

EXPERT OPINION

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Itraconazole: an update on pharmacology and clinical use for treatment of invasive and allergic fungal infections

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Introduction: Fungal infections are a major source of global morbidity and mortality. Itraconazole is a triazole antifungal agent that is widely used for the prevention and treatment of fungal infection. While newer antifungal agents are now available, itraconazole is an orally bioavailable agent with broad-spectrum antifungal activity. Itraconazole remains a useful drug for the management of allergic and invasive mycoses worldwide.

Areas covered: This article provides a summary of the pharmacokinetics, pharmacodynamics and clinical uses of itraconazole. Additionally, the authors summarise the safety and recently described toxicodynamics and discuss the value of therapeutic drug monitoring (TDM) with itraconazole. The following search criteria were constructed in order to identify relevant literature using PubMed and Ovid-MEDLINE: itraconazole, triazole, pharmacokinetics, pharmacodynamics, toxicodynamics and TDM. Relevant abstracts and articles identified from reviewing secondary citations were additionally retrieved and included if relevant.

Expert opinion: Itraconazole remains an important agent in the prevention and treatment of fungal infection. Itraconazole has a broad-spectrum of activity and is available in both an intravenous and oral form making long-term use in chronic mycoses practical. Itraconazole is widely used for the treatment of endemic fungal infections. Pharmacokinetic variability and clinically important drug interactions make TDM of itraconazole an important consideration.

Keywords: antifungal, itraconazole, pharmacodynamics, pharmacokinetics, toxicodynamics

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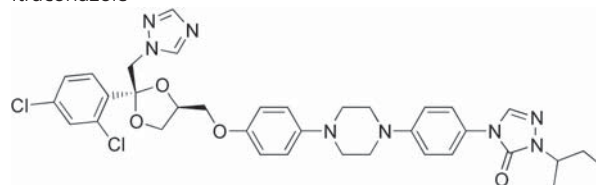
1. Introduction

The triazoles are first-line agents for the prevention and treatment of invasive and allergic fungal infections. Itraconazole (*cis*-4-[4-(4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-1,3-dioxolan-4-yl]-1-piperazinyl]phenyl)-2,4-dihydro-2-(1-methyl-propyl)-3*H*-1,2,4-triazol-3-one) was initially synthesised in 1980 and has broad-spectrum antifungal activity. Itraconazole was the first orally bioavailable triazole with activity against medically important opportunistic filamentous fungi such as *Aspergillus* spp. [1]. Itraconazole is still used for the treatment of allergic and invasive aspergillosis, superficial candidiasis, dermatophyte infections, sporotrichosis, blastomycosis, histoplasmosis, penicilliosis and coccidioidomycosis [2-13]. Itraconazole is available in capsule, oral suspension and intravenous preparations. Intravenous itraconazole is not universally available; in particular, supply was discontinued in the USA in 2007. Itraconazole is highly lipophilic, poorly soluble at physiological pH

Box 1. Drug summary.

Drug name	Itraconazole
Phase	I – IV
Indication	Invasive, allergic and mucocutaneous fungal infections
Pharmacology description	Triazole
Route of administration	Oral and i.v.
Chemical structure	Itraconazole

Pivotal trials



[17,19,20,60,67,94,96,98,99,116,120,121,128]

and extensively protein-bound in circulation. This review summarises the clinical pharmacology and use of itraconazole.

2. Structure and formulations

The structure of itraconazole is shown in Box 1. The active site of the molecule (triazole ring) is attached to a side chain that is responsible for the spectrum of antifungal activity, potency and toxicity profile, all of which are the subject of much of this review. There are three formulations that are available for clinical use: capsules, an oral solution and an intravenous formulation. The original capsule formulation is manufactured by Janssen and currently marketed as Sporanox®. The oral suspension and intravenous formulation, also originally manufactured by Janssen, are both formulated with hydroxypropyl-β-cyclodextrin. Cyclodextrins are carbohydrate ring structures (or glucose oligomers) produced by the enzymatic degradation of starch [14]. β-Cyclodextrin is a by-product of starch metabolism produced by *Bacillus macerans* and other bacteria [14]. Cyclodextrins form water-soluble complexes with lipophilic agents because they have hydrophobic interiors with hydrophilic exteriors (Box 1). Cyclodextrins are not necessarily biologically innocuous; they cause osmotic diarrhoea and some cyclodextrins are either nephrotoxic or accumulate with renal impairment [15,16]. Oral itraconazole suspension has improved oral bioavailability that results in ~30% higher systemic drug exposure compared with itraconazole capsules [17]. Improved oral bioavailability and systemic drug exposure is associated with improved clinical outcomes for patients with oropharyngeal candidiasis [18] and prevention of invasive aspergillosis [19]. Intravenous itraconazole is used for the treatment of life-threatening systemic mycoses and enables target concentrations of > 0.5 mg/l to be achieved in the first 48 h of treatment [20].

Itraconazole has served as a model agent for the development of new formulations to improve the safety and efficacy of antifungal compounds. There have been attempts to incorporate the active compound into liposomes and nanoparticles [21,22]. Older formulations include polyethylene

glycol and pelleted preparations [23]. The pharmacokinetics of these alternative preparations remain largely undefined. While generic formulations of itraconazole are widely available, there is relatively little information documenting pharmacokinetic equivalence. There have been reported cases of substitutions with generic formulations resulting in sub-therapeutic itraconazole levels and treatment failure [24].

3. Drug targets and mechanism of action

The triazoles inhibit cytochrome P450 (CYP) enzymes, which are a superfamily of haemproteins involved in the synthesis and detoxification of compounds via hydroxylation reactions [25]. In fungi, CYP enzymes are important for the biosynthesis of sterols that are vital components of fungal cell membranes. The putative target for triazoles, the enzyme 14-α-demethylase is essential (known also as P450DM, ERG11, ERG16 and CYP51) and is involved in the progressive removal of methyl groups from lanosterol as part of the biosynthesis of ergosterol (Figure 1). In the absence of antifungal exposure, ergosterol is the predominant sterol in the fungal membrane. Triazoles induce a profound disruption in the normal balance of sterols [26,27] leading to a decrease in ergosterol content and an accumulation in methylated precursors [26]. Structural models of Cyp51 in *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans* suggest the active site of the enzyme is buried within the core of the protein. The floor of the active site has a haem moiety [28–30]. A highly conserved cysteine residue at position 470 forms the axial thiolate ligand [28]. Additional conserved residues adjacent to the haem moiety may establish the redox potential of this site [31]. In addition to the active site that is common to the triazole antifungal class, itraconazole has a comparatively long side chain. The terminal alkyl group of this side chain (Box 1) interacts with residues in the substrate access channel that enables the triazole ring to be brought into proximity with haem moiety at the base of the active site. Itraconazole is initially recognised by a hydrophobic patch of amino acids on the protein surface adjacent to the access channel before

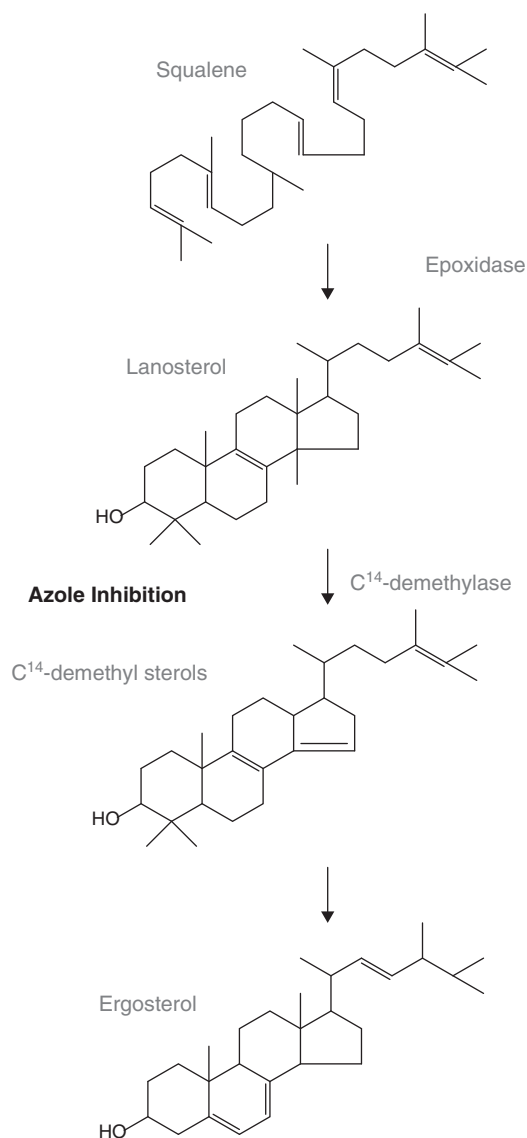


Figure 1. Sterol synthesis.

being partitioned down the channel to the active site with the aid of a series of hydrophobic interactions [28].

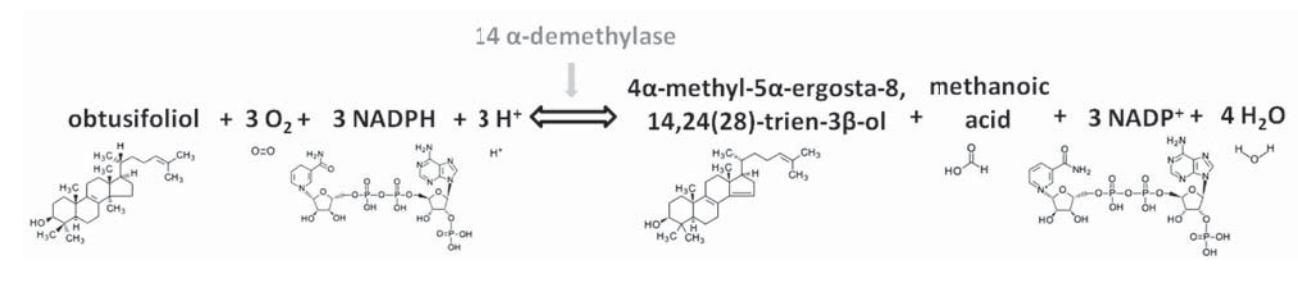
The oxidative demethylation of the natural substrate is catalysed by 14- α -demethylase requires NADPH and molecular oxygen and hydrogen (Figure 2). This reaction is also inhibited by carbon monoxide (CO) [32]. The nitrogen atom (N4 in triazoles and N3 in the imidazoles) in the heterocyclic ring of the imidazoles and triazoles binds the protohaem iron, which leads to exclusion of the oxygen that is required for the oxidation reaction [33]. The degree of enzyme inhibition is likely a function of the strength of binding between the triazole and the enzyme and this is thought to be largely mediated by the side arm that binds to the apoprotein [27]. The large side arm group of itraconazole may facilitate close and tight binding between the triazole ring and the haem iron [34].

4. Mechanisms of resistance to itraconazole

Most commonly, triazole resistance results from point mutations in the gene encoding the target protein Cyp51A. However, a significant proportion of isolates with elevated itraconazole minimum inhibitory concentrations (MICs) do not have CYP51A mutations [35]. Other resistance mechanisms such as efflux pumps or up-regulation of target proteins may be important [35]. Infection with a triazole-resistant strain may theoretically develop via two potential mechanisms: *in vivo* selection within patients with chronic fungal infection who are exposed to triazoles for prolonged periods (months to years); or, primary infection with environmental strains with acquired resistance resulting from widespread use of agricultural azole compounds. The latter appears to especially be the case in the Netherlands and other countries in continental Europe [36]. Multiple resistance mechanisms have been documented in isolates from single patients receiving long-term itraconazole [37]. Recently, identified additional resistance mechanisms include induction of the alternative respiratory pathways, transporter genes that may affect drug efflux, transcriptional regulation of sterol biosynthesis genes and mutation in sterol-C5-desaturase (required for sterol synthesis) [38-41].

The first cases of itraconazole resistance in *A. fumigatus* were reported in the 1990s and characterised in laboratory animal models of disseminated aspergillosis [42]. Until recently, the true incidence of triazole resistance has remained largely undefined because many institutions do not routinely perform susceptibility testing of clinical *Aspergillus* isolates. A rapid screening method has been devised that uses an agar dilution technique [43]. Molecular assays have also been developed that enable the direct detection of resistance from clinical samples [44]. Resistant clinical isolates of *A. fumigatus* are now being reported in Europe, the USA, Canada, South America, China, Japan and India (Figure 3) [36,43-53]. Importantly, many isolates of *A. fumigatus* demonstrate cross-resistance to other triazoles, and this significantly limits therapeutic options by depriving patients of any effective orally bioavailable compounds [54]. MIC values for non-*fumigatus* species such as *A. niger*, *A. terreus* and *A. flavus* may be higher than for *A. fumigatus* [55], whether this translates to poorer clinical outcomes is not known. Triazole resistance in *A. terreus* and *A. flavus* caused by amino acid substitutions in Cyp51 has been recently reported [56,57].

In vitro susceptibility breakpoints for itraconazole against *Candida* spp. for mucocutaneous disease have been determined by the Clinical and Laboratory Standards Institute (CLSI), and are as follows: susceptible ≤ 0.125 mg/l, susceptible dose-dependent 0.25 – 0.5 mg/l and resistant > 1 mg/l. Breakpoints for itraconazole against *Aspergillus* spp. have not yet been determined by CLSI. Recently, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has set breakpoints for itraconazole against *Aspergillus* spp. [55]. These breakpoints are based on epidemiologic cut-off values and not supported by extensive pharmacodynamic

Figure 2. Reaction catalysed by 14- α -demethylase.Figure 3. Global distribution of reported resistant clinical *Aspergillus fumigatus* isolates.

or clinical data, neither of which is available. The current breakpoints are designed to ensure isolates that have a defined genetic mutation in CYP51 are classified as resistant. Breakpoints using EUCAST susceptibility testing methodology for itraconazole against *A. fumigatus* are ≤ 1 mg/l (susceptible), 2 mg/l (intermediate) and > 2 mg/l (resistant) [55]. The EUCAST MIC breakpoints for non-wild-type isolates are generally > 4 mg/l for the most commonly identified mutants (alterations at G54, G138, M220 and TR-L98H) with some variation depending on the underlying resistance mechanism. An *in vitro* pharmacodynamic study suggests these resistance mechanisms cannot be overcome with higher drug concentrations [58].

5. Pharmacokinetics

5.1 Population pharmacokinetics

The pharmacokinetics of itraconazole are highly variable (e.g., [59,60]). Some of this variability is related to erratic oral bioavailability. Itraconazole exhibits non-linear (or saturable)

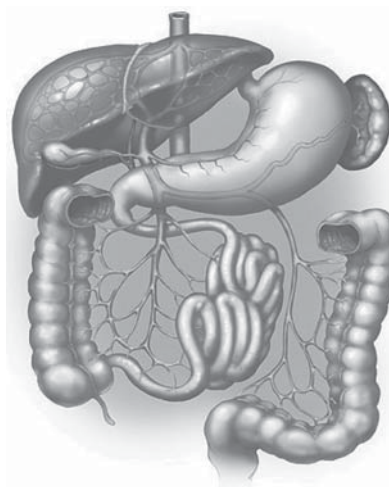
pharmacokinetics although this is not as well characterised as voriconazole [61]. Itraconazole exhibits prolonged terminal clearance and accumulates slowly. The terminal half-life is approximately 24 h and the time to steady state may be as long as 14 days [60]. While these estimates are of dubious value for a non-linear agent, they provide a guide for the time taken to develop serum concentrations that are likely to be therapeutic.

A number of population pharmacokinetic models have been developed to describe the pharmacokinetic of itraconazole in various patient populations including bone marrow transplant recipients, cystic fibrosis [62,63] and HIV-positive patients [64]. Some models have also estimated the pharmacokinetics of hydroxy-itraconazole. In the majority of cases, linear structural models have been used, simply because most datasets do not enable robust estimates for non-linear pharmacokinetics to be obtained (i.e., a single fixed regimen has been used making it difficult to characterise non-linear pharmacokinetic behaviour). The most significant consequence of non-linear

Distribution and elimination

Itraconazole is highly protein bound in systemic circulation and levels in aqueous body fluids (e.g., CSF, eye, saliva) are low. Excretion is chiefly through hepatic oxidation to produced active and inactive metabolites

Approximately 50% of the drug is removed by first pass metabolism in the liver and intestinal lumen resulting in a maximal oral bioavailability of approximately 50%. The terminal elimination half-life of itraconazole after a single oral dose is approximately 24 hours and 14 hours for the active hydroxy-metabolite. A small amount (3 – 18%) of itraconazole is excreted unchanged in the faeces. In some tissues (e.g., vaginal mucosa, skin and nails) concentrations of itraconazole are 2 – 10 fold higher than plasma concentrations

**Gastric dissolution**

Itraconazole is high lipophilic and a weak base making it virtually insoluble in water and ionised only at low pH-. Sufficient dissolution in the stomach after oral administration is therefore important and dependent upon gastric pH (necessitating administration with acidic food/drinks) and gastric emptying rate (necessitating administration with food)

Intestinal absorption

Plasma membrane transporters and metabolic enzymes within intestinal enterocytes act on itraconazole. The luminal drug transporter P-glycoprotein (P-gp) and cytoplasmic enzyme CYP3A4 act as a co-ordinated non-specific "detoxification" mechanism that transport and metabolise many xenobiotics from the enterocyte cytoplasm. Itraconazole is both an inhibitor and substrate of P-gp and CYP3A4

Figure 4. Summary of the pharmacokinetic characteristics of itraconazole.

pharmacokinetics is the rapid accumulation of drug in those patients with saturated clearance mechanisms.

5.2 Absorption

The absorption of itraconazole capsules is facilitated by an acidic environment, which is the basis for recommendations for administration with food or acidic soft drinks [65]. The oral bioavailability of itraconazole capsules doubles when administered after food [61,66]. Conversely, absorption is impaired by co-administration with agents that reduce gastric acidity (e.g., proton pump inhibitors), and in achlorhydria (or hypochlorhydria) that is frequently associated with critical illness. There is no food effect with the oral suspension, and oral bioavailability increases in the fasted state [67].

5.3 Metabolism

Itraconazole is predominantly metabolised via the CYP isoenzyme CYP3A4 with the production of an active metabolite, hydroxy-itraconazole. Other metabolites include keto-itraconazole and *N*-dealkyl-itraconazole [68]. Hydroxy-itraconazole, the only biologically active metabolite, has antifungal potency that is comparable with the parent compound. Concentrations of hydroxy-itraconazole are approximately double those of the parent compound [61].

5.4 Disposition

The volume of distribution is approximately 11 l/kg or 700 – 800 l for an average adult [60]. Such a large volume suggests extensive distribution into tissues.

5.5 Excretion

Systemically available itraconazole undergoes extensive oxidative metabolism to form a large number of metabolites, which

are subsequently excreted in the bile [60]. Approximately 3 – 18% of itraconazole (non-absorbed) is passed unchanged in the faeces and none is found in the urine [60,69].

5.6 Tissue pharmacokinetics

The penetration of itraconazole into non-inflamed aqueous compartments (e.g., cerebrospinal fluid (CSF) and aqueous humour) is negligible [70,71]. In the presence of inflammation, drug concentrations may be significantly higher. For example, itraconazole concentrations in the aqueous humour of the inflamed eye increase from virtually 0 to ~ 50% of concomitant serum concentrations [70].

Studies in both laboratory animals and humans consistently report very low concentrations of itraconazole within the CSF [71-73]. Despite this observation, itraconazole clearly has clinically relevant antifungal activity within the CNS. Both itraconazole and hydroxy-itraconazole penetrate the cerebral parenchyma in laboratory animal models of fungal infection [74], but there is a relative paucity of data compared with other agents. Much of the clinical efficacy of itraconazole for CNS infections likely reflects adequate drug concentrations in the cerebrum and meninges rather than the CSF. Itraconazole possesses high affinity to keratin and accumulates in the stratum corneum or the skin [75]. Dosages of 100 – 200 mg are associated with tissue concentrations in the sebum and stratum corneum that exceed corresponding plasma concentrations by up to 10-fold. Itraconazole concentrations persist in the skin for 3 – 4 weeks after cessation of antifungal therapy [76]. Both itraconazole and hydroxy-itraconazole penetrate various sub-compartments of the lung of healthy volunteers, including epithelial lining fluid and pulmonary alveolar macrophages (PAMs) [77]. Concentrations

in PAMs are four to five times higher than those achieved in serum, although the clinical relevance of this finding is not known [77].

6. Drug–drug interactions

Drug–drug interactions occur via several different mechanisms and are an important consideration for the safe and effective use of itraconazole. Agents that inhibit gastric acid secretion, such as antacids, proton pump inhibitors and H₂-antagonists all reduce the absorption of itraconazole capsules, these agents should be stopped if at all possible. At the very least, adequate absorption should be verified and an alternative formulation or antifungal agent used if concentrations are low or undetectable. Itraconazole metabolism is accelerated by concomitant administration of rifampicin, phenytoin and carbamazepine, which potentially results in an inability to achieve therapeutic serum concentrations [78]. Such a scenario is frequently seen in patients with chronic pulmonary aspergillosis who also have atypical mycobacterial infection that requires a rifampicin-containing regimen. In addition, many clinically significant interactions relate to the suppression of intra- and extrahepatic CYP activity by itraconazole that leads to higher exposures of agents that are metabolised via this route. Itraconazole-induced inhibition of vincristine metabolism may result in neuropathy that produces neurological impairment and SIADH (syndrome of inappropriate antidiuretic hormone) [79]. Itraconazole is also a potent inhibitor of cyclosporine and tacrolimus metabolism.

In addition, itraconazole prolongs the action of benzodiazepines, digoxin, statins and warfarin [80–83]. Of note, digoxin metabolism does not occur via oxidative mechanisms, but rather through inhibition of P-glycoprotein-mediated secretion within the renal tubules [81]. Interactions between itraconazole and both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have recently been reported. Co-administration of NNRTIs with itraconazole results in sub-therapeutic itraconazole concentrations [84,85]; whereas, co-administration with PIs results in elevated itraconazole levels necessitating dose modification [86].

Interactions between itraconazole and corticosteroids vary from compound to compound. Itraconazole significantly increases methylprednisolone concentrations, but interactions with prednisolone appear minor and do not result in suppression of the adrenal axis [87,88]. Itraconazole also markedly decreases clearance of dexamethasone and enhances adrenal suppression [88]. Interactions with inhaled steroids have also been reported, in particular with budesonide and fluticasone and this may be an important consideration for the treatment of allergic fungal disease [89]. In a small series of 25 patients receiving itraconazole and inhaled budesonide, approximately 45% of patients developed clinically significant adrenal suppression [90].

7. Pharmacodynamics

The pharmacodynamics of itraconazole have been characterised in a well-validated rabbit model of invasive pulmonary aspergillosis [91]. Concentrations of itraconazole 6 mg/l (measured 2 h post dose by bioassay) are associated with near-maximal reduction in pulmonary fungal burden when estimated using log₁₀CFU/g lung [91]. Similarly, a concentration of 3.72 mg/l (again measured 2 h post dose by bioassay) is associated with half-maximal reduction in fungal burden. The implication of these results for humans are slightly difficult to interpret because the usual clinical measure of drug exposure in clinical settings is a trough concentration measured using high-performance liquid chromatography (HPLC). The conversion of drug concentrations estimated by HPLC and bioassay is possible [92], but is only valid if the ratio of active compounds measured by these two assays is constant. Bioassay:HPLC ratios have been shown to vary significantly between laboratories and therefore standardised conversion formulae may not be valid and must be established locally [93].

In clinical studies, steady-state trough concentrations of 0.25 mg/l (measured by HPLC) were initially considered sufficient for the prevention of invasive fungal infections in neutropenic patients [94]. Subsequently, higher trough concentrations of 0.5 mg/l were proposed on the basis of MICs of itraconazole against *Aspergillus* spp. [95]. Adequate trough concentrations required for the successful treatment of confirmed infection have not been formally defined in the majority of endemic fungal pathogens against which itraconazole is active. In one open-label multicentre study, itraconazole concentrations of > 5 mg/l (estimated using bioassay) were associated with improved survival of patients with invasive aspergillosis [96], although itraconazole is no longer considered a first-line agent in this condition (see below). Trough concentrations > 0.5 mg/l are associated with improved clinical outcomes for patients with mucocutaneous disease [97].

8. Clinical use and efficacy

8.1 Prevention of invasive fungal infections in immunocompromised patients

The clinical uses and recommended regimens for itraconazole are summarised in Table 1. Oral itraconazole (capsule or oral suspension) is licensed for the prevention of fungal infection in the presence of HIV or prolonged neutropenia where invasive mould infections are likely (fluconazole, the commonly used alternative oral agent, is not active against *Aspergillus* spp.). The safety and efficacy of itraconazole for the prevention of invasive fungal infections has been extensively studied. Much of the early clinical experience was inconclusive because the trials were not powered to detect any difference in mortality. Nevertheless, a meta-analysis of 3597 patients from 13 clinical trials demonstrated that itraconazole prevents invasive fungal infections and is also associated with decreased

Table 1. Clinical indications and dosing regimens.

Diagnosis	Dose and duration
Mucocutaneous candidiasis and dermatophyte infections	Candidiasis (vulvovaginal): 200 mg b.i.d. for 1 day and Tinea corporis, tinea cruris and pityriasis versicolor: 200 mg b.i.d. for 7 days Tinea pedis/manuum: 100 mg o.d. for 30 days or 200 mg b.i.d. for 7 days Onychomycosis: 200 mg o.d. for 3 months or pulse therapy (200 mg twice daily for 7 days repeated after 21 days)
Oropharyngeal candidiasis	Oral solution 200 mg o.d., continued for 7 – 14 days after clinical resolution
Prophylaxis in HIV and neutropenia due to haematological malignancy or bone marrow transplantation	200 mg o.d., increased to b.i.d. if proven low circulating levels Oral solution 5 mg/kg daily in 2 divided doses continued until neutrophil count or CD4 count recovers
Chronic pulmonary aspergillosis	200 mg o.d. or b.i.d., usually lifelong treatment required
Allergic bronchopulmonary aspergillosis	200 mg b.i.d. for 4 – 6 months followed by 4 – 6 months tapered dose, longer course if relapses occur
Blastomycosis	200 mg t.i.d. for 3 days and then o.d. or b.i.d. for 6 – 12 months
Sporotrichosis	Lymphocutaneous disease: 200 mg o.d. for 2 – 4 weeks after clinical resolution (usually 3 – 6 months) Osteoarticular/non-life-threatening pulmonary disease: 200 mg b.i.d. for at least 12 months
Histoplasmosis	Mild-to-moderate acute pulmonary histoplasmosis and 'step-down' therapy for severe disease: 200 mg t.i.d. for 3 days and then 200 mg b.i.d. for 6 – 12 weeks Chronic cavitary pulmonary histoplasmosis: 200 mg t.i.d. for 3 days and then 200 mg o.d. or b.i.d. for at least 1 year
Coccidioidomycosis	Oral 200 mg b.i.d. or t.i.d. continued until clinical resolution (often months-years)
<i>Penicillium marneffei</i>	Consolidation therapy in severe disease: 200 mg b.i.d. for 10 weeks Mild-to-moderate disease: 200 mg b.i.d. as monotherapy for 8 weeks then 200 mg o.d. until CD4 count are > 100/ μ l for over 6 months

fungal-associated mortality [19]. Importantly, the protective benefit of itraconazole is likely related to the greater systemic drug exposure that is achieved with the oral suspension. The protective benefit is only present with the use of itraconazole suspension as opposed to the capsule formulation. More recently, there have been a number of well-designed and appropriately powered clinical trials comparing itraconazole with fluconazole [98,99]. These trials suggest that itraconazole is an effective agent for preventing mould infections, but that adverse events including gastrointestinal intolerance and deranged liver function tests are frequently seen. Itraconazole is still used in some institutions, principally because it is cheaper than other newer triazoles. Itraconazole does, however, alter the kinetics of a number of commonly used immunosuppressive and antineoplastic agents such as cyclophosphamide [100] and vincristine. Itraconazole oral solution enhanced vincristine neurotoxicity in five patients with malignant lymphoma [101]. To avoid an interaction with cyclophosphamide, itraconazole is generally only used in the initial phase of neutropenia in haemopoietic stem-cell transplant recipients [102,103].

8.2 Acute invasive aspergillosis

Invasive aspergillosis remains a significant public health problem. The development of itraconazole was a significant advance for the management of invasive aspergillosis because it provided an orally bioavailable alternative to amphotericin B deoxycholate. There are only limited data supporting the use of itraconazole for primary treatment of invasive aspergillosis, and no randomised clinical trials. Itraconazole

600 mg/day for 4 days followed by 400 mg/day appears effective for treatment of invasive aspergillosis [96] although diagnostic criteria and criteria for clinical response have changed over the past 20 years making comparisons with current agents somewhat difficult. Itraconazole (i.v. followed by oral capsules) is effective as salvage therapy for invasive pulmonary aspergillosis in a variety of clinical settings including profoundly immunocompromised patients, chronic granulomatous disease and AIDS [3].

8.3 Chronic pulmonary aspergillosis

Chronic pulmonary aspergillosis is a debilitating infection with significant 5-year mortality [104]. The pathogenesis is distinct from acute invasive disease and involves the colonisation of pre-existing cavities by *Aspergillus* spp. Patients frequently require lifelong antifungal therapy. Itraconazole is frequently used as a first-line agent [104] and does appear to penetrate into fungal balls [105]. Capsules or oral suspension can be used; the limitations of these formulations include difficulties in achieving therapeutic drug concentrations and poor tolerability, respectively. Resistance to itraconazole has been documented following long-term therapy, and this usually mandates use of an alternative antifungal agent [51].

8.4 Dermatophyte infections and mucocutaneous candidiasis

Prolonged or intermittent courses of oral itraconazole are used in the treatment of widespread dermataceous skin and nail infections. Most commonly, itraconazole is prescribed for

recalcitrant onychomycosis. Pulse therapy (200 mg b.i.d. for 1 week of each month with 3 weeks off between consecutive pulses) has been shown to have equivalent efficacy and improved tolerability when compared with continuous therapy. Generally, 2 and 3 months of therapy are required for fingernail and toenails, respectively [106-108]. Itraconazole is used for oropharyngeal and oesophageal candidiasis, most commonly in patients with fluconazole-refractory disease. Oral itraconazole solution is recommended at a dosage of 200 mg daily continued until disease resolution and for 7 – 14 days after clinical improvement [109].

8.5 Endemic fungi

Itraconazole is a first-line agent for the treatment of many endemic mycoses including blastomycosis, sporotrichosis, histoplasmosis and coccidioidomycosis. While oral itraconazole is reasonably inexpensive it is not universally available, particularly in the developing world.

Sporothrix schenckii isolates are, in general, highly sensitive to itraconazole [7]. Itraconazole is a first-line agent for the treatment of both localised and disseminated sporotrichosis. For lymphocutaneous sporotrichosis oral itraconazole 200 mg daily is recommended to be given for 2 – 4 weeks after all lesions have resolved (typically a total of 3 – 6 months therapy is required). Dosage escalation may be appropriate in patients who fail to respond. Prolonged oral therapy (at least 12 months) of itraconazole 200 mg b.i.d. is recommended for osteoarticular and non-life-threatening pulmonary disease [8,110].

Similarly, itraconazole is the treatment of choice for mild-to-moderate pulmonary and disseminated blastomycosis caused by *Blastomyces dermatitidis*. Treatment regimens of 200 – 400 mg for 8 – 12 months have historically been used with efficacy in ~ 90% of patients [10]. Doses of 200 mg 3 times per day for 3 days and then once or twice per day for 6 – 12 months, are now recommended [11]. Patients with severe life-threatening or CNS disease should receive liposomal amphotericin B for 1 – 2 weeks (or longer guided by clinical improvement) followed by itraconazole 'step-down' therapy (usually 400 mg for at least 12 months).

Itraconazole is a first-line agent for the treatment in histoplasmosis caused by *Histoplasma capsulatum* and *capsulatum* var. *duboisii*. Oral itraconazole 200 mg t.i.d. for 3 days and then 200 mg b.i.d. for 6 – 12 weeks is recommended for mild-to-moderate acute pulmonary histoplasmosis and as 'step-down' therapy for severe disease. Prolonged therapy (at least 1 year) is required for chronic cavitary pulmonary histoplasmosis [111].

Where active treatment is required itraconazole is a first-line agent in the management of coccidioidomycosis (i.e., in patients with extensive spread of infection or who are at high risk of complications, e.g., because of immunosuppression) [112]. Therapy often ranges from many months to years in duration and should be directed by clinical response. In some patients, lifelong antifungal therapy is needed to prevent relapses. Itraconazole may be superior for the treatment of

skeletal lesions [10]. Measurement of drug concentrations is recommended, though target therapeutic drug concentrations are extrapolated from data acquired from other clinical contexts [10].

8.6 Cryptococcal meningitis

Itraconazole has potent *in vitro* activity against *C. neoformans*, and is effective in laboratory animal models of cryptococcal meningitis [71]. The efficacy of itraconazole for the prevention of cryptococcal meningitis in patients with AIDS has been studied in Thailand where there are additional concerns regarding *Penicillium marneffei* [113]. In this context, itraconazole appears effective, although it is not widely used for this indication. Itraconazole is not used for induction therapy (polyenes alone or in combination with flucytosine are generally used for this purpose), although there is some evidence that itraconazole 200 mg b.i.d. – 200 mg t.i.d. (depending on serum concentrations) is effective [114]. Similarly, itraconazole is generally not used for consolidation therapy. A trial comparing fluconazole and itraconazole, 200 mg daily, for consolidation therapy was stopped early because of the higher rate of relapse in the itraconazole arm (23 vs 4%; $p = 0.006$) [115]. A dose of 200 mg/day is now considered to be low, especially if there is suboptimal absorption, which is frequently the case in the setting of HIV/AIDS. In contrast, however, itraconazole 200 mg b.i.d. following a loading dose of 600 mg/day for 3 days has been used successfully in another clinical trial of cryptococcal meningitis [116].

Collectively, therefore, itraconazole is not used as first-line agent for either induction or maintenance therapy for cryptococcal meningitis [117]. The potential reasons that may account for suboptimal clinical outcomes despite demonstrated *in vitro* and *in vivo* activity include sub-therapeutic systemic drug exposure, suboptimal penetration into the CSF, reduced *in vitro* susceptibility of some isolates and the use of relatively low dosages (e.g., 200 mg daily) given the reduced absorption of orally administered itraconazole in HIV/AIDS [114].

8.7 *Penicillium marneffei*

Disseminated infections caused by *P. marneffei* in HIV-positive patients with AIDS is usually treated with amphotericin B deoxycholate (0.6 mg/kg) for 2 weeks followed by oral itraconazole 400 mg/day for 10 weeks. For mild disease itraconazole 400 mg/day as monotherapy for 8 weeks can be used, followed by maintenance therapy with 200 mg/day to prevent relapse until CD4 counts are > 100/μl for over 6 months [118]. Treatment with itraconazole alone has also been shown to be effective for all forms of infection, but is associated with a marginally higher rate of relapse [13]. Itraconazole is erratically absorbed in patients with AIDS patients who have variable gastric pH [119]. Furthermore, there is limited information on the pharmacokinetics of generic formulations of itraconazole that are widely used in South East

Asia. The efficacy and pharmacokinetics of itraconazole for penicilliosis are currently being studied.

8.8 Allergic fungal syndromes (asthma and ABPA)

Itraconazole is increasingly used for the treatment of allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS) [120]. In patients with ABPA, the use of itraconazole is associated with improved disease control and reduced doses of corticosteroids [121]. In SAFS, itraconazole (200 mg twice daily) results in significant improvements in quality of life and a trend towards improved respiratory function (as indicated by spirometry) and rhinitis symptoms. Clinicians must be wary of potential interactions with inhaled and oral steroids (see above). The optimal duration of therapy remains to be defined and relapse following discontinuation of therapy is common.

9. Use in special populations

9.1 Neonates and children

There are relatively limited data describing the use of itraconazole in infants and older children. A single intravenous or oral dose of itraconazole solution of 2.5 mg/kg day in children aged 7 months to 17 years is well tolerated, but results in considerable variability in drug exposure and trough concentrations < 0.5 mg/l measured using HPLC [122]. An oral dosage of 5 mg/kg day results in lower concentrations in infants compared with children > 2 years of age [123]. Oral itraconazole solution given 2.5 mg/kg twice daily is effective for treatment of oropharyngeal candidiasis in HIV-positive children [124], and for prevention of invasive fungal infection in children with neutropenia [125].

9.2 Renal insufficiency

Limited data are available on the use of oral itraconazole in patients with renal impairment. A pharmacokinetic study using a single 200 mg dose of i.v. itraconazole in 19 patients with renal impairment (uraemia: $n = 7$; haemodialysis: $n = 7$ and continuous ambulatory peritoneal dialysis: $n = 5$) suggested no significant effect of haemodialysis or peritoneal dialysis on the pharmacokinetics of itraconazole [126]. In moderate-to-severe uraemia (mean creatinine clearance of 13 ml/min/1.73 m²) AUCs were slightly reduced compared with estimates obtained from patients with normal renal function. Renal accumulation of cyclodextrin is seen in laboratory animal studies [16]. Therefore, use of the i.v. formulation is not recommended in setting of renal impairment although the clinical implications of cyclodextrin accumulation in humans are not well understood.

9.3 Hepatic insufficiency

Itraconazole is predominantly hepatically metabolized. Patients with impaired hepatic function receiving itraconazole require assiduous monitoring. A pharmacokinetic study using a single oral dose of 100 mg daily in cirrhotic subjects

demonstrates an increase in the elimination half-life compared with healthy volunteers (37 ± 17 vs 16 ± 5 h, respectively) [127]. Careful consideration should be given to the prolonged elimination half-life when dosing itraconazole in this setting.

10. Adverse events and toxicodynamics

Toxicodynamic relationships have recently been described [128]. A mean serum concentration of 17.1 mg/l (measured by bioassay) splits a population of patients into two groups each with a high and low probability of toxicity. Thus, a mean concentration of 17.1 mg/l provides a useful upper limit for therapeutic drug monitoring (TDM) and can be used to minimise the probability of toxicity.

Itraconazole is generally reasonably well tolerated, although this is dependent on the formulation that is used. The adverse events from 9065 patients enrolled in all clinical studies published in 1987 – 2008 are summarised in Table 2. Gastrointestinal symptoms occur in ~ 20% of patients, which has a significant impact on compliance [128]. Cardiac failure is a serious, albeit relatively uncommon adverse event [129,130]. In some cases, reversible depressed left ventricular function has been documented with echocardiography [130]. The mechanism is unknown. More commonly, itraconazole causes isolated peripheral oedema that is reversible with cessation of drug. Itraconazole can cause hepatic inflammation, which may manifest as a hepatic or obstructive pattern, or on occasions a mixed picture. Rare cases of acute hepatic failure have been described, which usually results from persistent use of itraconazole despite laboratory or clinical evidence of underlying drug-induced hepatic inflammation [131]. A non-puritic maculopapular rash is seen in 2 – 5% of cases [106,128]. Higher incidences reported in earlier studies may relate to the use of itraconazole in the setting of HIV/AIDS where rash and hypersensitivity are common. Hair loss may be marked but is generally reversible with cessation of the drug. A range of neurological symptoms have also been described, including headache, sensorimotor peripheral neuropathy, tremor and sleep disturbance. Peripheral neuropathy occurs in ~ 10% of patients treated with long-term itraconazole and can persist for several months after discontinuation [132]. A range of metabolic and/or endocrinological disturbances have also been documented, including isolated reversible hypo- and hyperkalaemia, hyponatraemia, Cushing's syndrome (in association with corticosteroids) and hypercholesterolaemia (Table 2) [133]. Consequently, blood pressure, electrolytes and a lipid profile should be checked during therapy.

11. Measurement of itraconazole, TDM and safe use

Itraconazole concentrations in serum and tissues can be measured by mass spectrometry, HPLC or bioassay [92,134]. A bioassay measures both itraconazole and its bioactive

Table 2. Frequency of adverse events with itraconazole from published data 1987 – 2008.

Adverse events	Cumulative data n = 9065
<i>Gastrointestinal</i>	
GI upset*	1658
Abnormal liver function tests [†]	416
Structural liver change	1
<i>Renal</i>	
Renal impairment [‡]	43
Polyuria/urinary frequency	7
<i>Metabolic disturbance</i>	
Hypokalaemia	202
Hypertriglyceridaemia/hypercholesterolaemia	18
Hypomagnesaemia	14
Hyponatraemia	10
Hyperkalaemia	8
Elevated uric acid	7
<i>Cutaneous</i>	
Rash/pruritus	250
Alopecia	19
Site reaction/vasculitis	4
Steven–Johnson syndrome	2
Hirsutism	1
Photosensitivity	1
Diaphoresis	1
<i>Psychiatric/neurological</i>	
Headache	111
Cognitive/mood/sleep disturbance [¶]	24
Dizziness	22
Taste disturbance	15
Seizure	8
Tinnitus	4
Visual disturbance [#]	4
Peripheral neuropathy	2
Tremor	6
Leg weakness	1
<i>Cardiovascular</i>	
Hypotension	87
Peripheral oedema	39
Dyspnoea	35
Hypertension	23
Arrhythmia/bradycardia/palpitations	21
<i>Haematological</i>	
Leukocytopenia	71
Anaemia	52
Thrombocytopenia	15
Eosinophilia	2
<i>Endocrine</i>	
Hyperglycaemia	3
Thyroid dysfunction	1
Sexual dysfunction**	16
Menstrual disturbance	15

*Including abdominal pain, nausea, vomiting, diarrhoea, constipation.

[†]Including increased alanine transaminase, aspartate transaminase, alkaline phosphatase, bilirubin, lactate dehydrogenase.

[‡]Including increased creatinine, blood urine nitrogen, proteinuria.

[¶]Including euphoria, depression, disturbed concentration, insomnia, hypersomnia, fatigue.

[#]Including photophobia and blurred vision.

**Including impotence and reduced libido.

metabolite hydroxy-itraconazole, while mass spectroscopy and HPLC measures enable concentrations of these species to be separately quantified. The inability to separate the biological effect attributable to the parent compound versus that from the active metabolite means that itraconazole concentrations measured by bioassay are typically 2 – 10 times higher than those estimated using HPLC. Thus, clinicians interpreting itraconazole serum concentrations must be aware of the laboratory method that has been used.

Pharmacodynamic and toxicodynamic relationships have been defined for itraconazole. TDM is widely advocated for optimising drug exposure [135]. In addition, TDM allows compliance to be assessed, as well as enabling modification of dosing, formulation and administration with food or acidic beverages. Data from clinical trials suggest a reasonable lower therapeutic target for steady-state trough itraconazole levels is 0.5 mg/l measured by HPLC [135]. When measured by bioassay, a reasonable lower limit for TDM is approximately 5 mg/l [135]. Lower target levels may be required in highly sensitive pathogens such as *H. capsulatum*, but these have not been formally defined. An upper therapeutic limit of 17.1 mg/l measured by bioassay is likely to optimally limit toxicity [128]. No upper limit has been formally defined for concentrations measured using HPLC.

12. Expert opinion

The broad-spectrum antifungal activity of itraconazole and the availability of both oral and intravenous formulations mean that this agent continues to be potentially useful for a wide range of clinical settings. Problematic drug interactions, relatively poor tolerability and increasing reports of triazole resistance have meant that alternative antifungal agents have largely superseding itraconazole in some common clinical situations. Furthermore, many newer antifungal compounds have been studied in a more rigorous manner, meaning that the evidence base to support their use is often significantly greater than is the case for itraconazole. Nevertheless, excessive costs of newer agents often mean that the use of itraconazole is considered, especially in resource-poor settings.

Itraconazole remains a key agent for the management of chronic and allergic aspergillosis, as well as in the treatment of endemic mycoses worldwide, where the broad spectrum of activity and availability of both an intravenous and oral form mean that long-term usage is affordable and practical. Optimised dosing regimens in many of these settings have not been formally defined for itraconazole and this is an important area of active research. In addition, the limited availability of intravenous itraconazole in many countries is problematic and means that clinical experience and trials exploring the potential utility of parenteral itraconazole have not been adequately explored. There has been a progressive understanding of several adjunctive factors that facilitate the clinical use of itraconazole. The pharmacokinetic variability of itraconazole and numerous potential drug interactions

Table 2. Frequency of adverse events with itraconazole from published data 1987 – 2008 (continued).

Adverse events	Cumulative data n = 9065
Gynaecomastia	5
Weight gain	3
Breast tenderness	1
Pathological fracture	1
Symptomatic adrenal suppression	1
Striae/bruising	1
Systemic/other	
Fever/rigours	75
Malaise/fatigue/myalgia	19
Rhabdomyolysis	3
Pancreatitis	1

*Including abdominal pain, nausea, vomiting, diarrhoea, constipation.

[‡]Including increased alanine transaminase, aspartate transaminase, alkaline phosphatase, bilirubin, lactate dehydrogenase.

[§]Including increased creatinine, blood urine nitrogen, proteinuria.

[¶]Including euphoria, depression, disturbed concentration, insomnia, hypersomnia, fatigue.

[#]Including photophobia and blurred vision.

^{**}Including impotence and reduced libido.

mean that TDM is now widely accepted to be clinically necessary in order to achieve systemic drug exposures that are safe and effective. Further work is needed to establish clear drug target levels, in particularly in the treatment of endemic mycoses.

Itraconazole resistance and azole cross-resistance have until recently been considered rare. With increased awareness of the

potential emergence of azole cross-resistance, however, surveillance studies have reported increasing incidence of itraconazole resistance. Routine *in vitro* susceptibility testing for *Aspergillus* spp., and the use of molecular techniques to directly detect resistance mechanisms are now becoming routine practice and are likely to facilitate the optimal use of itraconazole. The values standardisation of internationally agreed interpretive epidemiological cutoff and clinical breakpoints will result in improved resistance reporting and surveillance. Mechanistic studies that examine the altered molecular interactions of azoles with fungal 14- α -demethylase resulting from mutations conveying resistance may provide targets for novel azole drugs and therapeutic strategies for overcoming resistance. Finally, itraconazole is a compound that can be reformulated to maximise oral bioavailability, promote tissue penetration and enable use of alternative routes of administration.

Declaration of interest

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