Caspofungin in the Treatment of Symptomatic Candiduria

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Background. Because the urine concentrations achieved by echinocandin antifungal agents are low, drugs from this class are excluded from consideration when candiduria treatment is selected.

Methods. We performed a retrospective view (sponsored by Merck Research Laboratories) of case records of patients participating in phase II–III clinical studies of caspofungin to identify patients with candiduria.

Results. Of 12 case records collected by Merck Research Laboratories, 6 met the criteria for significant candiduria, allowing the evaluation of caspofungin therapy as judged by J.D.S. Three reported cases of candiduria secondary to hematogenous renal candidiasis were promptly eradicated. Of greater significance are 3 cases of complicated, ascending Candida glabrata infection (i.e., C. glabrata infection plus renal insufficiency), which were successfully treated with caspofungin.

Conclusions. Caspofungin may have a role in treating complicated Candida urinary tract infections, especially when the infection is caused by non-albicans species of Candida.

Management of candiduria remains immersed in controversy [1–4]. Much of the confusion involves determining the indication for and justifying the initiation of antifungal therapy for candiduria [5]. This occurs as a consequence of clinicians’ continued inability to recognize the significance and clinical implications of this finding. Candiduria is common, is usually asymptomatic, and is mostly seen in subjects with bladder catheters, for whom only rare indications for antifungal therapy exist [6]. Indications for therapy were published by the Infectious Diseases Society of America [7].

Treatment of symptomatic candiduria is far less controversial, and drug selection depends primarily on 2 host factors: anatomical site of urinary tract infection and renal function. In the past, relatively few antifungal agents were available, which significantly limited drug selection. Accordingly, local irrigation of the bladder or nephrostomy catheters with amphotericin B was frequently used. Fluconazole therapy has extremely efficient glomerular filtration, resulting in both high tissue and urinary concentrations, and the availability of this agent served as a major advancement in treatment, limited only by the parallel increase in the number of patients with urinary tract infections due to non-albicans Candida species [8, 9]. Matters were not made better by the availability of voriconazole, an azole with a broader spectrum that achieves minimal urinary excretion [10].

The echinocandin class of antifungals was recently introduced. Given its broad spectrum of anti-Candida activity and its rapid fungicidal activity [11], caspofungin, the first approved agent of this class, is considered a first-line therapy for candidiasis. Unfortunately, the entire echinocandin class of drugs share a major pharmacokinetic disadvantage: extremely poor glomerular filtration or tubular secretion in vivo, resulting in subtherapeutic antifungal concentrations in the urine. Accordingly, caspofungin and all echinocandins are usually excluded from the selection of antifungal agents for candiduria, regardless of their favorable in vitro activity. In spite of the predicted lack of therapeutic efficacy for the treatment of symptomatic candiduria, several successful outcomes have been observed and
noted for patients participating in phase II–III clinical studies sponsored by Merck Research Laboratories. Herein, we describe the results for 6 patients who responded favorably to caspofungin for the treatment of complicated urinary tract infection caused by Candida species.

METHODS

Twelve case record forms were collected by Merck Research Laboratories in a study of patients with candiduria who had received caspofungin in 1 of the 2 phase II–III clinical studies: Protocol 014, a randomized, double-blind, comparator-controlled study of invasive candidiasis (9 patients), and protocol 024/025, a compassionate-use study that included patients with invasive candidiasis that was refractory to at least 1 intravenous formulation of amphotericin B (3 patients). The case records were submitted to an independent expert (J.D.S.) for review and adjudication. All patients whose case records were supplied had provided signed informed consent, and no patient identifiers were present or available, thereby providing total anonymity. All patients had at least 1 urine culture positive for Candida species before receiving caspofungin therapy, and each patient received at least 7 days of parenteral caspofungin therapy during the course of the study.

Six (50%) of the 12 patients with candiduria met the strict criteria, enabling the independent adjudicator to determine whether the candidiasis was significant and not the result of contamination or concomitant Candida urinary catheter colonization. Criteria included identical blood and urine Candida species culture identity, which accompanied evidence of urinary tract (pyuria) and multiple, replicate, identical urinary isolates. All 6 patients were symptomatic at the time of initiation of antifungal therapy (table 1). A detailed description of each of these 6 patients is included below.

CASE REPORTS

Patient 1. A 71-year-old man with type II diabetes mellitus, coronary artery disease, and progressive renal insufficiency had experienced symptomatic Candida cystitis for many years. The patient had no prior history of nephrolithiasis. For several years, urine cultures were positive for Candida glabrata, necessitating bilateral stent placement for progressive hydronephrosis. Efforts to eliminate candiduria with prior regimens of fluconazole and itraconazole had failed, as had multiple courses of amphotericin B deoxycholate and its lipid formulations. Discontinuation of these noncurative therapies in the past led to acute obstructive uropathy and thick purulent discharge. In the context of disease persistence and recurrence, he had been receiving amphotericin B (20 mg 3 times per week) for several months, but worsening renal insufficiency, with a creatinine level of 4.2 mg/dL, led to reconsideration of therapy. The patient became symptomatic, with weight loss, fever, progressive incontinence, and purulent urine; urinalysis revealed 500 WBCs/hpf and 180 RBCs/hpf, and a urine culture was positive for C. glabrata. He was treated with caspofungin for 19 days in the compassionate-use study (Protocol 024/025). During follow-up, he became asymptomatic and afebrile, and urine culture results became negative for the first time in months, although pyuria persisted. No long-term follow-up data on this patient are available.

Patient 2. A 78-year-old man with diabetes mellitus and urinary bladder papillomatosis had experienced recurrent urinary tract infections due to Candida species over several months. In the prior 4 months, he had received therapy with oral itraconazole and weekly bladder washes with amphotericin B while symptomatic. During this time, he developed fever and flank pain. Examination of a urine specimen revealed significant pyuria and hematuria, and cultures were positive for C. glabrata. The patient was treated with a 9-day course of caspofungin in the compassionate-use study (Protocol 024/025). At the end of therapy, he was asymptomatic, afebrile, and without flank pain. Follow-up urine culture results were negative.

Two months later, the patient developed symptoms of dysuria and flank pain, and recurrent pyelonephritis was diagnosed. An ultrasound examination revealed bilateral upper urinary tract dilatation. He received a 4-week course of oral fluconazole (200 mg per day), but the urine cultures remained positive for C. glabrata, and he continued to have persistent symptoms. He received a second course of caspofungin for 10 days; dysuria resolved, and he again achieved negative urine culture results. No further long-term follow-up data are available.

Patient 3. A 46-year-old woman with non–insulin-dependent diabetes mellitus and a known 2-year history of symptomatic nephrolithiasis had received an unsuccessful course of lithotripsy therapy. She underwent successful laparoscopic removal of a stone from the left kidney, but the postoperative course was complicated by non-albicans Candida urinary tract infection. For her symptoms of dysuria and polyuria, she received fluconazole (200 mg per day), followed by itraconazole suspension (400 mg per day), each of which she received for 2 weeks. However, therapy provided no benefit, because the patient’s posttherapy urine microscopy and culture results remained positive for C. glabrata. Both isotopic scan and CT examination revealed active pyelonephritis of the left kidney, prompting treatment with intravenous amphotericin B deoxycholate (50 mg per day for 19 days), ultimately resulting in improvement of symptoms but a decrease in renal function. Three weeks later, symptoms, including fever, nocturia, dysuria, and urinary urgency, recurred. Gram stain and culture results were positive for C. glabrata, with at least 2 samples yielding positive results. The patient then received a 28-day course of therapy with caspofungin in the compassionate-use study (Pro-
tures were positive for yeast (not speciated) and pyuria occurred in the presence of a Foley catheter. He was treated with intravenous caspofungin for 21 days in the comparative invasive candidiasis study (Protocol 014), with rapid eradication of candida species. The patient 4.
A 74-year-old man with extensive burns developed sepsis due to candidemia that was characterized by fever and hypotension. In addition to the burns, other risk factors for candidemia included the presence of a central venous catheter and receipt of total parenteral nutrition and broad-spectrum antibiotics. Blood cultures were positive for Candida albicans for 5 successive days, during which time urine cultures were positive for yeast (not speciated) and pyuria occurred in the presence of a Foley catheter. He was treated with intravenous caspofungin for 21 days in the comparative invasive candidiasis study (Protocol 014), with rapid eradication of candidaemia and candiduria and recovery from sepsis.

Patient 5.
A 77-year-old woman with known peripheral vascular disease underwent a leg amputation for ischemia. The patient’s course was complicated by stump infection with evidence of fever and purulent drainage. At that time, blood cultures were positive for C. albicans, and 2 days later, urine cultures were positive for the identical Candida species. The patient received an 11-day course of caspofungin therapy in the comparative invasive candidiasis study (Protocol 014). By the end of caspofungin therapy, the candidemia and candiduria had resolved, with diminished purulent wound drainage. Follow-up blood and urine cultures were negative for Candida species. However, the patient died shortly thereafter; the cause was thought to be related to leg gangrene.

Patient 6.
A 65-year-old woman with a past history of non-Hodgkin lymphoma and acute myelogenous leukemia was admitted to the hospital with fever, pancytopenia, cholestatic hepatitis, jaundice, arm cellulitis, and ischemic cardiomyopathy. Blood cultures were positive for Candida tropicalis, with concomitant candiduria due to C. tropicalis. Caspofungin therapy was initiated in the comparative invasive candidiasis study (Protocol 014), but the candidemia persisted until a central venous catheter was removed. Thereafter, the patient’s urine and blood culture organisms cleared. The total duration of caspofungin therapy was 23 days, with no recurrence of candidemia and candiduria identified during the follow-up period.

**DISCUSSION**

Urinary tract infections, especially those involving the lower tract (cystitis or cystourethritis), are often superficial in nature and depend on high urine (as opposed to serum) concentrations of antimicrobial agents [12]. In contrast, invasive parenchymal infections involving the kidney (pyelonephritis or renal candidiasis secondary to candidemia) and the bladder (invasive cystitis with associated bladder pathology, such as papillomatosis) depend on therapeutic serum and tissue (as opposed to urine) concentrations.

Few antifungal agents achieve high urine concentrations. The introduction of fluconazole, which uniquely achieves high tissue and urine concentrations, proved to be a major advancement in therapy after the frequent failures observed with ketoconazole and itraconazole treatment [9–13]. However, fluconazole use is limited in the context of advanced renal
failure and infections with non-\textit{albicans} species of \textit{Candida}, especially \textit{C. glabrata}. Amphotericin B has always been limited by nephrotoxicity and difficulty in measuring urine concentration [14]. A useful agent for non-\textit{albicans} species of \textit{Candida}, notably \textit{C. glabrata}, is oral flucytosine; however, renal insufficiency profoundly reduces its utility.

The low urine concentrations achieved by the echinocandin class agents have precluded their use in urinary tract infections. However, as indicated by the 6 cases presented in this article, in complicated urinary tract infections in which high antifungal drug concentrations in the tissue are required to control invasive fungal disease, caspofungin was highly effective. In 3 of the presented cases (cases 4–6), candiduria was secondary to renal candidiasis complicating candidemia. Under these circumstances, renal candidiasis and, thus, candiduria were eradicated by parenteral caspofungin therapy, which achieved high renal tissue concentrations independent of glomerular filtration [15, 16]. Moreover, although filtration of caspofungin is low, 2%–3% of active drug is eliminated in the urine [16]. It is unclear whether similar efficacy would be seen in scenarios in which high urine concentrations are essential to sterilize the urine (e.g., nephrolithiasis or the presence of a fungal ball); whether caspofungin administration via a nephrostomy tube would be feasible in such cases remains to be determined. Particularly valuable is the potent activity of caspofungin against \textit{C. glabrata}, a frequent uropathogen.

In the first 3 cases presented (in patients 1–3), which are of greater significance, candiduria reflected invasive, complicated urinary tract infection in the absence of renal candidiasis (i.e., bladder or ascending pyelonephritis) but in the presence of diabetes and, invariably, \( \geq 1 \) complicating factor that contributed to urinary stasis and obstruction. Both bacteriuria and candiduria can be extremely difficult to eradicate under these circumstances, especially when they are accompanied by renal insufficiency, as was evident in all 3 patients. Yet, contrary to prediction, caspofungin therapy was effective in the short term in all 3 cases caused by azole-resistant \textit{C. glabrata}—once more a function of potent cidal activity in bladder and renal tissue.

In conclusion, management of candiduria is a common challenge, and most cases represent asymptomatic candiduria, which does not require antifungal therapy. Symptomatic candiduria most often represents complicated urinary tract infection in patients with a number of comorbidities (principally diabetes, urinary obstruction, and renal insufficiency). Caspofungin may play an integral role achieving effective tissue concentrations of a therapeutic agent, particularly in infections caused by non-\textit{albicans} \textit{Candida} species.

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\textbf{References}