequate in those cases in which the indication was thought to be justified, but inadequate if there was disagreement with the indication, in which cases the dose was judged too low for presumed systemic infection.

Of the 21 patients diagnosed with disseminated infections in hospital B, only two had positive blood cultures. Four patients had positive cultures of the catheter tip and the insertion site, and were presumed to have a catheter-related infection. Treatment of all of these six cases was considered justified. In 15 patients, presumed disseminated candidosis was diagnosed because of several positive culture results from other specimens. Treatment of seven of these cases was judged appropriate since positive cultures had been obtained from normally sterile sites and the clinical course was compatible with disseminated candidosis.[13,20] In the remaining eight cases, the diagnosis of disseminated candidosis was considered inappropriate, since positive cultures were obtained from colonized surfaces only (e.g. bronchus or skin wound), without further clinical signs of invasive infection. Follow-up blood cultures during antifungal therapy were not performed routinely in either hospital.

Deep localized infections

In hospital A, the indication for treatment was considered appropriate in 93% of the cases of deep localized infection, dosage was adequate in 80% and the duration of treatment was adequate in 87% of the cases. In hospital B, the expert reviewers agreed with the indication in only 42% of the cases, mainly because of disagreement with the diagnosis 'pneumonia', which had been made on the basis of positive tracheal aspirates or sputum cultures without further signs of invasive infection. Dosage was considered adequate in 83% of the cases, but the duration of treatment was appropriate in only 50% of the cases.

Prophylaxis

Prophylactic use of fluconazole outside standard protocols accounted for only 11% of the indications in hospital A and 6% in hospital B. In these cases, the reviewers agreed with the prophylaxis in 100 and 80% of the cases in hospitals A and B, respectively.

Discussion

The general conclusion from this study is that fluconazole is being appropriately prescribed in daily practice. However,

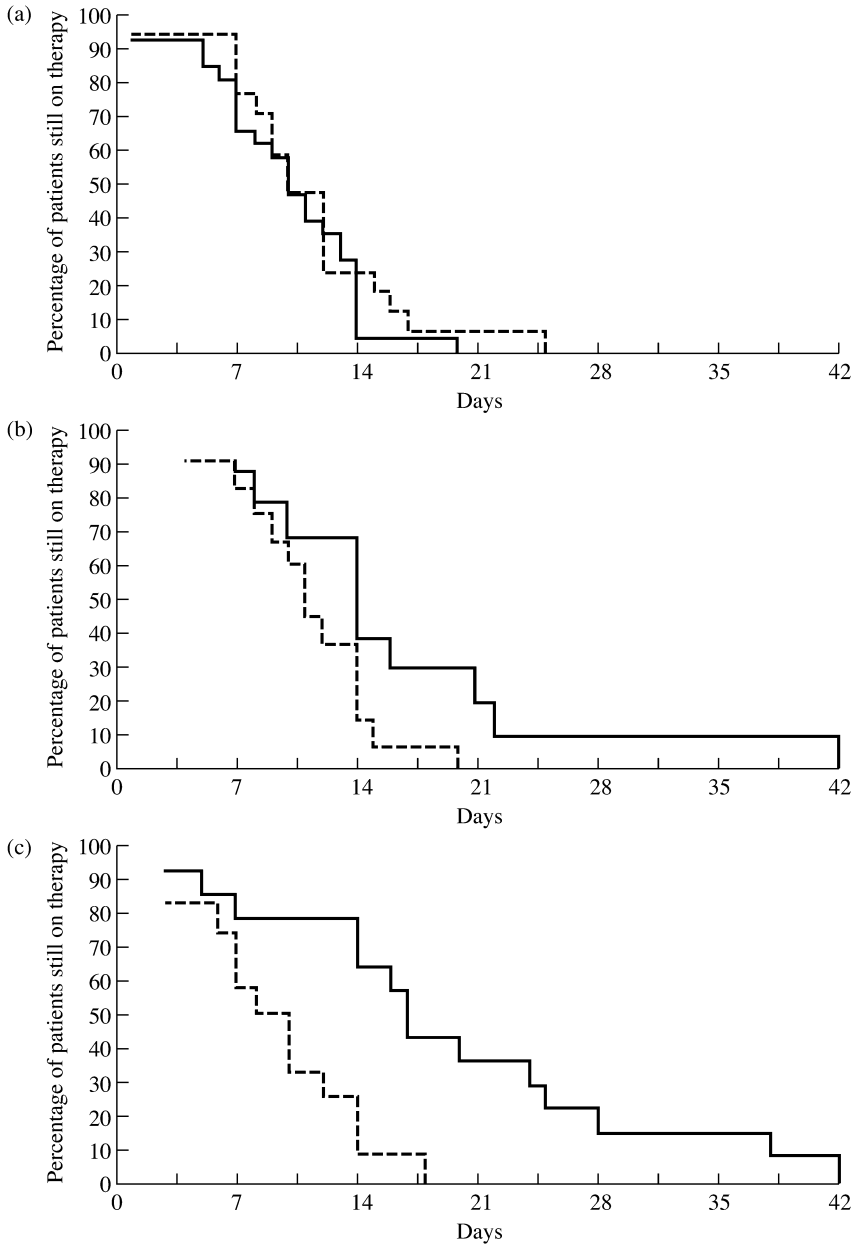

Figure 2. Duration of treatment with fluconazole for (a) superficial infections; (b) oesophagitis; and (c) disseminated infections, in hospital A (—) and hospital B (- - - -).

there are points that need improvement, especially in the non-university hospital (hospital B). First of all, even though samples for culture have been obtained in many cases, the quality of microbiological examinations could be improved. Cultures should be obtained from all patients with presumed oropharyngeal or oesophageal candidosis who are switched to fluconazole after treatment with another antifungal drug has failed. Because of the increasing incidence of *Candida* spp. other than *C. albicans*, all *Candida* isolates should be speciated, especially as some species have very predictable susceptibility profiles, and speciating may therefore guide the choice of antifungal therapy. Susceptibility testing should be performed and reported on all clinically relevant isolates, especially in those cases that are at an increased risk of resistance to fluconazole.

In the non-university hospital (hospital B), the dosage and duration of treatment needs to be addressed. Especially for the treatment of oesophageal and disseminated candidosis, low dosages were prescribed for a rather short duration, which does not follow the current treatment guidelines.[13]

Another point of concern is the use of fluconazole in cases of colonization rather than true infection. This is the

case in the patients diagnosed as suffering from '*Candida* pneumonia', which is based solely on isolation of *Candida* from bronchial secretions.[21] Also, in the case of presumed disseminated infections, diagnosis was based on positive cultures from sites indicative of colonization, leading to disagreement with the indication in this situation.

The study was performed in two different hospitals, a university and a non-university hospital. The most important differences detected were the lower dosages and the shorter duration of treatment prescribed in the non-university hospital. Another interesting difference was the lower prevalence of disseminated infections with positive blood cultures in the non-university hospital, which was probably due to a patient population that was less severely ill or the fact that blood cultures were less likely to be taken in this setting. Finally, the use of fluconazole in cases of colonization was more prevalent in the non-university hospital, as was reflected by the observation that *Candida* pneumonia was diagnosed six times during our study, whereas none of these diagnoses could be substantiated.

There are very few data in the literature to compare with the current study. An audit on antifungal drugs by Gutierrez *et al.*[22] revealed that 58% of the regimens in their study were compliant with a predefined standard. Fluconazole was the drug most often used for non-approved indications, mostly for superficial infection in non-neutropenic patients. In only 20 of the 74 patients studied were microbiological results known.

Overall, in our drug use evaluation study, we could not detect major inappropriate use of fluconazole. However, it did highlight important issues, and areas for improvement could be identified. Discussion of these issues with the hospital staff and refinement of local guidelines should result in improved use. Direct feedback of the results of a comprehensive audit of prescribing habits is one of the most successful means of influencing physicians' performance, especially when feedback is supported by a chart review, as we did in our study.[23,24]

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