Current experience with itraconazole in neutropenic patients: a concise overview of pharmacological properties and use in prophylactic and empirical antifungal therapy

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ABSTRACT

Itraconazole is a triazole broad-spectrum antifungal agent that can be given as capsules, oral solution or intravenous solution. Bioavailability in neutropenic patients is different between capsules (*c.* 23%) and oral solution (*c.* 55%). A dose–response relationship has been established for the use of itraconazole in antifungal prophylaxis: HPLC-determined trough concentrations of itraconazole need to be above 500 ng/mL for effective prevention of invasive *Aspergillus* infections. A meta-analysis of 13 randomised clinical trials and 3597 neutropenic patients with haematological malignancies has demonstrated a 53% reduction in the incidence of invasive *Aspergillus* infections with a sufficient dose of itraconazole. Two randomised clinical trials evaluated itraconazole for empirical antimycotic therapy in neutropenic patients with persisting fever despite broad-spectrum antibiotic therapy in comparison to conventional amphotericin B. Both demonstrated significantly reduced nephrotoxicity and at least comparable efficacy. In conclusion, itraconazole should be regarded as the standard for antifungal prophylaxis in high-risk patients and a valuable therapeutic option for empirical antifungal therapy in these patients.

Keywords Antifungal prophylaxis, empirical antimycotic, invasive fungal infections, itraconazole

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INTRODUCTION

Itraconazole is a broad-spectrum triazole antifungal agent that was first introduced for use in patients with invasive fungal infections in 1987, when amphotericin B and fluconazole (new at that time) were the limited options for effective systemic therapy [1,2]. The form in which itraconazole was first used clinically was a capsule containing sugar-coated pellets. This was extremely successful in the treatment of fungal infections of skin and nails [3] but, despite some initially encouraging results, did not deliver sufficiently reliable bioavailability in neutropenic patients. The achlorhydria, mucositis, nausea and anorexia that complicate the management of these patients reduce significantly the intake and absorption of the drug [4–6]. It is estimated that only about 22% of the substance is taken up by the patient in this clinical situation [7].

The formulation of the drug changed with the production of an oral solution of this highly lipophilic drug. Establishing a new principle in drug galenics, β-hydroxy-propyl-cyclodextrin, an oligosaccharide formed from seven glucose molecules, was used to incorporate itraconazole into an aqueous solution that could be swallowed and absorbed or infused intravenously [8–10]. Externally hydrophilic and internally lipophilic, cyclodextrin brings itraconazole into the systemic circulation, where it separates instantaneously. Cyclodextrin is inert and undergoes renal elimination without any metabolism.

With these new oral and intravenous solutions, new trials were designed to evaluate the efficacy of itraconazole in antimycotic prophylaxis, in empirical antifungal therapy and, to a lesser extent, in the treatment of proven invasive fungal infections. At the same time, clearer data on the drug's dose–response relationship became

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Table 1. The role of itraconazole in antifungal treatment strategies

Clinical problem	Role of itraconazole	References
Prevention of invasive fungal infections	Only antifungal agent with clear evidence that it prevents invasive fungal infections, including those caused by *Aspergillus*, in neutropenic patients with haematological malignancies	[31,32]
Empirical antifungal therapy	Efficacy comparable to that of conventional amphotericin B; much lower toxicity	[52,53]
Bioavailability	Available as oral or intravenous solution (loading dose and drug monitoring required)	[7,11,34,54]
Drug–drug interaction	Co-administration with drugs that are metabolised by cytochrome P450 3A4 to be avoided or adjusted for	(Hurlé, this issue)

available and explained some of the earlier disappointments. This article reviews the most important pharmacological and clinical data on itraconazole and attempts to define its role in today's much larger armamentarium of antifungal agents (Table 1).

CLINICAL PHARMACOLOGY AND PHARMACODYNAMICS

The bioavailability of itraconazole capsules in neutropenic patients has been estimated at 22%, while the oral solution achieves about 55% bioavailability [7,11,12]. Several papers have reviewed itraconazole's pharmacokinetic properties in detail [3,7,10,13–17]. The elimination half-life after a single dose is about 24 h, which increases to an apparent elimination half-life of 34 h in the steady state. Itraconazole is highly lipophilic and therefore it has a large volume of distribution (11 L/kg). This means that without a loading dose it may take up to 14 days to achieve steady state [6,7].

Itraconazole's protein-binding fraction is high (99%), and therefore it cannot be removed by haemodialysis [18–20]. The drug is metabolised in the liver by the cytochrome P450 pathway, and it is a substrate and a strong inhibitor of the isoenzyme 3A4, which is an important regulator of drug elimination pathways. Safe use of itraconazole requires careful attention to its interactions with other drugs. In cases of renal insufficiency, dose reduction of oral itraconazole is not necessary, whereas the intravenous solution is contraindicated in patients with a creatinine clearance below 30 mL/min. In patients with minor or moderate degrees of hepatic insufficiency, dosing of itraconazole does not need to be changed; the standard dose can be used initially and then adapted according to the drug monitoring results (recommended range 500–2000 ng/mL itraconazole; see below) [17].

Itraconazole is the only azole that forms an active metabolite, hydroxy-itraconazole, which has the same spectrum of antimicrobial activity as the parent compound [5]. In the steady state, this metabolite is found at concentrations approximately two-fold those of the parent compound, indicating that total serum antifungal activity is much higher than that corresponding to the itraconazole concentration alone.

Itraconazole inhibits 14-α-demethylase, the rate-limiting enzyme for the synthesis of ergosterol, which is an important component of the fungal cell membrane [6]. While its effects on *Candida* spp. are fungistatic, it can achieve fungicidal activity on *Aspergillus* spp. at higher doses [21,22].

DEFINITION OF THE TARGET DRUG CONCENTRATION

An early study of the efficacy of antifungal prophylaxis with itraconazole in neutropenic patients found a lower rate of invasive fungal infections in patients who had serum concentrations above 250 ng/mL for at least 2 weeks [23]. In