Posaconazole therapy for severe abdominal candidiasis: a case report

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Summary We report the successful treatment of a fluconazole-resistant intra-abdominal *Candida* infection (*Candida albicans* and *Candida tropicalis*) with posaconazole (SCH56592) in a 68-year-old woman with a recent history of intra-abdominal surgery.

Key words Candidiasis, *Candida albicans*, *Candida tropicalis*, Human, SCH56592, Posaconazole, Fluconazole

Tratamiento de un caso de candidiasis abdominal severa con posaconazol

Resumen Se informa el tratamiento exitoso con posaconazol (SCH56592) de un episodio de candidiasis intrabadominal severa causada por *Candida albicans* (y *Candida tropicalis)* resistente al fluconazol en una mujer de 68 años con historia de cirugía intra-abdominal reciente.

Palabras clave Candidiasis, Paciente, *Candida albicans*, *Candida tropicalis*, SCH56592, Posaconazol, Fluconazol

An increase in the incidence of nosocomial *Candida* infections was first noted in the 1980s, particularly in surgical patients but also in other high-risk patient populations [6,13]. Although more recent data suggest that the overall incidence of hospital-acquired *Candida* infections is decreasing, it appears that infections caused by non-*albicans* species of *Candida* are now on the rise [1,7,15]. This shift has been partly attributed to increased therapeutic and prophylactic use of fluconazole [7,15].

Although amphotericin B and fluconazole constituted the foundation of antifungal therapy in patients with *Candida albicans* infections in the past, growing reports of resistance to these drugs among non-*albicans* species of *Candida* indicate a need for additional effective antifungal therapies [7].

Candida tropicalis is one of the more common non-*albicans* species identified, accounting for up to 25% of all *Candida* isolates (range: 4-25%) and up to 45% of non-*albicans* isolates from blood (range: 20-45%) [7]. Specifically, in Latin America, the percentage of bloodstream infections caused by *C. tropicalis* has increased; in the SENTRY Antimicrobial Surveillance Program, the percentage increased from 11.9 to 20% from 1997 to 1998 [9]. *C. tropicalis* is the third most common *Candida* species isolated from patients in Colombia, Ecuador, and Venezuela; approximately 5% of these isolates are resistant to fluconazole [5]. Although fluconazole resistance is more commonly observed in other non-*albicans* species, such as *Candida glabrata* and *Candida krusei* [3], the resistance of *C. tropicalis* to amphotericin B and fluconazole is increasing [1,3-5,12-14]. Additionally, poor clinical outcomes appear to be associated with greater fluconazole minimum inhibitory concentrations (MICs) (>16 µg/ml) [3]. We report the successful treatment of severe abdominal candidiasis with posaconazole in a woman after fluconazole therapy had failed.

Case report

A 68-year-old, 47-kg woman was admitted to a local hospital for surgical resection of a giant benign hepatic cyst (December 2001) with removal of liver segments 2, 3 and 4 and her gall bladder. Four days after surgery, the patient had upper digestive tract hemorrhaging and vomiting; endoscopic exploration of the upper digestive tract performed the following day confirmed Mallory-Weiss syndrome. Ascites was documented by ultrasound six days after surgery.

Eleven days after surgery, the patient had abdominal distension, diarrhea, and lower limb edema; two days later, her temperature spiked to 39.5 °C. Subsequent blood cultures were positive for Gram-negative bacilli, which were eventually identified as *Burkholderia cepacia*; a course of imipenem-cilastatin therapy was initiated.

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Table 1. Patient's laboratory findings.

Test	Before antifungal therapy	After 7 days fluconazole	After 1 month posaconazole	After 2 months posaconazole	After 4 months posaconazole	After 5 months posaconazole
Hemoglobin, g/dl	11.4	11.5	13.7	14	13.7	14.2
Hematocrit, %	34	32	42	42	40	43
Leukocytes, mm^3	6,000	5,900	8,500	6,300	4,500	5,500
PMNs, %	62	60	50	44	34	32
Monocytes, %	7	3	6	8	5	7
Lymphocytes, %	25	25	40	43	60	57
Eosinophils, %	0	0	4	5	1	4
Platelets, mm^3	218,000	175,000	195,000	165,000	Not done	150,000
Sedimentation rate, mm; 1st hour	94	89	36	14	13	10
C-reactive protein, mg/dl	15-40	Not done	Nonreactive	Nonreactive	Nonreactive	Nonreactive

PMNs, polymorphonuclear neutrophils

Despite a 12-day course of antibiotic therapy, the patient remained pale and had a distended abdomen that was tender to palpation. Her temperature fluctuated between 38.3 °C and 38.9 °C, her pulse was 104/min, and her blood pressure was 140/60 mm Hg. Computed tomography (CT) of the abdomen revealed partial left hepatectomy, mild splenomegaly, moderate ascites, and multiple intra-abdominal fluid collections (especially in the left subphrenic and perihepatic spaces, pouch of Douglas sac, and mesogastrium). Increased fat density around the peritoneum and mesentery suggested diffuse peritoneal involvement. CT-guided aspiration did not yield fluid; transvaginal, ultrasound-guided needle aspiration, however, resulted in the drainage and collection of 1.2 ml ascitic fluid. *C. albicans* was isolated from the ascitic fluid, and fluconazole therapy (200 mg intravenously [IV] twice daily) was initiated. The patient's condition continued to deteriorate, and a repeat intra-abdominal culture five days later showed *C. tropicalis* (fluconazole MIC, 20 µg/ml). Fluconazole therapy was increased to 400 mg IV twice daily. The patient continued to exhibit abdominal symptoms and fever despite 16 days of IV fluconazole therapy. At this time, *C. tropicalis* (fluconazole MIC, 13 µg/ml) was isolated from two different peritoneal fluid samples taken three days apart. Key laboratory findings over the course of fluconazole therapy for abdominal candidiasis are presented in table 1.

Fluconazole therapy was discontinued, and posaconazole therapy was initiated (400 mg by mouth twice daily). Because she had been in the hospital for more than two months and was at risk for iatrogenic infection, the patient was discharged on posaconazole therapy and was monitored closely. At discharge, she was pale, lethargic, and afebrile, but she had no respiratory difficulties, and her blood pressure was normal (120/70 mm Hg). Physical examination showed diffuse distension of the abdomen, apparent ascites, and tenderness to palpation. The patient was anorectic and had diarrhea. Her lower limbs were edematous and atrophic, and their strength was diminished; she walked only with assistance.

Clinical response to posaconazole was observed at two weeks. The patient no longer had abdominal distension or diarrhea, though abdominal pain on palpation persisted. Her temperature was normal, she was less lethargic, and the lower limb edema was no longer present. Ascites was not apparent on physical examination. After 28 days of posaconazole therapy, the patient weighed 45 kg and was still weak, but she had regained her appetite and was able to walk unassisted. Abdominal ultrasonography revealed a moderate volume of liquid in the lower pelvis that was markedly less than that observed during previous abdominal CT. The patient's condition continued to improve with posaconazole therapy. She regained the ability to perform some daily chores after two months of therapy and attained nearly normal health after three months of therapy. After 88 days of posaconazole therapy, she weighed 46 kg, was energetic, had normal muscle strength and tone, and had no ascites or pain on palpation (only occasional abdominal cramps attributed to postsurgical bridles).

Posaconazole therapy was discontinued after approximately four months (June 2002), at which time abdominal ultrasonography showed no accumulation of abdominal fluid. No signs or symptoms of relapse were evident at a follow-up examination one month after posaconazole discontinuation. The patient was admitted to the hospital four months later (October 2002) for resection of an incisional hernia; at that time, she was found to be otherwise in good health. Laboratory findings over the course of posaconazole therapy are presented in table 1.

Discussion

This case supports the clinical activity of posaconazole in the treatment of non-*albicans Candida* infection. In vitro studies have consistently shown the superior activity of posaconazole over that of fluconazole against a variety of *Candida* species, including *C. albicans* and *C. tropicalis* (Table 2) [2,8-12]. Furthermore, posaconazole has confirmed in vitro activity against *Candida* isolates with decreased susceptibility to fluconazole and/or itraconazole (posaconazole MIC, 0.03 to 8.0 µg/ml for both *C. albicans* and *C. tropicalis*) [8,11,12].

The patient did not respond clinically to increasing fluconazole doses, despite the results of susceptibility tests indicating dose-dependent susceptibility to this drug. In contrast, her clinical response to posaconazole was rapid (two weeks) and was maintained long-term (throughout four months of posaconazole therapy). In addition, she showed no signs of relapse after posaconazole therapy was discontinued. These observations suggest that posaconazole has activity against intra-abdominal *Candida* infection and that it warrants further study for this indication.

Table 2. Comparative in vitro activity of posaconazole and fluconazole against *C. albicans* and *C. tropicalis.*

Study	Organism (No. of isolates)	MIC Range (µg/ml)	
		Posaconazole	Fluconazole
Pfaller et al. 2001 (10)	*C. albicans* (1,992)	0.007 to >8	0.12 to >128
	C. tropicalis (243)	0.015 to 8	0.12 to >128
Barchiesi et al. 2000 (2)	*C. albicans* (84)	≤0.0078 to >4.0	≤0.125 to >64
	C. tropicalis (20)	≤0.0078 to >0.125	0.125 to 2.0
Pfaller et al. 1998 (11)	*C. albicans* (660)	0.008 to >8.0	0.12 to 128
	C. tropicalis (139)	0.015 to >8.0	0.25 to >128
Pfaller et al. 1999 (12)	*C. albicans* (90)	0.015 to 1.0	0.12 to 16
	C. tropicalis (10)	0.015 to 0.25	0.25 to 2.0
Laverdiere et al. 2002 (8)	*C. albicans* (85)	≤0.008 to >8	≤0.025 to >256
	C. tropicalis (21)	0.016 to >8	≤0.025 to >256

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