Oral versus intravenous therapy in the treatment of systemic mycosis

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ABSTRACT

The great majority of systemic fungal infections require long-term therapy that often extends 6–12 months, particularly in immunosuppressed patients. It can be difficult to comply with this requirement when the drug to be used is only available for intravenous administration, because problems related to maintaining a permeable venous pathway for long periods arise. The availability of an intravenously (IV) and orally (PO) administered drug can solve this problem by making sequential therapy possible. Voriconazole is a new antifungal agent that, apart from satisfying this requirement because it has a high oral bioavailability, presents a broad spectrum of antifungal activity that makes its use possible, *a priori*, in the initial and/or sequential IV/PO treatment of any systemic mycotic infection. Based on current costs there is potential for savings compared with liposomal amphotericin B.

Keywords Systemic mycosis, antifungal therapy, voriconazole

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INTRODUCTION

Mycosis in general, and systemic mycosis in particular, present a number of particular features that differentiate them from any other kind of infectious process. The incidence when compared with bacterial or viral infections is clearly lower. Moreover, mycoses are infectious processes that usually affect patients with complex conditions in clinical situations of serious deterioration at a high iatrogenic risk. Finally, they are infectious processes that produce high morbidity and mortality despite the use of very aggressive drug therapy characterised by long duration and the adverse effects of existing antifungal agents.

Recently, antifungal therapy has been extended through the introduction of two new drugs, caspofungin and voriconazole. These can be very useful in the treatment of some of the more problematic systemic infections. The latter has a very interesting feature: the possibility of both oral and intravenous administration. This is a real novelty in this group of drugs, at least among broad-spectrum antifungal drugs.

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PATIENTS AND SYSTEMIC MYCOTIC INFECTION. CONSIDERATIONS ON THE METHOD OF ADMINISTRATION OF ANTIFUNGAL DRUGS

As indicated in the introduction, in contrast to bacterial and viral infections, systemic mycoses present almost exclusively in certain special types of patient. The presence of any kind of immunosuppression is one of the most important risk factors; the patient who presents with neutropenia [1,2], who has undergone bone marrow or solid organ transplantation [3–5], who needs immunosuppressive therapy for any kind of disease, who has acquired immune deficiency syndrome (AIDS) with a low CD4 count, or who is a critically ill patient in an intensive-care unit [6,7], is therefore part of a group in which systemic mycotic infections present with special frequency and virulence because these processes may be the second and third causes of infection.

Some of these patients are particularly susceptible to the presence of maximum levels of immunosuppression: severe neutropenia, treatment of episodes of acute rejection or graft-

versus-host disease, etc. In these patients *Aspergillus*, mucorales and yeasts of the *Candida* type appear as particularly prevalent micro-organisms.

For various reasons the critical patient usually requires broad-spectrum antibiotic therapy which is considered a major factor in the development of mycosis, especially those varieties produced by the selection of *Candida*-type yeasts in the patient's own flora. It is not uncommon for these patients to receive fluconazole prophylaxis for deep mycotic infection, and this has been associated with the selection of some species of yeast that are particularly resistant to this azole [1,8–14]. An identical situation has been described among patients with AIDS who have received prophylaxis with this drug for oesophageal candidiasis [15].

The patient with a systemic mycotic infection therefore presents a disease baseline profile and a well-defined clinical situation. The requirement for a permeable central venous access is critical, either because the patient is not in the right condition for acceptable oral intake or because he/she needs drugs that can only be administered intravenously. In these circumstances, and at least initially while oral intake is not possible, antifungal administration for systemic infections is almost always done intravenously. This can be seen in any of the protocols [16–22] that specifically indicate the need to administer some intravenous drugs initially, such as amphotericin B deoxycholic, the lipid forms of the same drug, casponfungin, 5-fluorocytosine, fluconazole, or voriconazole, the latest azole to be marketed.

In any event, there is a possibility that the patient presenting a systemic mycotic infection can also take drugs orally, so this provides the opportunity to start antifungal therapy using this route of administration. This should lead us to consider the risk, albeit theoretical, of the systemic repercussion of the infection generating problems that limit the absorption of orally administered drugs [23,24] and therefore reduce their efficacy. Although this situation does not always arise, it is clear that it cannot be definitively ruled out in practice. This fact, together with the high mortality associated with systemic mycosis, means that attempts should be made to ensure the efficacy of the therapy, and therefore administer antifungal drugs intravenously.

The situation can change considerably when a clear improvement in the infectious condition has occurred after the first few days of intravenous therapy, and with it the general clinical situation of the patient. The need to maintain intravenous therapy thus becomes a continual source of problems: loss of the pathway with the need to puncture veins frequently, the presence of effusion or phlebitis (with or without catheter-associated bacteria), a high risk of infection and/or deterioration of the venous reservoir related to daily use, etc. These situations are always problematic but are worse in this kind of patient who, as already indicated, is highly likely to present severe complications in the face of any of these intercurrent iatrogenic processes.

This explains why, when the antifungal therapy lasts longer than 7–10 days, the possibility of using an orally administered antifungal drug to replace intravenous therapy becomes a high priority. This method is currently given the generic name of 'sequential therapy'.

Sequential therapy is clearly attractive under any circumstances. Nevertheless, for it to be viable one needs to be certain that the change from intravenous to oral administration does not lead to a loss of efficacy, either because the selected drug needs to be absorbed or because a change of drug involves a reduction in the intrinsic antifungal activity. In other words, it is a case of being sure that intravenous to oral sequential therapy does not mean a risk of reduced efficacy or, obviously, an increase in adverse effects.

MYCOTIC INFECTION AND THE DURATION OF THE THERAPY

A typical feature of the treatment of most systemic fungal infections is that they need long-term therapy. Table 1 shows the recommended duration under a range of widely accepted guides and protocols for the treatment of deep mycoses of greatest interest. A review of the information shows that almost all systemic mycotic infections need antifungal therapy over a very long period of time. In many situations this includes the need to administer one of the antifungal drugs intravenously on a daily basis for weeks, months, or even years.

The availability of an antifungal drug that can be administered orally and demonstrates appropriate activity may mean that the great majority of fungal diseases could be treated

Table 1. Duration of therapy for the main types of mycosis

Infection	Medical treatment and duration
Coccidioidomycosis	
Diffuse pneumonia [16]	Initial therapy with amphotericin B for several weeks. Sequencing to azole orally when clinical improvement is observed. Total duration of the therapy is 1 year, although if there is immunosuppression indefinite administration may be required.
Symptomatic pulmonary nodule, symptomatic pulmonary cavity [16]	Similar to that of diffuse pneumonia.
Chronic cavitary pneumonia [16]	Oral azole for 1 year, if there is no initial response consider amphotericin B IV
Non-meningeal extrapulmonary localisation [16]	Similar to that of chronic cavitary pneumonia.
Meningitis [25–27]	High-dose fluconazole IV/oral for an indefinite duration. If the clinical response is not satisfactory, consider intrathecal amphotericin B.
Candidiasis (Rex)	
Candidemia and acute disseminated candidiasis [28]	In a stable patient begin with an azole parenterally, if the patient is unstable amphotericin B. Maintain the therapy for 2 weeks after the last positive haemoculture and all symptoms and signs of the infection have been resolved.
Fever in a neutropenic patient [29–31]	Maintain the therapy (amphotericin B or parenteral azole) while the neutropenia persists.
Hepatosplenic candidiasis [32–34]	Maintain prolonged therapy (amphotericin B or parenteral/oral azole), probably for several months and, in any event, for the duration of the chemotherapy.
Neonatal disseminated cutaneous candidiasis [17]	Amphotericin B or parenteral azole until the complete resolution of symptoms and signs.
Urinary candidiasis [35]	Fluconazole for 7–14 days.
Pneumonia [17]	Similar to acute disseminated candidiasis.
Laryngeal form [36,37]	Similar to acute disseminated candidiasis.
Osteomyelitis and arthritis [38–40]	Amphotericin B for 6–10 weeks or IV/oral azole for 6–12 months.
Intra-abdominal [41,42]	Amphotericin B or parenteral azole. It is usually necessary to maintain the therapy for at least 2–3 weeks.
Endocarditis [43–45]	Amphotericin B with or without flucytosine for at least 6 weeks. If an azole is used parenterally the therapy should extend for a long period of time. If valve replacement is not possible indefinite therapy may be required.
Pericarditis, suppurative phlebitis [46,47]	Amphotericin B or parenteral azole. It is usually necessary to maintain the therapy for at least 2–3 weeks, although a much longer period may occasionally be necessary.
Meningitis [48,49]	Amphotericin B with flucytosine until the complete resolution of all symptoms and signs and the normalization of all image and analytical studies. If an azole is used, IV administration and maintain the therapy for at least 4 weeks after the resolution of condition.
Endophthalmitis [17]	Amphotericin with or without flucytosine and fluconazole can be effective. The therapy should last from 6 to 12 weeks.
Oesophageal candidiasis [50,51]	Oral azole for 2–3 weeks. Amphotericin B if results are ineffective. In patients with AIDS the indefinite oral administration of fluconazole is effective in the prevention of episodes.
Blastomycosis [52–56]	Amphotericin B total dose of 1.5 g [1 mg/kg for 3 weeks) or a oral azole for 6 months.
Sporotrichosis	Amphotericin B, total dose of 2 g [1 mg/kg for 4–6 weeks) and/or itraconazole for a minimum of 3–6 months.
Pulmonary [57,58]	Amphotericin B, total dose of 2 g [1 mg/kg for 4–6 weeks) and/or itraconazole for a minimum of 3–6 months.
Osteoarthritis [57,59]	Oral itraconazole for 6–12 months.
Meningitis and disseminated forms [57,58]	Amphotericin B until the complete resolution of all symptoms and signs.
Histoplasmosis	Itraconazole for a minimum of 6–12 weeks. If there is intolerance or ineffectiveness, amphotericin B until the complete resolution of symptoms and signs.

Table 1. Continued.

Infection	Medical treatment and duration
Acute pulmonary [20]	Itraconazole for a minimum of 6–12 weeks. If there is intolerance or ineffectiveness, amphotericin B until the complete resolution of symptoms and signs.
Chronic pulmonary [60–63]	Itraconazole for a minimum of 12–24 months. If there is intolerance or ineffectiveness, amphotericin B until the complete resolution of symptoms and signs.
Disseminated [60,64,65]	Amphotericin B until the complete resolution of symptoms and signs. If there is intolerance or ineffectiveness, itraconazole for a minimum of 12–24 months.
Cerebral [66]	Amphotericin B total dose of 35 mg/kg [0.7–1 mg/kg/day) for 3–4 months. If there is intolerance or ineffectiveness, fluconazole for a minimum of 9–12 months.
Aspergillosis	Amphotericin B or caspofungin or voriconazole until the complete resolution of symptoms and signs (a minimum of 4–6 weeks). It is recommended to maintain the therapy in situations where there may be an increase in immunosuppression. The combination of two of these drugs may be useful.
Invasive pulmonary form [67–70]	Amphotericin B or caspofungin or voriconazole until the complete resolution of symptoms and signs (a minimum of 4–6 weeks). It is recommended to maintain the therapy in situations where there may be an increase in immunosuppression. The combination of two of these drugs may be useful.
Cerebral or meningeal [69,71]	Amphotericin B and/or voriconazole IV/oral.
Cryptococcosis	Immunocompetent patient with asymptomatic form: fluconazole for a minimum of 3–6 months. If the patient presents symptoms of active infection the therapy is extended between 6 and 12 months. If there is intolerance or ineffectiveness, or the infection is serious: amphotericin B, total dose of 1–2 g. Patient with AIDS: maintain the therapy with oral fluconazole indefinitely.
Pulmonary [72–76]	Immunocompetent patient with asymptomatic form: fluconazole for a minimum of 3–6 months. If the patient presents symptoms of active infection the therapy is extended between 6 and 12 months. If there is intolerance or ineffectiveness, or the infection is serious: amphotericin B, total dose of 1–2 g. Patient with AIDS: maintain the therapy with oral fluconazole indefinitely.
Cerebral [72,74,77–79]	Immunocompetent patient: amphotericin B with or without flucytosine for 6–10 weeks. Once 2 weeks of IV therapy have been completed it may be useful to replace it with oral fluconazole for 8–10 weeks. Patient with AIDS: it may be necessary to maintain therapy with oral fluconazole indefinitely.

sequentially, initiating therapy with the intravenous antifungal agent and then continuing with oral therapy when possible and/or there is a clinical improvement. At present only three antifungal agents can be administered both orally and intravenously: flucytosine, fluconazole and voriconazole. The first two demonstrate a moderate level of activity because some frequent and important fungi, such as *Aspergillus*, which are susceptible to these drugs, cannot be included in their spectrum. The third antifungal agent, voriconazole, has favourable in-vitro activity against almost all pathogenic fungi (Table 2). Indeed, one of the most interesting aspects of this drug is that it is even active against fungi that are resistant to the other drugs in the same family.

PHARMACOECONOMIC CONSIDERATIONS

It is clear that oral therapy for any disease should mean much lower costs than intravenous therapy. It may be sufficient to point out the saving involved in replacing the cost of intravenous administration, decreasing hospital stay, or eliminating the need to visit a day hospital to administer the drug, plus the cost of some intravenously administered antifungal agents and the lipid forms of amphotericin B, to appreciate the considerable reduction in daily cost from the moment the change from intravenous to oral administration occurs.

Moreover, it should be noted that therapy with different forms of amphotericin B has

Table 2. Antifungal activity. CMI_{90} (mg/L)or range of CMI

Species	Fluconazole	Itraconazole	Voriconazole	Ref.
Aspergillus flavus	512	0.125	0.5	[80–84]
Aspergillus fumigatus	512	0.5	0.5	[80–84]
Aspergillus nidulans	256	0.125	0.125	[81,82,84]
Aspergillus niger	256	0.5	0.5	[81–84]
Aspergillus terreus	64	0.125	0.5	[80–82,85,86]
Blastomyces dermatitidis	1–64	0.03–1	0.03–1	[80,87–89]
Candida albicans	2	0.25	0.06	[90–92]
Candida glabrata	64	4	1	[90–92]
Candida guilliermondii	4	1	0.5	[85,92]
Candida krusei	128	2	1	[90–92]
Candida lusitaniae	8	1	0.5	[92,93]
Candida parapsilosis	8	0.5	0.25	[90–92]
Candida tropicalis	1	0.5	0.125	[90–92]
Coccidioides immitis	2–64	0.125–2	0.03–1	[87,89]
Cryptococcus neoformans	16	0.5	0.25	[94–96]
Fusarium solani	> 64	> 8	8–16	[80,81,88,93]
Histoplasma capsulatum	0.125–64	0.03–8	0.03–1	[80,87–89]
Malassezia furfur		< 0.03–0.03	0.03–0.125	[81,97]
Penicillium marneffei	1–8	0.03–2	0.03–2	[87]
Pracoccidioides brasiliensis	0.125–64	0.03–1	0.03–2	[87]
Pseudallescheria boydii	4–64	1–4	0.06–1	[85]
Sporothrix schenckii	32–128	0.25–4	0.5–6	[80,85,87]
Trichosporon beigelii	0.5–128	0.125–2	0.03–1	[81,85,87]

frequently involved some adverse effects on patients that lead to high costs. Some of these are related to the need to administer drugs to avoid the adverse effects. Others involve making an early diagnosis of the adverse effect (daily tests) and finally, the highest costs arise from the treatment of some of the adverse effects. It is also necessary to add the costs arising from nonspecific complications linked to intravenous therapy: punctured veins, phlebitis, bacteremia, etc.

Nevertheless, the simple addition of the cost of purchasing the drugs, even without including the costs indicated above, leads to the conclusion that the replacement of intravenous therapy by oral therapy with voriconazole would mean a cost reduction of such magnitude that it could represent a daily saving of 400–900 euros (as an approximate estimation), depending on the dose of liposomal amphotericin B used. Indeed, the association of voriconazole and caspofungin represents a daily cost lower than the maximum dose of this form of amphotericin B.

ANTIFUNGAL DRUGS, ORAL ADMINISTRATION AND SEQUENTIAL THERAPY

The need to avoid long-term intravenous administration of antifungal agents has been the reason why itraconazole is used as a sequential therapy for other intravenous drugs, especially amphotericin B. This has been possible because of its availability for oral use in solid form, and more recently in liquid form. Unfortunately, the first presents a highly variable bioavailability with a major reduction in bioavailability when the level of gastric pH rises [98]. Moreover, the solid form is presented in units of 100 mg, so it is necessary to administer a large number of pills every day. Unfortunately, the intravenous form has not been marketed yet, so intravenous to oral sequential therapy is not possible with this drug.

Voriconazole, a recently marketed azole, offers a number of advantages that make it an interesting drug for use as a broad-spectrum antifungal agent in sequential therapy. It has a broad antifungal spectrum (reviewed in detail in various sections of this report and referred to in Table 2). It presents activity against almost all fungal pathogens at concentrations that are reached with a conventional dose, regardless of whether the drug is administered intravenously or orally. All the reference pathogens that require long-term treatment are included in its spectrum, including the most common in our medium such as yeasts of the *Candida* type and fluconazole-resistant varieties.

Regarding the pharmacokinetics, voriconazole stands out because it presents a very high oral bioavailability (98.99%), close to 100%. This drops slightly when it is administered with food [101], so its administration is recommended at intervals of approximately 1 hour before or after food intake. Figure 1 shows a simulation of plasma concentrations obtained with the pharmacokinetic parameters described for the indicated doses [99]. It shows similar exposures [from the area under the curve(AUC)] that indicate its high bioavailability, which is clearly higher than that of the solid form of itraconazole.

A careful examination of this curve shows that the maximum plasma concentration stands at approximately 5 mg/L, even when the drug is administered intravenously with a dose of 4 mg/kg. This low plasma concentration in relation to the dosage administered indicates that this drug is not present in the plasma but has been distributed quickly and extensively. This is expressed both by its volume of distribution, which ranges between 2 and 4.6 L/kg, and the fact that it reaches concentrations in tissues that other antifungal drugs find hard to access, such as the cerebrospinal fluid [102–106]. This high distribution is facilitated by the low percentage of protein binding (58%).

The elimination of voriconazole is slow, mostly mediated by CYPP450 isoenzymes 2C19, 2C9 and to a lesser extent, 3A4 [99,102]. This method of elimination explains why it is not necessary to adjust the dose in patients with renal insufficiency, although the accumulation of the intravenously administered excipient (cyclodextrine) means that it is best to avoid the intravenous

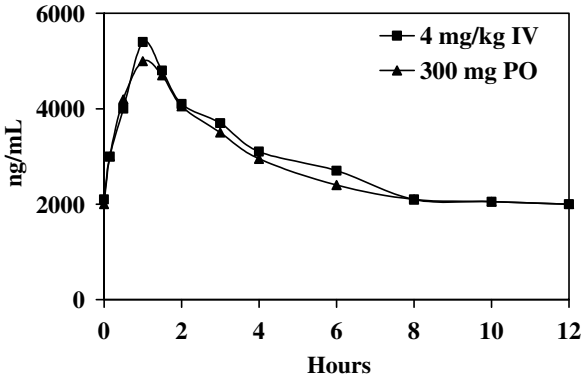

Fig. 1. Plasma concentrations of voriconazole Oral and IV (99).

administration of voriconazole in patients with this disease [107]. In patients with hepatic impairment the dose needs to be reduced by half [108]. In children, at the doses studied, the pharmacokinetics were more linear, and it is recommended to adjust the dose based on weight, independent of the method of administration [109].

Moreover, like all azoles such as fluconazole and itraconazole, voriconazole can inhibit the metabolism of the isozenymes that participate in its own metabolism, which leads to at least two consequences: certain risk of interaction [110–120] and the inhibition of its own metabolism. The saturation of metabolism is responsible for non-linear pharmacokinetics, both in the dose and over time. As a result, dose increases generate higher concentrations than expected, plus maximum plasma concentration, and the AUC and the half-life increases with the multiple dose in relation to single first doses [99].

CYP2C19 is involved in the metabolism of voriconazole, and it also participates in the metabolism of fluconazole and itraconazole. CYP2C19 exhibits genetic polymorphism, and consequently there may be a part of the Caucasian (3–5%) and the Asian (15–30%) population that metabolises these drugs more slowly. Following the trajectory marked out by its predecessors within the pharmacological group and as a result of all these circumstances, this drug presents high variability in pharmacokinetics. It is therefore recommended to adjust the dose to weight, specifically 4 mg/kg/12 h as a maintenance dose, at least when the drug is used intravenously.

Voriconazole has been authorized for use as first-line treatment of invasive aspergillosis, serious infections caused by *Candida* spp, (including *C. krusei*) that are resistant to fluconazole, and also in serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. Its availability on the market will give rise to real expectations regarding its usefulness in the treatment of other mycotic infections, where voriconazole will be used intravenously and orally in sequential therapy, either with intravenous voriconazole or with other antifungal drugs such as caspofungin or amphotericin B, which cannot be administered orally. To date, the results of sequential therapy with this drug have been published or reported for different indications: fever and neutropenia [121], aspergillosis [103,122–125], infection by *Scedosporium* spp. [126,127], infection by

Pseudallescheria boydii [106], and visceral infections of different aetiology [128], including those diagnosed in children [129].

The experience accumulated over the next few months and years will determine the usefulness of this drug, which is highly attractive and an interesting option for the treatment of systemic mycotic infections intravenously and/or orally, at least in terms of its pharmacological profile.

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