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FUNGAL PERITONITIS IN PERITONEAL DIALYSIS PATIENTS: SUCCESSFUL PROPHYLAXIS WITH FLUCONAZOLE, AS DEMONSTRATED BY PROSPECTIVE RANDOMIZED CONTROL TRIAL

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◆ ***Objectives:*** **To determine whether oral administration of the antifungal fluconazole during the entire period of treatment of bacterial peritonitis (BP), exit-site infection (ESI), or tunnel infection (TI) prevents later appearance of fungal peritonitis (called secondary) in patients with chronic kidney disease stage 5 in a peritoneal dialysis (PD) program.**

◆ ***Patients and Methods:*** **All patients treated in the PD program in RTS Ltda Sucursal Caldas, during the period 1 June 2004 to 30 October 2007 were screened. Patients that had infectious bacterial complications (BP, ESI, TI) were included in a prospective randomized trial to receive or not receive oral fluconazole (200 mg every 48 hours) throughout the time period required by the administration of therapeutic antibiotics via any route. It was evaluated whether the fungal peritonitis complication appeared within 30 – 150 days following the end of antibacterial treatment. Based on local results, the sample size necessary to obtain statistically significant results was determined to be 434 episodes of peritonitis.**

◆ ***Results:*** **The 434 episodes of peritonitis presented between the previously specified dates and during this same period there were 174 ESI or TI, of which only 52 received oral antibiotic treatment. Information in relation to consumption of antibiotics for purposes other than BP, ESI, and TI was not reliable and thus this variable was excluded. Among the episodes of peritonitis, 402 (92.6%) were of bacterial origin and 32 (7.3%) were mycotic, mainly *Candida* species [30 (93.75%)]. Of the fungal peritonitis, 14 (43.73%) were primary (without prior use of antibiotics) and 18 (56.25%) were secondary. In the group of patients that received prophylaxis with fluconazole (210 for BP and 26 for ESI or TI), only 3 occurrences of fungal peritonitis were observed within 30 – 150 days of its administration, which is opposite to the group without prophylaxis (210 for BP and 26 for ESI or TI), in which 15 occurrences of fungal peritonitis were detected. Statistical analysis of the group of patients with BP found comparisons of the proportions of those receiving fluconazole (0.92%) or not (6.45%) presented a highly significant difference in favor of prophylaxis ($p = 0.0051$, $Z = 2.8021$). Given that only 1 patient in each group with ESI or TI, with or without prophylaxis, presented the complication fungal peritonitis, it was concluded that this result was not statistically significant. During laparoscopic surgery attempting reintroduction of the peritoneal catheter, it was found that 11 patients had severe adhesions or peritoneal fibrosis leading to obliteration of the peritoneal cavity. In 19 patients, reintroduction of the catheter was possible and the patients returned to PD without consequence.**

◆ ***Conclusion:*** **In patients with bacterial peritonitis, administration of prophylactic oral fluconazole throughout the time they received antibiotics significantly prevented the appearance of secondary fungal peritonitis.**

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KEY WORDS: Fungal peritonitis; prophylaxis; fluconazole.

Peritonitis is a common complication in patients with chronic kidney disease who are receiving treatment with peritoneal dialysis (PD). Its incidence worldwide varies from one center to another, with fluctuations between 1 episode per 24 patient-months of treatment to 1 episode per 60 patient-months (1). The main causes of peritonitis are gram-positive and gram-negative microorganisms and a lesser percentage of other agents. Of this latter, fungi represent about 2% – 23.8% (2–5), with *Candida* species reported more frequently (2,5,6). The treatment for fungal peritonitis is disappointing because, in most cases, the peritoneal catheter must be removed, requiring transfer of patients to hemodialysis, and a high percentage of patients experience obliteration of the peritoneal cavity (7,8). Preventive measures to reduce the incidence of fungal peritonitis are clearly necessary.

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In RTS Ltda Sucursal Caldas, Manizales-Caldas, Colombia, South America, between 1 March 2000 and 30 June 2003, the incidence of peritonitis was 1 episode per 19 patient-months, of which 8.8% had mycotic origins, mainly *Candida* species. The facts that in 88.9% of these cases (mycotic), the patient presented bacterial peritonitis 2 months before (secondary fungal peritonitis) and was treated with antibiotics, and that 11.1% of cases did not present this condition (primary fungal peritonitis) suggest that antimicrobial treatment could encourage further development of fungal peritonitis.

Based on the observations described above, this research began with the aim of evaluating, in a prospective randomized control trial, the effectiveness of prophylaxis with fluconazole in preventing the emergence of fungal peritonitis in PD patients that required the administration of oral or parenteral antibiotics. A period of 30 days after the end of the treatment was necessary to exclude relapsing peritonitis, and another at 150 days since there were reports of fungal peritonitis until 6 months later.

MATERIAL AND METHODS

From 1 June 2004, patients with chronic kidney disease stage 5 that were programmed for PD [continuous ambulatory PD (CAPD) or automated PD (APD)] were observed in RTS Ltda Sucursal Caldas in order to detect signs compatible with peritonitis, exit-site infection (ESI), or tunnel infection (TI) until the number of cases necessary to treat were found. The patients or their families were asked to report if at any time during the observation period they were prescribed an antibiotic (oral or parenteral) for a different purpose than treatment of peritonitis, ESI, or TI. In those patients for which there was confirmed peritonitis, empirical intraperitoneal antibiotic treatment was done with an initial covering of gram-positive and gram-negative (cephradine 15 mg/kg + gentamicin 0.6 mg/kg) organisms. We used an intermittent daily dosage of antibiotics that, in our experience reported in recent years, had the same result therapeutically as that of continuous therapy (9); at no time did we use cream to prevent ESI. Subsequently, according to the results of culture sensitivity reports, the intraperitoneal antimicrobial was changed to achieve adequate coverage for as long as necessary, in accordance with the recommendations of the guidelines of the International Society for Peritoneal Dialysis (ISPD) (1). Exit-site infections were initially managed with topical treatment, depending on the result obtained in the Gram stain when abundant purulent drainage or local inflammatory reaction (swelling or redness) was not observed. Gentamicin ointment, ophthalmic drops, or ciprofloxacin in the ear was used for gram-negatives, and fusidic acid or mupirocin was used for gram-positive micro-organisms. If a significant local inflammatory reaction was present, hypertonic saline was administered in the dressing twice daily, accompanied by oral antibiotic therapy. The same procedure was used for abundant purulent drainage, depending on the Gram stain, as follows: penicillin-resistant penicillinase (dicloxacillin) for gram-positive or ciprofloxacin for gram-negative organisms.

Exuberant inflammatory tissue (pyogenic granuloma) was handled using the same oral antibiotics as prior, in addition to topical gentian violet or topical application of silver nitrate (cauterization). Tunnel infections were treated with empirical oral antibiotics covering gram-positive and gram-negative (dicloxacillin and ciprofloxacin) organisms.

Patients were grouped in a prospective randomized control trial to receive (fluconazole treatment group) or not receive (control group) prophylactic fluconazole (200 mg orally every 48 hours) for as long as antibacterial treatment was needed. A patient could be again randomized if presenting a new episode of peritonitis 150 days after the initial episode. The randomization procedure was performed by drawing from a bag cards indicating whether the patient would or would not receive this treatment.

The sample size was calculated at 434 episodes of peritonitis, based on observations made in previous years in connection with the occurrence of peritonitis in our service, and for an expected absolute reduction in the rate of events of fungal infection of 6%, with a power of 80%.

Patients with ESI or TI were given prophylaxis with fluconazole only in the event of receiving an oral antibiotic. This was carried out by the same system of randomization as for peritonitis patients. Seasonal factors were not taken into account since, in our region, there are not so severe seasonal changes that the appearance of fungal peritonitis during a specified period of years may be impacted.

The exclusion criteria were antecedents of allergy to fluconazole, imidazoles, or triazoles; hepatic disease, pregnancy, less than 18 years of age, more that 70 years of age, and those patients that did not wish to participate in the study.

The effectiveness of prophylaxis was evaluated in a time period of 30 – 150 days after antibacterial treatment by observing the appearance of fungal peritonitis. Bacterial peritonitis was demonstrated by the presence of at least two of the following: clinical signs and symptoms (fever, abdominal pain, presence of cloudy dialysate for more than 4 hours), Gram stain positive for

bacteria, >100 leukocytes/mL in the peritoneal dialysate, or positive cultures for micro-organisms. An ESI was defined by the presence of purulent drainage, swelling, or redness of the skin with confirmation by Gram stain and culture. A TI was defined as swelling or redness of the subcutaneous tract occupied by the peritoneal catheter.

Secondary fungal peritonitis was defined as a case in which peritonitis occurred within a period longer than 30 days and less than 150 days after treatment for bacterial peritonitis was begun. Primary fungal peritonitis was defined as a case presenting without the above characteristics for secondary fungal peritonitis and confirmed with a KOH test, positive culture for fungi, and white blood cell counts in peritoneal fluid >100 cells/mL. To detect complications due to fluconazole, every patient was evaluated with hemogram, electrolytes (sodium, potassium, calcium, phosphorus), glycemia, creatinine, blood urea nitrogen, and albumin and globulin every month, and with liver function tests [alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, direct and indirect bilirubin], blood lipids (total cholesterol, high and low density lipoprotein cholesterol, and triglycerides), uric acid, and coagulation tests (prothrombin time and partial thrombin time) every 3 months.

All patients received detailed information on the objectives of the study and side effects of treatment and all gave their written consent. The Ethics Committee of RTS Ltda Sucursal Caldas approved the study.

The statistical analysis of quantitative variables used averages and standard deviations; qualitative variables used proportions and chi-square test. There was comparison of proportions of incidence of peritonitis between the groups using Fisher's exact test $p < 0.001$. We used the program EpiData 3.1 applications (The EpiData Association, Odense, Denmark) and graphics in Excel 2003 spreadsheet software (Microsoft Corp., Redmond, WA, USA).

RESULTS

In RTS Ltda Sucursal Caldas, Manizales, Caldas, Colombia, South America, an average of 160 patients per year attended PD programs (CAPD and APD) during the defined period of observation. Frequency of peritonitis was 1 episode per 19.1 patient-months of treatment and frequency of ESI and TI was 1 episode per 46.9 patient-months.

Patient demographics were as follow: 52.7% of patients were men, average age 50.9 years; 47.3% were women, average age 47.9 years. The etiology of chronic kidney disease was diabetic nephropathy in 36.3%, unknown causes in 15.3%, hypertensive nephropathy in 14.4%, chronic glomerulonephritis in 9.3%, chronic obstructive nephropathy in 8%, and other etiologies in 16.7% (Table 1). Throughout the study period, patients on CAPD used a double-bag Y system (Ultrabag; Baxter Healthcare, Deerfield, IL, USA), with flush before fill. Patients on APD used HomeChoice (Baxter).

It was not possible to get reliable information from the patients or families about the use of parenteral or oral antibiotics for causes other than peritonitis, ESI, and TI because a high percentage (83%) of patients in our region live in rural areas, where they are attended by other medical services for nonrenal pathology; therefore, we chose not to consider this variable for statistical analysis.

Between 1 June 2004 and 30 October 2007, 434 episodes of peritonitis were identified in 226 patients; also during this period there were 174 ESI or TI in 114 patients, of which only 52 required oral antibiotic treatment. The etiology of peritonitis had a presumed bacterial origin in 402 episodes (92.6%): gram(+) bacteria in 181 (45.0%), gram(–) bacteria in 67 (16.7%), and unidentified causative agent in 154 episodes (38.3%) but the clinical criteria, laboratory results, and good response to antibiotic treatment regimen confirmed this suspicion. There were no episodes of peritonitis caused by Mycobacterium. In 32 of 434 episodes (7.3%), the causative agent was

TABLE 1
General Characteristics of the Population Studied

	Fluconazole			
	Yes (n=210)		No (n=210)	
	(n)	(%)	(n)	(%)
Sex				
Female	117	55.7	94	44.76
Male	93	44.29	116	55.24
Age (years)				
18–30	30	14.29	33	15.71
31–40	34	16.19	31	14.76
41–50	46	21.90	58	27.62
51–60	63	30.00	55	26.19
61–70	37	17.62	33	15.71
Etiology of CKD				
Diabetic nephropathy	70	33.33	78	37.14
Unknown	35	16.67	31	14.76
Hypertensive nephropathy	36	17.14	30	14.29
Chronic glomerulonephritis	19	9.05	18	8.57
Chronic obstructive nephropathy	15	7.14	17	8.10
Chronic interstitial nephropathy	6	2.86	6	2.86
Lupus nephropathy	5	2.38	8	3.81
Other causes	24	11.43	22	10.48

CKD = chronic kidney disease.

fungus (*Candida* spp 30, *Trichosporon beigelii* 1, and *Geotrichum* 1). The etiology of ESI and TI was bacterial in 138 patients (79.3%): 108 gram(+) bacteria and 30 gram(–) bacteria; fungus was identified in 6 patients (3.4%) (*Candida* spp) and cultures were reported negative for 30 patients (17.2%). Among the fungal peritonitis, 14 (43.75%) were considered primary fungal peritonitis and 18 (56.25%) secondary fungal peritonitis. In the group of patients with peritonitis, ESI, or TI that received prophylaxis with fluconazole (the fluconazole treatment group; 210 with peritonitis and 26 with ESI or TI), only 3 fungal peritonitis occurred within 30 – 150 days of its administration (2 after bacterial peritonitis and 1 post ESI or TI; all between 30 and 60 days). In the group that received no prophylaxis with fluconazole (control group; 210 with peritonitis and 26 with ESI or TI), 15 fungal peritonitis presented, with a history of bacterial peritonitis in 10 patients 30 – 60 days before, in 2 patients 60 – 90 days before, and in 1 patient for each of the periods 90 – 120 days and 120 – 150 days before; only 1 patient presented ESI 30 – 60 days before fungal peritonitis (Table 2).

Two patients died from fungal peritonitis. In all cases of fungal peritonitis the peritoneal catheter was withdrawn and the patient was transferred to hemodialysis therapy after implantation of a central double-lumen catheter. Subsequently, all patients received oral fluconazole at a dose of 200 mg every 48 hours for 3 weeks. After this time, reinsertion of the peritoneal catheter was attempted peritoneoscopically because of the advantage of providing visual information (10). Severe adhesions or peritoneal fibrosis were detected in 11 patients, leading to obliteration of the peritoneal cavity. Reintroduction of the catheter was successful in 19 patients, who returned to PD without consequence.

TABLE 2
Clinical Results of the Administration of Prophylactic Fluconazole

Aspect	Frequency
Episodes of peritonitis in 226 patients	434
Suspected bacterial origin	402
Gram-positive bacteria	181 (45.0%)
Gram-negative bacteria	67 (16.7%)
Unidentified	154 (38.3%)
Source mycotic	32
Exit-site/tunnel infection in 114 patients	174
Source bacterial	138 (79.3%)
Gram-positive bacteria	108 (62.1%)
Gram-negative bacteria	30 (17.2%)
Source mycotic	6 (3.4%)
Culture negative	30 (17.2%)
Type of mycotic peritonitis	
Primary	14
Secondary	18
Use of fluconazole in peritonitis	
Yes	210
No	210
Secondary mycotic peritonitis	
Prophylactic fluconazole: yes	3
Prophylactic fluconazole: no[a]	15

[a] $p = 0.0051$.

Determination of sensitivity to antifungal agents was possible in only 10 patients, all of whom had candida infections, but with sensitivity to fluconazole in only 4 patients (3 *Candida parapsilosis* and 1 *C. guilliermondii*), resistance in 6 (2 with secondary peritonitis and 4 primary; 5 *C. albicans* and 1 *C. tropicalis*), which obliged the use of intravenous caspofungin 50 mg daily for 14 days in the last group, with improvement in all cases. During administration of prophylactic and therapeutic fluconazole treatment, there were no significant side effects related to its use.

The statistical analysis demonstrated that, on comparing proportions, a statistically significant difference was found between the use of prophylactic fluconazole in patients with bacterial peritonitis (0.92%) and nonuse of prophylactic fluconazole (6.45%), demonstrating the drug's ability to prevent emergence of secondary fungal peritonitis ($Z = 2.8021$, $p = 0.0051$; Figure 1). In risk analysis, strong association was found between the use of fluconazole and prophylaxis for peritonitis (relative risk 0.20, 95% confidence interval 0.06 – 0.68). In relation to its ability to prevent the onset of peritonitis in patients with fungal ESI or TI, there was not a statistically significant difference between administration and non-administration of prophylactic fluconazole.

DISCUSSION

Fungal peritonitis is a rare complication in patients with chronic kidney disease in a PD program. The incidence has been reported as being 2% – 23.8% of documented cases of peritonitis (11–15), most caused by

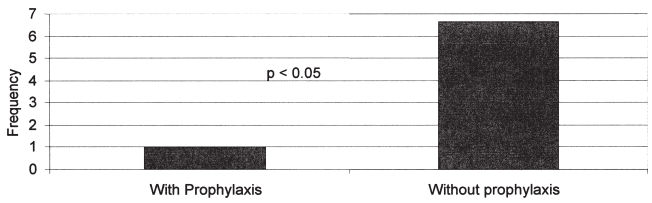

Figure 1 — Percentage of fungal peritonitis secondary to use of prophylactic fluconazole.

Candida albicans and to a lesser extent other species of *Candida* (6,13,15–19) — although recent evidence suggests that the latter group may be increasing in impact (4) —and filamentous fungi in a very low proportion (20,21). Its mortality rate is 5% – 40% (22), being at the highest level in patients with loss of residual kidney function (23) and in those whose peritoneal catheter was not removed quickly once diagnosed (4,11,14,17,18). The practice of rapid removing the peritoneal catheter accompanied by oral antifungal therapy on confirming the diagnosis is very common in some centers, including ours (24–26), although the use of intracatheter or intravenous amphotericin B, combined with oral flucytosine and intraperitoneal fluconazole in short intervals, has saved a few patients and catheters (27). Other groups recommend treatment of fungal peritonitis and simultaneous catheter removal (28), or delaying catheter removal until the dialysate effluent has cleared (29), the current suggestion being that this scheme is recommended only for elderly or frail patients with little capacity to support a move to hemodialysis (30,31).

It has been suggested that antibiotic therapy destroys the normal bacterial flora of the colon, can be a risk factor for development of fungal peritonitis, and promotes colonization and overgrowth of yeast in the digestive tract, with future migration into the peritoneal cavity by routes not well defined so far. There are many reports relating to the time fungal peritonitis occurs following treatment of bacterial peritonitis, from a short time of 4 weeks to a longer duration of 5 months (5,12,17,18, 21,22,32–34). Gram-negative and polymicrobial peritonitis encourages further formation of fungal peritonitis (35). In 3 years' observation in our renal unit, it was found that, in 88.9% of cases of fungal peritonitis, antibiotics were used 2 months before fungal peritonitis, which led us to propose use of the antifungal fluconazole in all patients with bacterial peritonitis, ESI, or TI to reduce the incidence of fungal peritonitis.

In the present study, a period of 30 days after the end the treatment was necessary to exclude relapsing peritonitis and extension to 150 days because there are reports of fungal peritonitis occurring up to 5 months later. The oral dose of fluconazole we used (200 mg every 48 hours) was chosen after analyzing the pharmacokinetics of this drug in patients with a glomerular filtration rate less than 20 mL/minute. Its elimination is predominantly via the kidneys, resulting in a significant increase in its half-life in this group of patients (36), so either doubling the administration interval or reducing the dosage to half is recommended (37).

The oral form is ideal for administration since its absorption in the digestive tract is excellent, with a bioavailability of 90%, and similar to that obtained by intraperitoneal administration (38). It is also important to note that, in patients whose peritoneal catheter has been removed, oral administration achieves very satisfactory intraperitoneal concentrations (39), which guarantees eradication of the fungus with the therapeutic scheme administered for 3 weeks. Administration of intravenous fluconazole has also shown that after 2 hours it manages intraperitoneal levels that exceed the minimum inhibitory concentration for *Candida* species (40). The disturbing findings of fluconazole resistance in the few studies of sensitivity to antifungal agents lead us to believe that its therapeutic usefulness may be limited in the future, with administration of this drug not to be selected for all PD patients.

It is suggested that using oral nystatin during antibiotic treatment, mainly for bacterial peritonitis, may be useful in preventing the emergence of future fungal peritonitis (41,42). Moreover, other studies found no significant reduction in the later appearance of fungal peritonitis (43–45), which leads us to accept the suggestion by Lye that, since so far there are no randomized studies to determine the effectiveness of oral nystatin, it should be used only for prophylactic purposes in centers with a high rate of fungal peritonitis related to treatment of bacterial peritonitis (46).

Nonrandomized prophylaxis with ketoconazole (10 mg/kg/day) in children was practiced by Robitaille *et al.* during the treatment of bacterial peritonitis with oral, intravenous, or intraperitoneal antibiotics, preventing the presence of fungal peritonitis in 100% of patients (47). Studies reporting oral fluconazole prophylaxis are very scarce to date and those existing used lower doses than ours (50 mg daily) or were not randomized and compared with historical controls. They suggested a significant reduction in the number of episodes of fungal peritonitis when prophylactic oral fluconazole was used in patients that received any antibiotic therapy (48–50).

In our renal unit, the antifungal caspofungin was used for the treatment of patients with strains of *Candida* resistant to fluconazole. The choice lies in its ease of application and recent information that this medicine achieves a significant therapeutic effect in patients with fungal peritonitis (51,52).

CONCLUSION

For the first time, we demonstrated in a randomized study that administration of prophylactic fluconazole in all patients receiving antibiotics for treatment of bacterial peritonitis successfully avoids the appearance of secondary fungal peritonitis and other complications, such

as obliteration of the peritoneal cavity, and inability to return to peritoneal dialysis therapy. The growing number of strains resistant to fluconazole, mainly *Candida albicans*, is very worrying because it made us use new antifungals to treat patients that develop fungal peritonitis. It is necessary to identify and treat a large number of patients with ESI or TI to obtain statistically significant data and conclusions for those infections.

DISCLOSURES

The authors have no relationships with pharmaceutical companies or other entities such as employment contracts, consultancy, advisory boards, speaker bureaus, membership on Board of Directors, or stock ownership that could be perceived to represent a financial conflict of interest and they declare that no financial conflict of interest exists.

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