# Voriconazole—a new therapeutic agent with an extended spectrum of antifungal activity

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## ABSTRACT

Voriconazole is a new antifungal agent that can be given orally and intravenously. It has proven efficacy for treating candidosis and invasive aspergillosis as well as other mould infections, such as those caused by *Fusarium* and *Scedosporium* spp. The drug is generally well tolerated.

**Keywords** Voriconazole, antifungal treatment, invasive fungal infection

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## INTRODUCTION

Voriconazole was discovered in the late 1980s. The discovery process was started with the idea of developing an antifungal agent with a spectrum of activity beyond that of fluconazole. Like fluconazole, voriconazole belongs to the triazole class of drugs (Fig. 1). It is relatively insoluble in water, so the intravenous formulation contains voriconazole in a sulphobutylether β-cyclodextrin (SBECD) solute to allow for parenteral administration.

The clinical development programme included the largest-ever randomised controlled trial in the treatment of invasive aspergillosis. The findings of this trial demonstrate the significantly superior efficacy of a clinical regimen that starts with voriconazole, over standard therapy starting with amphotericin B deoxycholate.

## MECHANISM OF ACTION

Voriconazole selectively inhibits the fungal cytochrome P450-dependent enzyme 14α-sterol demethylase, thereby interrupting an essential step in ergosterol biosynthesis (Fig. 2). The drug is about

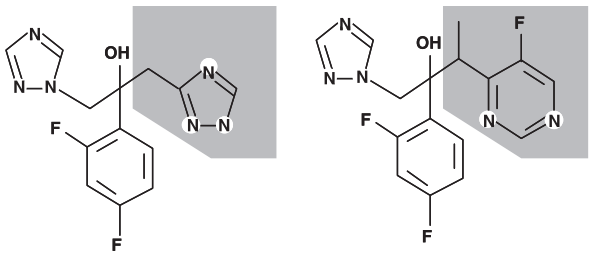


**Fig. 1.** Structural relationship between voriconazole and fluconazole.

250-fold more active against the fungal demethylase enzyme than against mammalian P450-dependent steroid hormone biosynthesis [1].

## SPECTRUM OF ACTIVITY

Voriconazole exhibits broad-spectrum activity at concentrations of ≤1 mg/L against the more common fungal pathogens such as *Candida* spp. (including fluconazole-resistant *C. krusei*) and is fungicidal to *Aspergillus* spp. as well as to *Scedosporium* and *Fusarium* spp. and certain other moulds (Fig. 3). The drug also exhibits good activity against less-common clinical isolates, including *Acremonium*, *Alternaria*, *Bipolaris*, *Cladophialophora*, *Curvularia* and *Chrysosporium* spp. [2], as well as the dimorphic fungi *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Coccidioides immitis* [3]. Voriconazole has little activity

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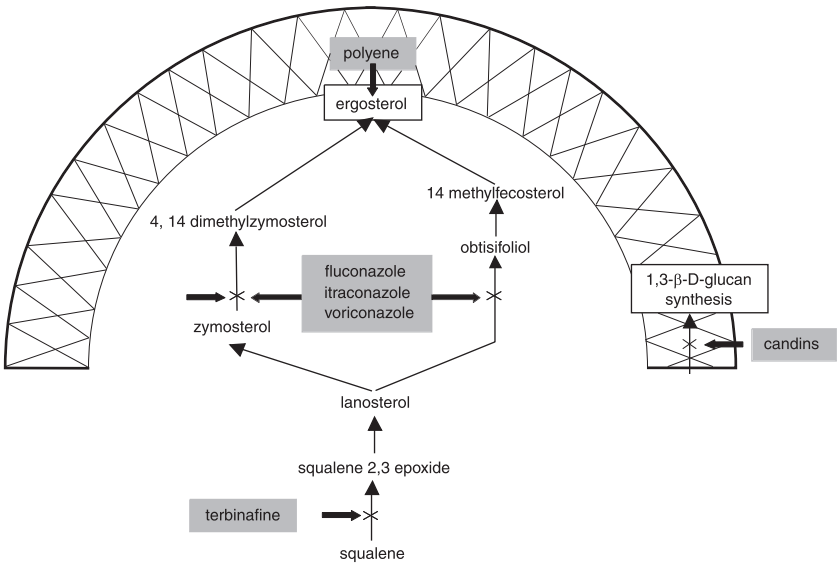


**Fig. 2.** Mode of action of antifungal agents.

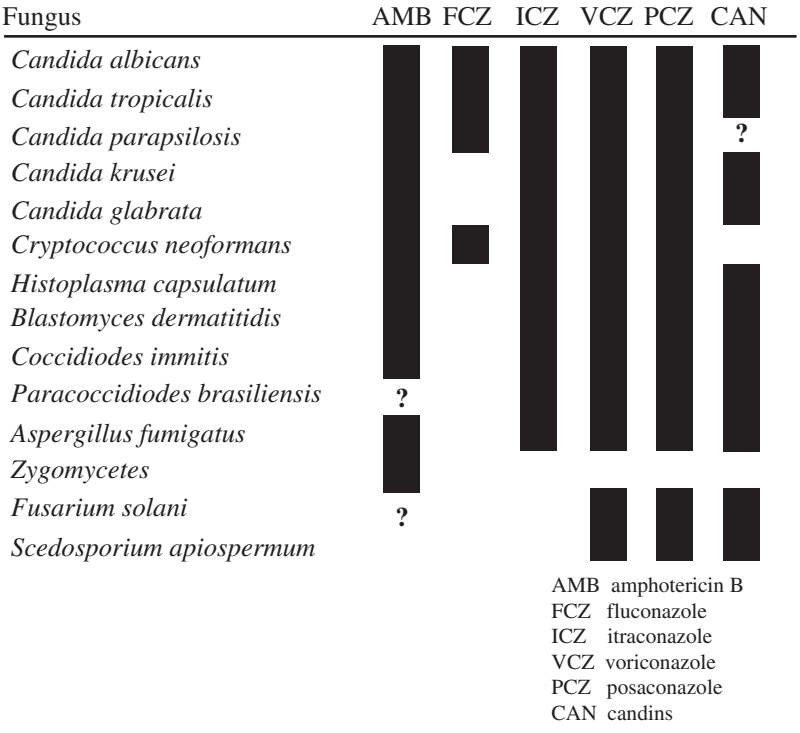


**Fig. 3.** Comparative spectrum of activity in-vitro of antifungal agents.

against *Sporothrix schenckii* [4] and the zygomycetes, such as *Mucor*, *Rhizopus* and *Absidia* spp. [2].

Correlating in-vitro activity with clinical outcome remains elusive because host factors other than pathogen susceptibility are involved. Breakpoints for voriconazole have yet to be established.

## PHARMACOKINETIC PROPERTIES

The pharmacokinetics of voriconazole are nonlinear, which leads to a greater than proportional increase in exposure with increasing dose. For instance, increasing the oral dose from 200 mg to 300 mg twice daily leads to a 2.5-fold increase in the area under the plasma

concentration-time curve (AUC). While there is a low intrapatient variability in plasma concentrations, the interindividual variability of voriconazole pharmacokinetics is high. Population pharmacokinetic data from therapeutic trials have revealed no association between plasma concentration and clinical outcome. The terminal half-life of voriconazole is dose dependent and is not predictive of its accumulation or elimination.

### Absorption

Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations being achieved 1–2 h after dosing. The oral bioavailability of voriconazole is estimated to be 96%, which may permit switching between intravenous (IV) and oral formulations when clinically appropriate. Absorption is not affected by changes in gastric pH. As the presence of high-fat food affects voriconazole absorption, oral voriconazole should not be taken within 1 h of a meal.

### Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58% and is independent of dose or plasma concentrations. The drug is also detectable in cerebrospinal fluid samples (data on file).

### Metabolism

In-vitro studies showed that voriconazole is metabolised by the hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. The isoenzyme CYP2C19 exhibits genetic polymorphism with 15–20% of Asian populations being poor/slow metabolisers [5], whereas the prevalence is much lower (3–5%) amongst Caucasians and Blacks. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on average, four-fold higher voriconazole AUC than homozygous extensive metabolisers, while the AUC of heterozygous extensive metabolisers is two-fold higher than that of homozygous extensive metabolisers.

The major metabolite of voriconazole is the N-oxide, which has negligible antifungal activity and accounts for 72% of the circulating radiolabelled metabolites in plasma. In all, metabolism produces at least eight compounds without clinically significant antifungal activity.

### Excretion

Approximately 80% of a single, radiolabelled dose of voriconazole is excreted in the urine, almost completely as metabolites. Less than 2% of the dose is excreted in the urine as unchanged drug. The majority (> 94%) of the total radioactivity is excreted in the first 96 h after both oral and intravenous dosing. Approximately 20% of the drug is excreted in the faeces.

## CLINICAL STUDIES OF EFFICACY

The strategy of evaluating the efficacy and safety of voriconazole for treating aspergillosis and candidiasis was rewarded by the drug being licensed for these indications. In addition, the results obtained from a study of documented invasive fungal infections with no approved antifungal therapy, or infections that were refractory to approved therapy (due to treatment failure or intolerance of therapy), and from compassionate use programmes indicate that voriconazole is an important therapeutic option for treating predominantly fatal infections caused by other less common moulds, including *Fusarium* and *Scedosporium* spp.

### Aspergillosis

An open, noncomparative study of 116 patients with invasive aspergillosis resulted in an overall efficacy of 48% (56 complete/partial responses) [6]. Fifty (60%) of the 84 patients with pulmonary infection responded well to treatment with voriconazole, 6 mg/kg twice a day on the first day, followed by 3 mg/kg twice daily for 6–27 days and 200 mg twice daily, given orally for up to 24 weeks. The results obtained in this population, which comprised newly diagnosed as well as previously treated patients, compared favourably to those achieved previously with other drugs [7–11]. Admittedly, differences in patient and disease characteristics make comparisons difficult, but the response rate of 42% observed in the 19

patients with aspergillosis of the central nervous system is promising.

The results of this noncomparative study were confirmed in the largest randomised controlled trial ever undertaken for any antifungal agent in the primary treatment of invasive aspergillosis [12]. Ninety-five centres world-wide treated 391 immunocompromised patients with either voriconazole (given as two 6 mg/kg infusions 12 h apart on the first day, followed by 4 mg/kg every 12 h for at least 7 days, after which treatment could be continued orally 200 mg every 12 h) or 1–1.5 mg/kg/day amphotericin B deoxycholate given intravenously. The protocol-defined treatment period was 12 weeks. At the investigators' discretion, initial randomised therapy could be switched to any other licensed therapy (lipid formulations of amphotericin B or itraconazole) when initial treatment was poorly tolerated or there was no response. Patients judged by an independent, blinded panel to have insufficient evidence to confirm their initial diagnosis of aspergillosis were excluded from the 'modified intent-to-treat' (MITT) population. These patients (50 randomised to voriconazole and 52 to amphotericin B) were not evaluated for efficacy. Hence, 277 patients were included in the MITT population and were evaluated for efficacy.

A satisfactory response (complete or partial resolution of all attributable symptoms and signs and of radiographic or bronchoscopic abnormalities present at baseline) was recorded for 76 (53%) of the 144 patients treated with voriconazole but only for 42 (32%) of the 133 patients treated with amphotericin B ($P = 0.0001$; Fig. 4). Response rates favoured voriconazole irrespective of whether the diagnosis was considered proven or probable, whether the infection was disseminated or pulmonary, and regardless of the underlying condition, or presence of neutropenia. The 12-week survival rate was also higher for the voriconazole group (71%, compared with 58% for amphotericin B group; $P = 0.02$). More than twice as many patients (29%) randomised to amphotericin B died from invasive aspergillosis as those randomised to voriconazole (13%).

Treatment with voriconazole was sustained longer, with a median duration of 77 days (range 2–84 days), compared with 10 days (range 1–84 days) for patients receiving amphotericin B. Fifty-two (36%) patients who started in the voriconazole arm were switched to other licensed therapy. By contrast, and not unexpectedly, 107 (80%) of patients who started in the amphotericin B arm were switched to other licensed therapy.

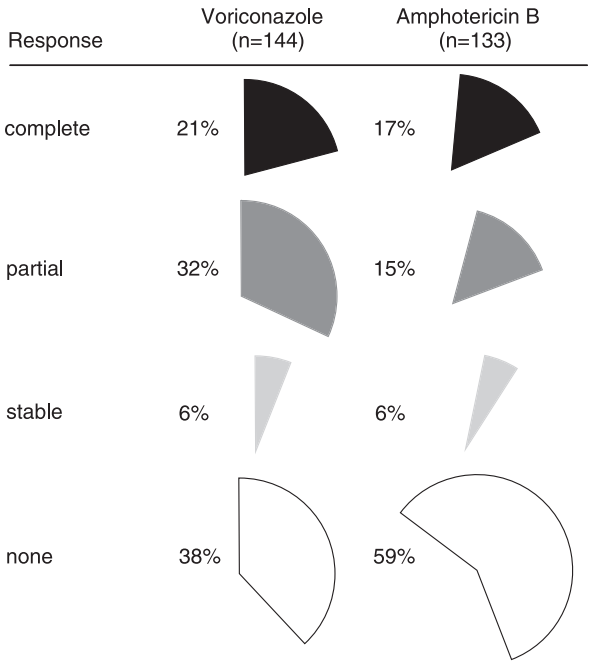


**Fig. 4.** Efficacy of voriconazole compared with amphotericin B for treating invasive aspergillosis.

Overall, fewer adverse events were reported for patients receiving voriconazole, despite the longer median duration of therapy, compared with amphotericin B. Although approximately 10 times more voriconazole patients (87, 45%) than amphotericin B patients (8, 4%) reported transient visual disturbances (blurred vision, altered visual or colour perception, or photophobia, which all resolved spontaneously), the converse was true of chills and fever, which affected 46 (25%) of those given amphotericin B, compared with six (3%) of those treated with voriconazole. Eighteen patients (9%) receiving voriconazole had an adverse event of hypokalemia, compared with 47 (25%) on amphotericin B. Strikingly, seven patients (4%) treated with voriconazole were recorded as having acute kidney failure, while this was considered an adverse event for 89 patients (48%) given amphotericin B/other licensed therapy. Serious side-effects also affected more patients treated with amphotericin (45 patients; 24%) than with voriconazole (26 patients; 13%). Other adverse events were infrequent and affected similar numbers in both groups.

### Candidosis

Voriconazole has been shown to be as effective as fluconazole for treating oesophageal candidiasis, achieving a cure rate among endoscopy-confirmed cases of 113 of 115 patients (98.3%), compared with 134 of 141 (95.0%) on fluconazole [13]. Both drugs were generally well tolerated, although 36 (18%) of the 159 patients treated with voriconazole experienced mild reversible visual abnormalities. Indeed, visual disturbance seems characteristic of voriconazole, but studies have shown no impact of long-term use on eye structure or function. This side-effect may only prove important to ambulatory patients who should not drive or use machinery while affected [14].

### Scedosporium and Fusarium infections

Sixteen of 28 patients treated with voriconazole for infections caused by *S. apiospermum* successfully responded, as did two of seven patients treated for *S. prolificans* infections (data on file). Seven of 17 patients were treated successfully with voriconazole for infections due to *Fusarium* spp. Most of the patients had either been intolerant of, or refractory to, prior antifungal therapy. In particular, the efficacy of voriconazole against potentially life-threatening infections by *Scedosporium* spp. is striking.

### Empirical therapy

Voriconazole and liposomal amphotericin B (AmBisome) were also shown to be similarly effective for empiric therapy [15], although voriconazole failed to meet the statistical endpoint of noninferiority to the comparator across all components of the study composite endpoint. Overall response rates were low, being 108 of 415 (26%) for voriconazole and 131 of 422 (31%) for AmBisome, and resolution of fever during neutropenia in only 137 (33%) and 152 (36%) of episodes, respectively. Nonetheless, the survival rates were 87% and 90%, respectively. The number of breakthrough fungal infections in patients treated empirically with voriconazole was 8 (2%), compared with 21 (5%) for those on liposomal amphotericin B. There were fewer severe infusion-related reactions related to voriconazole and less nephrotoxicity than was encountered with liposomal amphotericin B, although transient visual changes affected almost a quarter of those treated with voriconazole.

Such studies are valuable for assessing the safety of the drugs used, but are difficult to assess in terms of efficacy since most patients do not have a fungal disease. Moreover, some of the breakthrough infections may only represent the further manifestation of an infection that was already present, but undetected, at the start of empiric therapy. The cases of fungal infection that occur can lead to a better understanding of the drug's potential but this necessitates subgroup analysis and essentially results in a series of cases, which, as such, has limited statistical power. It also brings into question the rationale for using fever to guide antifungal therapy decision-making.

### Experience in paediatric patients

Sixty-one paediatric patients aged 9 months up to 15 years who had definite or probable invasive fungal infections were treated with voriconazole. This population included 34 patients aged from 2 to $<12$ years old and 20 patients aged 12 to 15 years. The majority (57/61) had failed previous antifungal therapies. Therapeutic studies included five patients aged 12 to 15 years, the remaining patients received voriconazole in the compassionate use programmes. Underlying diseases in these patients included haematological malignancies and aplastic anaemia (27 patients) and chronic granulomatous disease (14 patients). The most commonly treated fungal infection was aspergillosis (43/61; 70%).

### Miscellaneous infections

Invasive aspergillosis involving the central nervous system is known to have a dismal outcome. A patient with acute leukaemia who developed a cerebral abscess due to *Aspergillus* has been successfully treated [16]. In the study of Denning *et al.* there were 19 cases of cerebral brain invasive aspergillosis, of which five were proven. Three patients (16%) had a partial response and five achieved a stable response [6]. In a retrospective study of eight consecutive cases of brain invasive aspergillosis admitted to a single intensive-care unit between 1990 and 1999, all five treated before 1997 died [17]. Of the three survivors, two had been treated with voriconazole and the other with itraconazole, as had one of those who had died.

More recently, in a study of refractory infections, four of 12 patient (33%) with cerebral aspergillosis had successful outcomes at the end of treatment with voriconazole [18]. A case of brain abscess due to *Pseudallescheria boydii* was successfully treated with surgical drainage and systemic voriconazole [19], as was an unusual case of chronic meningitis due to the same fungus [20]. Although far from conclusive, these results offer hope of successful treatment for a hitherto intractable disease.

## OFFICIAL LABELLING AND INDICATIONS

In Europe, voriconazole is indicated for the treatment of invasive aspergillosis, fluconazole-resistant serious invasive candida infections (including *C. krusei*), and serious fungal infections caused by *Scedosporium* and *Fusarium* spp. It is recommended that voriconazole should be administered primarily to immunocompromised patients with progressive, possibly life-threatening infections. In the US, voriconazole is indicated for the treatment of invasive aspergillosis and serious fungal infections caused by *S. apiospermum* and *Fusarium* spp., including *F. solani*, in patients intolerant of, or refractory to, other therapy.

## DRUG ADMINISTRATION

An intravenous loading dose of 6 mg/kg at 12-hourly intervals should be administered on day 1, followed by a maintenance dose of 4 mg/kg 12-hourly. Voriconazole should be administered at a maximum rate of 3 mg/kg per hour over 1–2 h. Maintenance therapy can be switched to oral form at a dose of 200 mg 12-hourly (for patients ≥ 40 kg) or 100 mg 12-hourly (for patients < 40 kg). If therapy is initiated with the oral form, a loading dose of 400 mg 12-hourly (200 mg 12-hourly for patients < 40 kg) should be administered on day 1. Administration of a loading dose on day 1 results in peak plasma concentrations close to steady state within 24 h. Treatment duration depends on the patient's clinical and mycological response. Oral voriconazole should be taken at least 1 h before or after a meal.

### Special patient groups

No dosage adjustment is necessary based on gender or age ≥ 12 years; however, a maintenance dose of 4 mg/kg IV (or the closest equivalent in oral form) every 12 h is recommended for children aged between 2 and < 12 years of age.

Patients with mild to moderate hepatic cirrhosis (Child–Pugh Class A or B) should receive the standard loading dose of voriconazole but the maintenance dose should be halved [21].

Patients with moderate to severe renal dysfunction (creatinine clearance < 50 mL/min) may experience accumulation of the vehicle SBECD when given voriconazole intravenously. Oral voriconazole should be administered to these patients, unless the benefit of IV therapy outweighs the risk. Serum creatinine levels should be closely monitored in these patients and consideration given to changing to oral therapy.

## INTERACTIONS

### Effects of other medicinal products on voriconazole

Voriconazole is metabolized by cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Inducers or inhibitors of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively.

Rifampicin (a CYP450 inducer; 600 mg once daily) decreased the $C_{max}$ (maximum plasma concentration) and AUC$\tau$ (area under the plasma concentration-time curve within a dose interval) of voriconazole by 93% and 96%, respectively [22]. Coadministration of voriconazole and rifampicin is contraindicated. Carbamazepine and phenobarbital are likely to significantly decrease plasma voriconazole concentrations and coadministration with voriconazole is contraindicated.

Cimetidine increased voriconazole $C_{max}$ and AUC$\tau$ by 18% and 23%, respectively. No dosage adjustment of voriconazole is recommended. Ranitidine had no significant effect on voriconazole $C_{max}$ or AUC$\tau$.

The macrolide antibiotics erythromycin and azithromycin had no significant effect on voriconazole $C_{max}$ and AUC$\tau$.

### Effects of voriconazole on other medicinal products

Voriconazole inhibits the activity of cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Thus, there is potential for voriconazole to

increase the plasma levels of substances metabolized by these CYP450 isoenzymes.

Coadministration of voriconazole with terfenadine, astemizole, cisapride, pimozide or quinidine is contraindicated, because increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes*.

Voriconazole increased sirolimus (2 mg single dose) $C_{max}$ and AUC$\tau$ by 556% and 1014%, respectively. Coadministration of voriconazole and sirolimus is contraindicated.

Voriconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. Coadministration of voriconazole with ergot alkaloids is contraindicated.

In stable renal transplant recipients, voriconazole increased cyclosporine $C_{max}$ and AUC$\tau$ by at least 13% and 70%, respectively. When initiating voriconazole in patients already receiving cyclosporine, it is recommended that the cyclosporine dose be halved and that the cyclosporine level be carefully monitored [23]. Increased cyclosporine levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporine levels must be carefully monitored and the dose increased as necessary.

Voriconazole increased tacrolimus $C_{max}$ and AUC$\tau$ by 117% and 221%, respectively. When initiating voriconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and that the tacrolimus level be carefully monitored [24,25]. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.

Coadministration of voriconazole with warfarin (an anticoagulant) increased the maximum prothrombin time by 93%. Close monitoring of prothrombin time is recommended if warfarin and voriconazole are coadministered [26]. Voriconazole may increase the plasma concentrations of coumarins, such as phenprocoumon and acenocoumarol, and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time should be monitored at close intervals and the dosage of anticoagulants should be adjusted accordingly.

Voriconazole may increase the plasma levels of sulphonylureas, such as tolbutamide, glipizide and glyburide, and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during coadministration.

Voriconazole has been shown to inhibit lovastatin metabolism *in vitro* in human liver microsomes, therefore voriconazole is likely to increase plasma levels of statins that are metabolised by CYP3A4. It is recommended that dose adjustment of the statin be considered during coadministration. Increased statin levels have been associated with rhabdomyolysis.

Although not studied clinically, voriconazole has been shown to inhibit the metabolism of midazolam (a benzodiazepine) *in vitro* (human liver microsomes). Voriconazole is likely, therefore, to increase the plasma levels of benzodiazepines that are metabolized by CYP3A4 (e.g. midazolam and triazolam) and lead to a prolonged sedative effect. It is recommended that dose adjustment of the benzodiazepine be considered during coadministration.

Voriconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity.

Voriconazole increased $C_{max}$ and AUC$\tau$ of prednisolone (60 mg single dose) by 11% and 34%, respectively. No dosage adjustment is recommended [27].

Voriconazole had no significant effect on $C_{max}$ and AUC$\tau$ of digoxin (0.25 mg once daily) [28] or mycophenolic acid (a UDP-glucuronyl transferase substrate; 1 g single dose) [29].

### Two-way interactions

*Phenytoin (CYP2C9 substrate and potent CYP450 inducer)*

Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended when phenytoin is coadministered with voriconazole. Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg intravenously twice daily or from 200 mg to 400 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients < 40 kg) [30].

*Rifabutin (CYP450 inducer)*

Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the

risk. If rifabutin coadministration with voriconazole is justified then the maintenance dose of voriconazole may be increased to 5 mg/kg intravenously twice daily or from 200 mg to 350 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg). Careful monitoring of full blood counts and adverse events to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole [22].

*Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate)*
Omeprazole (40 mg once daily) increased voriconazole $C_{max}$ and AUC$\tau$ by 15% and 41%, respectively. No dosage adjustment of voriconazole is recommended. Voriconazole increased omeprazole $C_{max}$ and AUC$\tau$ by 116% and 280%, respectively. When initiating voriconazole in patients already receiving omeprazole, it is recommended that the omeprazole dose be halved [31,32]. The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole.

*Indinavir (CYP3A4 inhibitor and substrate)*
Indinavir (800 mg three times daily) had no significant effect on voriconazole $C_{max}$, $C_{min}$ and AUC$\tau$. Voriconazole did not have a significant effect on $C_{max}$ and AUC$\tau$ of indinavir (800 mg three times daily) [33].

*Other HIV protease inhibitors (CYP3A4 inhibitors)*
In-vitro studies suggest that voriconazole may inhibit the metabolism of human immunodeficiency virus (HIV) protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir). In-vitro studies also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors. Results of the combination of voriconazole with other HIV protease inhibitors, however, cannot be predicted in humans only from in-vitro studies. Patients should be carefully monitored for any occurrence of drug toxicity and/or loss of efficacy during the coadministration of voriconazole and HIV protease inhibitors.

*Non-nucleoside reverse transcriptase inhibitors (NNRTI) (CYP3A4 substrates, inhibitors or CYP450 inducers)*
In-vitro studies show that the metabolism of voriconazole may be inhibited by delavirdine and efavirenz. Although not studied, the metabolism of voriconazole may be induced by efavirenz and nevirapine. Voriconazole may also inhibit the metabolism of NNRTIs. Due to the lack of in-vivo studies, patients should be carefully monitored for any occurrence of drug toxicity and/or lack of efficacy during the coadministration of voriconazole and NNRTIs.

## ADVERSE EXPERIENCES

Data on the safety of voriconazole is derived from 2000 subjects, of whom 1493 were patients treated in therapeutic trials [34]. The most commonly reported adverse events are displayed in Table 1. Visual disturbances, dermatological reactions and liver function test abnormalities were common. Age, race and gender had no influence on the nature or frequency of adverse events.

### Visual disturbances

In clinical trials, approximately 30% of subjects experienced altered/enhanced visual perception, blurred vision, colour vision change, or photo-

**Table 1.** Treatment-emergent adverse events[a] reported by at least 1% of patients in voriconazole therapeutic studies, by body system ($n$ = 1493)

| |
|---|
| Special senses |
| Abnormal vision (20.6%); Photophobia (2.4%); Chromatopsia (1.3%) |
| Body as a whole |
| Fever (6.2%); Chills (4.1%); Headache (3.2%); Abdominal pain (1.7%) |
| Cardiovascular system |
| Tachycardia (2.5%); Hypertension (1.9%); Hypotension (1.7%); Vasodilatation (1.5%) |
| Digestive system |
| Nausea (5.9%); Vomiting (4.8%); Liver function tests abnormal (2.7%); Diarrhoea (1.1%); Cholestatic jaundice (1.1%); Dry mouth (1.0%) |
| Metabolic and nutritional systems |
| Alkaline phosphatase increased (3.6%); Hepatic enzymes increased (1.9%); ASAT (SGOT) increased (1.9%); ALAT (SGPT) increased (1.8%); Hypokalaemia (1.6%); Peripheral oedema (1.1%); Hypomagnesaemia (1.1%) |
| Nervous system |
| Hallucinations (2.5%); Dizziness (1.3%) |
| Skin and appendages |
| Rash (5.8%); Pruritus (1.1%); Maculopapular rash (1.1%) |

[a]Events recorded as possibly related to therapy or of unknown causality.
ASAT, aspartate aminotransferase; ALAT, alanine transaminase.

phobia. The visual disturbances usually occurred around half an hour after administration of voriconazole, usually spontaneously resolved within an hour, and were commonest during the first week of treatment [14]. The reactions are generally mild, seldom necessitating stopping treatment, are transient and completely reversible, and do not appear to lead to long-term sequelae. The mechanism behind these reactions is unknown. Visual disturbances may be associated with higher plasma concentrations and/or doses.

### Dermatological reactions

Mild or moderate dermatological reactions tend to affect patients with serious underlying diseases who were receiving various other medications. Serious cutaneous reactions, including Stevens–Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme, are rare. Photosensitivity reactions have been reported, especially during long-term treatment.

### Liver function tests

Liver function test abnormalities were seen in 13.4% of trial subjects, and may be associated with higher plasma concentrations or dosages of voriconazole. Liver function test abnormalities resolved either without any alterations in dosage or after dose adjustment or stopping treatment (seldom required). Voriconazole has been infrequently associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, and rare cases of hepatitis and hepatic failure leading to death.

### Infusion-related reactions

As with other drugs, anaphylactic reactions such as flushing, fever, sweating and tachycardia have occurred rarely, immediately upon starting an infusion of voriconazole.

## THE PLACE OF VORICONAZOLE

Compared with a decade ago, we seem to be spoiled for choice when it comes to antifungal drugs, but appearances can be deceptive, especially when considering the treatment of invasive fungal infection. Essentially, there are three classes of drugs—the polyenes (amphotericin B in its various forms), the triazoles (fluconazole, itraconazole and voriconazole), and the candins (caspofungin)—and two strategies available to us, one that relies entirely on intravenous therapy and the other that aims to switch from parenteral to oral treatment. Each class of drug can be employed parenterally but only the azoles can be used to complete the second strategy.

The frustration at not being able to identify patients with mould infections at an early stage may drive clinicians to resort to giving voriconazole for prophylaxis, even though there are no clinical data available on the use of the drug in this setting. Early detection, resulting in early initiation of treatment, is crucial in the management of many mould infections, and is likely to remain an area of focus in the future. The true value of voriconazole may only become apparent once management strategies achieve a better balance between diagnosis and treatment, and risks are better defined so that patients who need therapy are treated optimally, and those who do not need it are identified and spared unnecessary exposure to antifungal agents.

Voriconazole represents a clear advance in the treatment of invasive aspergillosis, with proven superiority over amphotericin B, in terms of both efficacy and patient survival. The study comparing voriconazole and amphotericin B for primary therapy of invasive aspergillosis, which is the largest therapeutic study undertaken of this disease, also indicated that voriconazole is better tolerated than amphotericin B [12]. Despite the median duration of therapy being longer in patients randomised to voriconazole than in those randomised to amphotericin B, there were still significantly fewer treatment-related adverse events in the voriconazole arm (343, compared with 421 in the amphotericin B arm; $P = 0.02$).

The population included in the invasive aspergillosis study [12] included severely ill patients. Due to their underlying conditions, such patients are liable to receive numerous concomitant medications, and are prone to drug–drug interactions and adverse events related to their antifungal therapy. Consequently, this population is difficult to treat, and previous clinical studies in these patients have been almost exclusively limited to trials using amphotericin B. The availability of oral

and intravenous formulations of voriconazole means that the therapeutic options available for the most seriously ill patients are increased. Earlier studies of azole therapy for invasive aspergillosis, using itraconazole, could not include the most severely ill patients, due to the lack of an IV formulation (oral dosing is not possible for the most ill). In one such study, 30 (39%) of 76 evaluable patients had a complete or partial response at the end of treatment with oral itraconazole, 600 mg/day for 4 days, followed by 400 mg/day [35]. Even though this study cannot be compared directly with the voriconazole study [12], the higher proportion of patients with a satisfactory response rate to voriconazole (76/144 patients, 53%) is particularly striking, considering the severely ill patient population enrolled in the latter study. Although an intravenous formulation of itraconazole has now been developed, its use to treat invasive aspergillosis has only been evaluated in a relatively small-scale (31 patients), noncomparative study [36,37].

In addition to its efficacy in the treatment of infections caused by *Aspergillus* [6,12] and *Candida* spp. [13], voriconazole also constitutes a potentially life-saving therapy for patients with infections caused by less-common fungal pathogens. A recent study has demonstrated the efficacy of voriconazole in treating patients with documented invasive fungal infections with no approved antifungal therapy or infections that were refractory to approved therapy (due to treatment failure or intolerance of therapy) [18]. Despite the seriously ill patient population, and the high risk of treatment failure (approximately 75% of the 301 patients evaluated for efficacy had failed to respond to other antifungal agents), there was an overall survival rate of 66% 90 days after starting voriconazole therapy, and a satisfactory global response rate of 50%. Efficacy rates by pathogen in this study included 62/142 (43.7%) and 50/87 (57.5%) for refractory aspergillosis and candidiasis, respectively, 9/10 (90%) for penicilliosis, 5/11 (45%) for fusariosis, and 3/10 (30%) for scedosporiosis. Again, voriconazole was acceptably tolerated, despite the diverse nature of the patients studied and their severe illnesses. Although visual events and elevated liver function test results were observed, if monitored closely, these findings rarely developed into serious adverse events, even in this complex patient group.

Voriconazole is clearly a valuable and important addition to the limited armamentarium currently at our disposal, and the information we now have about this agent is sufficiently compelling for it to earn a place in any antifungal management strategy.

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