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Antifungal drug penetration in soft tissue abscesses: a comparative analysis

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Background: Invasive fungal infections (IFIs) are severe and difficult-to-treat infections affecting immunocompromised patients. Antifungal drug penetration at the site of infection is critical for outcome and may be difficult to achieve. Data about antifungal drug distribution in infected human tissues under real circumstances of IFI are scarce.

Methods: Multiple samples were obtained from soft tissue abscesses of a lung transplant patient with *Candida albicans* invasive candidiasis who underwent recurrent procedures of drainage, while receiving different consecutive courses of antifungal therapy [itraconazole (ITC), fluconazole, caspofungin]. Antifungal drug concentrations were measured simultaneously at the site of infection (surrounding inflammatory tissue and fluid content of the abscess) and in plasma for calculation of the tissue/plasma ratio (R). The concentration within the infected tissue was interpreted as appropriate if it was equal or superior to the MIC of the causal pathogen.

Results: A total of 30 tissue samples were collected for measurements of ITC ($n=12$), fluconazole ($n=17$) and caspofungin ($n=1$). Variable concentrations were observed in the surrounding tissue of the lesions with median R of 2.79 (range 0.51–15.9) for ITC and 0.94 (0.21–1.37) for fluconazole. Concentrations ranges within the fluid content of the abscesses were 0.39–1.83 for ITC, 0.66–1.02 for fluconazole and 0.23 (single value) for caspofungin. The pharmacodynamic target (tissue concentration $\geq$ MIC) was achieved in all samples for all three antifungal drugs.

Conclusions: This unique dataset of antifungal drug penetration in infected human soft tissue abscesses suggests that ITC, fluconazole and caspofungin could achieve appropriate concentrations in soft tissue abscesses.

Introduction

Invasive fungal infections are frequent complications in immunocompromised patients. Their treatment is challenging because of the limited number of antifungal drugs, their toxicity, drug–drug interactions and variable penetration in affected tissues/organs. This later point is particularly critical for outcome. Our knowledge about antifungal drug penetration is mainly derived from animal models and human data are scarce.[1] However, drug distribution in human pathogenic conditions may substantially differ from that observed in standardized animal models.[1] It may be affected by the patient's underlying conditions, the characteristics

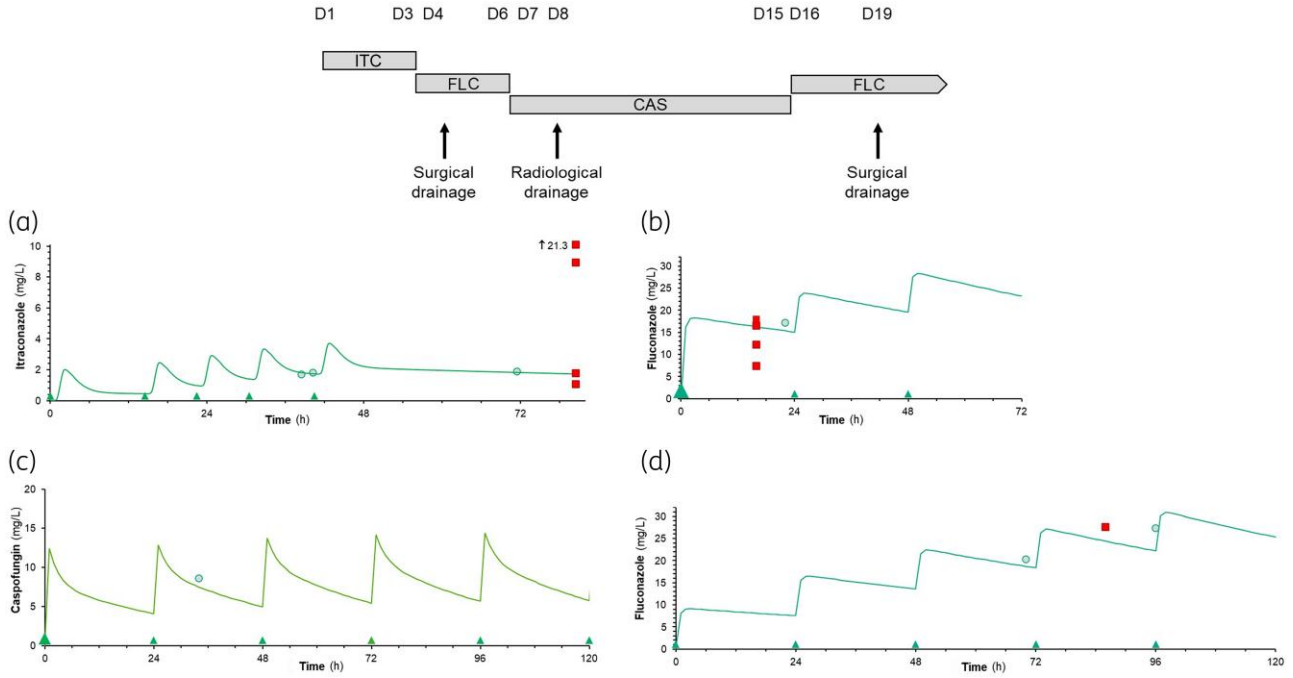

Figure 1. Measured plasma and tissue concentrations and estimated pharmacokinetic profiles of antifungal drugs. The sequence of administration of the different antifungal drugs and interventions for tissue sampling over time is represented on the top of the figure. Timing is expressed in days (D) from the start of antifungal therapy (=D1). ITC, itraconazole; FLC, fluconazole; CAS, caspofungin. Maximum-likelihood plasma concentration curves were constructed using a Bayesian approach,[7] based both on population pharmacokinetic models for each drug[8–10] and on actual plasma concentration measurements. (a) itraconazole, (b) first course of fluconazole, (c) caspofungin, (d) second course of fluconazole. Green triangles, doses of antifungal drugs; green circles, concentration of the antifungal drug measured in plasma (based mainly on trough concentrations when available); red squares, mean concentration of antifungal drug from the same tissue sample (note: concentrations measured in the liquid content of the lesions were not included as they represent a different type of material. No tissue sampling was obtained for caspofungin). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

of infection and the degree of tissue inflammation, necrosis or fibrosis. The adjustment of antifungal drug dosing often relies on therapeutic drug monitoring (TDM) of plasma trough concentrations, which is recommended for some triazoles (voriconazole, posaconazole).[2,3] However, this parameter does not necessarily reflect the actual drug concentrations within the site of infection. A limited set of clinical data suggests that antifungal drug penetration in deep abscesses may be quite low.[4–6]

The aim of the present study was to measure and compare the concentrations of different antifungal drugs in soft tissue abscesses from the same patient.

Methods

Ethics

This study was performed as part of a monocentric prospective observational study of antimicrobial drug penetration in tissue samples. The study protocol was approved by the local ethics committee (protocol 2020-01689) and the patient provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and national/institutional standards.

Samples

Biological samples of this study were obtained from a 61-year-old male lung transplant recipient who developed invasive candidiasis with multiple soft tissue abscesses in the legs. The patient was receiving immunosuppressive therapy with tacrolimus, mycophenolate mofetil and prednisone (25 mg daily). He had normal hepatic and renal function, and no signs of sepsis at admission. *Candida albicans* grew on culture of all the tissue samples (4/4) obtained after surgical drainage, but not in initial blood cultures. No other pathogen was recovered. Oral itraconazole (ITC) (200 mg q8h for 2 days, then 200 mg q24h) was introduced because of the presence of mycelial elements at direct examination. ITC was stopped on Day 3 and switched to oral fluconazole from Day 4 (800 mg q24h loading dose, then 400 mg q24h) on the basis of culture results.

Surgical drainage of four subcutaneous abscesses was performed on Day 4, 40 h after the last dose of ITC and 16 h after the first dose of fluconazole. On Day 6, fluconazole was interrupted because of worsening renal function (estimated glomerular filtration rate according to Cockroft–Gault formula 46 mL/min), which was attributed to drug–drug interaction of fluconazole with tacrolimus. IV caspofungin (70 mg q24h loading dose, then 50 mg q24h) was started on Day 7. A drain was inserted in one of the subcutaneous abscesses on Day 8 (10 h after the second dose of caspofungin). On Day 16, oral fluconazole was re-introduced (400 mg q24h) after normalization of renal function. Surgical drainage of the same subcutaneous abscess was performed on Day 19 (14 h after the fourth dose of fluconazole). Fluconazole was continued for a total of 12 months after the last surgical intervention and no recurrence of the infection was observed.

The timing of antifungal therapy and tissue sampling is shown in Figure 1.

Table 1. Antifungal drug concentrations in infected tissues/fluids and plasma

Drug (dosing)	Days of therapy[a] (*n* doses) Dose interval[b]	Sample site	Sample type	C sample (mg/kg)	C plasma (mg/L)	Ratio (R)
Itraconazole (ITC) (200 mg q8h on Day 1 and 2, then 200 mg q24h)	3 days (5 doses) 40 h	Right calf	Tissue	1.27	1.75	0.73
			Tissue	0.9		0.51
			Fluid	0.69		0.39
		Right knee (para-articular)	Tissue	1.27		0.73
			Tissue	2.32		1.33
			Fluid	0.76		0.43
		Left thigh	Tissue	14.87		8.5
			Tissue	27.82		15.9
			Fluid	3.21		1.83
		Left leg	Tissue	7.43		4.25
			Tissue	10.49		5.99
			Fluid	1.03		0.59
Fluconazole (800 mg q24h on Day 1, then 400 mg q24h)	1 day (1 dose) 16 h	Right calf	Tissue	17.2		1
			Tissue	15.81	17.2	0.92
			Fluid	15.11		0.88
		Right knee (para-articular)	Tissue	19.07		1.11
			Tissue	16.84		0.98
			Fluid	11.31		0.66
		Left thigh	Tissue	11.18		0.65
			Tissue	3.64		0.21
			Fluid	16.27		0.95
		Left leg	Tissue	13.54		0.79
			Tissue	10.96		0.64
			Fluid	15.74		0.92
Fluconazole (400 mg q24h)	4 days (4 doses) 14 h	Right thigh	Tissue	13.48		0.46
			Tissue	28.74		0.99
			Tissue	28.32	29.1	0.97
			Tissue	39.86		1.37
			Fluid	29.7		1.02
Caspofungin (70 mg q24h on Day 1, then 50 mg q24h)	2 days (2 doses) 10 h	Right thigh	Fluid	2	8.6	0.23

C sample, concentration measured in the infected tissue or fluid; C plasma, concentration measured in a plasma sample concomitant to the timing of surgical sampling (±1 h); R, ratio between C sample and C plasma.
[a]Days of therapy at time of sampling.
[b]Interval (h) from the last dose and time of sampling.

Measurement of antifungal drug concentrations

Antifungal drug concentrations were measured in per-operative tissue samples (fluconazole, ITC) or samples collected via an inserted drain (caspofungin) and in concomitant plasma samples drawn within ±1 h from the tissue sampling. When feasible, surgical samples were obtained from the surrounding tissue of the abscess (shell) and its content (fluid/pus). Additional plasma samples were collected for measurement of plasma trough concentrations. Plasma and tissue concentrations were measured by LC-MS/MS, as previously described.[11] The tissue samples were kept frozen at −20°C until the analysis and then treated according to the method previously described.[6]

Analyses

The tissue/plasma ratio (R) was calculated for each sample. The drug concentration in tissue samples was considered as appropriate if ≥MIC of the antifungal drug for the *C. albicans* isolated from cultures. Antifungal susceptibility testing was performed by broth microdilution method (Sensititre YeastOne™, Thermo Fisher Scientific Inc., Waltham, MA, USA). Because ITC is not included in the kit, this drug was tested according to the CLSI procedure.[12]

Results

Tissue and plasma concentrations of antifungals, as well as R values of each sample are shown in Table 1.

ITC concentrations were measured in 12 samples from four distinct soft tissue lesions after 3 days of therapy and 40 h after the last dose. Median R value was 2.79 (range 0.51–15.9) in the surrounding tissues of the abscesses and 0.51 (range 0.39–1.83) in their liquid content.

Fluconazole concentrations were measured in the same 12 samples (four lesions) 16 h after the first dose, with a median R value of 0.86 (0.21–1.11) in the surrounding tissues and 0.9 (0.66–0.95) in the liquid content of the abscesses. In addition, fluconazole measurements were performed in five samples from a single soft tissue abscess after 4 days of therapy, with a median R of 0.98 (0.46–1.37) in the surrounding tissue and 1.02 (single value) in the abscess content.

Caspofungin concentration was measured in a single abscess fluid sample after 2 days of therapy with this drug. The R value was 0.23.

The MICs for the *C. albicans* recovered by culture were <0.03 mg/L for ITC, 0.25 mg/L for fluconazole and 0.06 mg/L for caspofungin.

A Bayesian estimation of pharmacokinetic parameters was performed for each drug, integrating the actual plasma concentrations that were measured at different timepoints (Figure 1).[7]

Concentrations in soft tissue samples were within the target (≥MIC) in 100% of tested samples for all three antifungal drugs (12/12 for ITC, 17/17 for fluconazole and 1/1 for caspofungin).

Discussion

Our knowledge about tissue distribution of antifungal drugs is mainly derived from animal models.[1] In healthy soft tissues, these data suggest better penetration of azoles compared with echinocandins.[1,13,14] However, data from infected tissues or abscesses (in soft tissues or other organs) are very scarce in both humans and animals. In a murine model of intra-abdominal candidiasis, micafungin demonstrated slow accumulation, with low concentrations in liver and kidney abscesses.[15] In one study on human subjects with *Candida* abdominal abscesses percutaneously drained, intra-abscess concentrations of fluconazole were interpreted as marginal.[16] Concentrations of ITC in brain abscesses have been measured in two human case reports, with variable results.[6,17]

In the present work, we took advantage of a unique clinical situation to measure concentrations of different antifungal drugs in soft tissue abscesses of the same patient. Samples were obtained from different layers of the abscesses (i.e. surrounding inflammatory tissue and fluid content) and coupled with a simultaneous plasma sample in order to assess the tissue/plasma ratio.

Concentrations of ITC at the periphery of the lesion were variable, but overall higher compared with those measured within the abscess. It is noteworthy that ITC was interrupted 40 h before the time of measurement, which suggests prolonged accumulation of the drug. Results for fluconazole were more reproducible, with median tissue/plasma ratios close to 1 in both the surrounding tissue and fluid content of the abscesses. Moreover, we observed that fluconazole achieved these concentrations rapidly after the first dose. For caspofungin, only one sample (pus of the abscess) was available with a tissue/plasma ratio of 0.2.

The heterogeneity of results obtained for the same drug may be related to different degrees of inflammation/fibrosis. It is noteworthy that most samples were collected early after the start of antifungal therapy. However, the trough concentrations were within the expected ranges according to pharmacokinetic studies in humans, and our predictive model suggests that the drug concentrations were close to steady-state at the time of sampling.[18–20] A phenomenon of hysteresis (i.e. discordance of the concentration–time profiles of tissue and plasma) has been described for antifungal drugs, which may have contributed to result heterogeneity.[1]

While we could detect substantial levels of the different antifungal drugs within all tissue samples, the interpretation of these results is difficult. We used a pharmacodynamic target (i.e. concentration at the site of infection ≥ MIC) to define the appropriateness of tissue penetration, which was achieved in 100% of samples. Whether these interpretations would correlate with clinical efficacy is unknown. While the rate of protein binding in plasma is known for these antifungals,[1] there are no data about the actual fraction of protein-bound and free (effective) drug in such tissue or pus samples, where the protein content can substantially differ from that in plasma. Moreover, these antifungal drugs have distinct effects (i.e. fungicidal or fungistatic), which may also impact outcomes. Finally, while the patient had a global favourable outcome of the infection, the respective contributions of appropriate antifungal therapy and source control cannot be determined.

In conclusion, this study provides a unique, albeit limited, dataset about the penetration of different antifungal drugs in human soft tissue abscesses under real clinical conditions of invasive candidiasis. Our results suggest that appropriate concentrations of fluconazole, ITC and caspofungin could be achieved in all samples, including within the liquid content of the abscess.

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Transparency declarations

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