View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

EUCAST TECHNICAL NOTE 10.1111/j.1469-0691.2008.02087.x

EUCAST Technical Note on voriconazole

*Subcommittee on Antifungal Susceptibility Testing (AFST) of the ESCMID European Committee for Antimicrobial Susceptibility Testing (EUCAST)**

Keywords breakpoints, EUCAST Technical Note, susceptibility testing, voriconazole

Clin Microbiol Infect 2008; **14:** 985–987

INTRODUCTION

Voriconazole is an azole antifungal agent active against *Candida* species, *Cryptococcus* species, *Aspergillus* species, *Scedosporium apiospermum* and other less common pathogens. The approved indications in Europe are the treatment of (i) invasive aspergillosis; (ii) candidaemia in non-neutropenic patients; (iii) serious invasive candidosis due to fluconazole-resistant *Candida* species (including *Candida krusei*); and (iv) serious invasive fungal disease caused by *Scedosporium* spp. and *Fusarium* spp.

The activity *in vitro* of voriconazole against species of *Candida* is not uniform. The species most frequently involved in causing human infections - *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Candida glabrata* and *C. krusei* - usually exhibit MICs of voriconazole of less than 1 mg/L. However the MICs of voriconazole for fluconazole-resistant isolates are proportionally higher than are those of fluconazole-susceptible isolates. Therefore, every attempt should be made to identify *Candida* to species level.

The Subcommittee on Antifungal Susceptibility Testing (AFST) of the European Committee for Antimicrobial Susceptibility Testing (EUCAST) has determined breakpoints for voriconazole for *Candida* species. These breakpoints are tentative and will be reviewed after two years. This Technical Note is based on the EUCAST voriconazole rationale document which provides more detail and published references related to the selection of EUCAST-AFST breakpoints (available on the EUCAST website: http://www.eucast.org).

DOSAGE

The EUCAST-AFST has determined clinical breakpoints for intravenous and oral doses. The intravenous dose of voriconazole for adults is 12 mg/kg/day on the first day followed by 8 mg/kg/day.

Oral doses are dependant on weight. Patients weighing >40 kg are given 400 mg twice daily on the first day followed by 200 mg twice daily. Patients weighing <40 kg are given 200 mg twice daily on the first day followed by 100 mg twice daily.

MIC DISTRIBUTIONS

The MIC values for wild-type *Candida* spp are shown in Table 1. The MIC distributions are based on the MIC values obtained with EUCAST, CLSI and E-test methods on and applied to large collections of strains from several investigators. Wild-type isolates of *C. albicans*, *C. tropicalis* and *C. parapsilosis* exhibit MICs of ≤0.125 mg/L, whereas MICs for *C. glabrata* and *C. krusei* are higher (commonly ≤1 mg/L. Updates on wild-type MIC distributions can be found at the EUCAST website (http://www.eucast.org).

ESTABLISHED BREAKPOINTS

No European country has established national breakpoints for voriconazole.

Corresponding author and reprint requests: J. L. Rodriguez-Tudela, Mycology Reference Laboratory, National Center for Microbiology, Instituto de Salud Carlos III, Ctra. Majadahonda-Pozuelo Km.2, E-28220 Majadahonda, Spain
E-mail: jlrtudela@isciii.es

*J. L. Rodriguez-Tudela (Chairman, Spain), J. P. Donnelly (Secretary, The Netherlands), M. C. Arendrup (Denmark), S. Arikan (Turkey), F. Barchiesi (Italy), J. Bille (Switzerland), E. Chryssanthou (Sweden), M. Cuenca-Estrella (Spain), E. Dannaoui (France), D. Denning (UK), W. Fegeler (Germany), P. Gaustad (Denmark), C. Lass-Flörl (Austria), C. Moore (UK), M. Richardson (Finland), A. Schmalreck (Germany), J. A. Velegraki (Greece), P. Verweij (The Netherlands).

© 2008 The Authors
Journal Compilation © 2008 European Society of Clinical Microbiology and Infectious Diseases

Table 1. Voriconazole MIC distributions[a] for *Candida* spp

	Number of isolates with indicated MIC (mg/L)																
Species	**0.002**	**0.004**	**0.008**	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**ECOFF≤ (mg/L)[b]**
Candida albicans	50	996	5139	5235	1107	530	207	106	63	42	18	13	18	22	78	6	0.125
Candida glabrata	0	5	26	63	192	534	1218	1244	781	341	196	139	69	20	2	6	1
Candida krusei	0	0	2	10	23	29	152	489	424	119	30	10	1	0	0	0	1
Candida parapsilosis	0	6	287	1326	510	197	123	77	23	16	3	2	1	0	0	0	0.125
Candida tropicalis	0	28	133	602	934	732	274	113	51	32	8	2	10	20	16	3	0.125

[a]MICs determined according to EUCAST, CLSI and Etest methods are included in the distributions. Separate distributions for the three methods are shown on http://www.eucast.org. [b]ECOFF, epidemiological cut-off value (mg/L) as defined by EUCAST.

Table 2. Pharmacokinetic data for voriconazole

Parameter		
Dosage	**6 mg/kg iv × 2 on day 1; maintenance dose 4 mg/kg × 2 Steady state in patients with venous haemofiltration**	**400 mg oral × 2 on day 1; maintenance dose 200 mg × 2**
Cmax (mg/L)	5.9 ± 2.9	2–2.3
Cmin (mg/L)	1.1 ± 0.3	NA
Total body clearance (L/h)	12.9 ± 6.7	19.9
T½ (h), mean (range)	6	6
AUC_{24h} (mg.h/L)	44.8	18–22
Fraction unbound (%)	42	42
Volume of distribution (L/kg)	4.6	NA

NA, Not available

PHARMACOKINETIC DATA

The pharmacokinetic data used to evaluate voriconazole were based on standard doses (Table 2). However the pharmacokinetics of voriconazole are non-linear and variable and the coefficient of variation of the AUC has been estimated to be 74–100%. Concentrations in plasma vary >100-fold among subjects (based on trough concentrations), depending partly on the CYP2C19 genotype of the hepatic cytochrome P450. CYP2C19 exhibits genetic polymorphism resulting in an approximately four-fold higher exposure in poor metabolizers than in extensive metabolisers.

PHARMACODYNAMIC DATA

The *f*AUC/MIC is the pharmacodynamic index best related to outcome. In an experimental model of murine candidosis a *f*AUC/MIC of 24 ± 17 (mean ± SD) was sufficient to achieve a reduction of approximately 1.5 $\log_{10}$ CFU per kidney after 24 h of treatment. Monte Carlo simulations showed that a target fAUC/MIC of 24 would inhibit 99% of isolates with an MIC ≤0.5 mg/L if treatment were given intravenously and 99% of isolates with MIC ≤0.25 mg/L if treatment were given orally.

CLINICAL EFFICACY

Clinical data have been obtained from Pfizer studies 608 (Global Candidemia Study), 603 (Empirical Therapy Study), 309/604 (Global Rare and Refractory Studies), 301 (Compassionate Use Protocol), and 606 (Emergency Use Protocol-U.S. and Canada). The response exceeded 72% for infections due to every species except *C. glabrata* where the response was only 55%. Geometric MICs were below 0.25 mg/L except for *C. glabrata* and *C. krusei*. CART analysis of the response vs MIC or Log_2MIC yielded a MIC value that allowed discrimination between successes and failures. However, the statistical support for this classification tree was limited as the relative risk was 1.09, the area under ROC curve was only 0.6 and the false positive rate exceeded 50%. CART analysis was also undertaken separately for infections due to *C. glabrata* because of the lower response rate but it failed to produce a valid result. Hence, there was insufficient evidence found for any correlation between MIC and clinical outcome.

Although the data are limited, it has been shown that there is a decrease in the clinical response of patients when voriconazole trough blood levels are below 1 mg/L. Conversely, voriconazole trough blood levels above 5.5 mg/L have been associated with an increase in toxicity. Others report a favourable response when random voriconazole blood concentrations exceed 2.05 mg/L. This suggests a potential role for monitoring blood concentrations of voriconazole but further studies are required.

© 2008 The Authors
Journal Compilation © 2008 European Society of Clinical Microbiology and Infectious Diseases, *CMI*, **12**, 985–987

Table 3. EUCAST clinical MIC breakpoints for voriconazole, 2008

	Species-related breakpoints (S≤/R>)					
	C. albicans	*C. tropicalis*	*C. parapsilosis*	*C. glabrata*	*C. krusei*	Non-species-related breakpoints S≤/R>
Voriconazole	0.125/*0.125*[a]	0.125/*0.125*[a]	0.125/*0.125*[a]	IE	IE	Note[b]

IE, there is insufficient evidence that the species in question is a good target for therapy with voriconazole.
[a]Strains with MIC values above the S/I breakpoint are rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and, if the result is confirmed, the isolate sent to a reference laboratory. A MIC above the current resistant breakpoint (in italics) should be considered resistant until more is known about the clinical response of infections due to such isolates. [b]The currently available data would suggest a non-species-related breakpoint of 0.25 mg/L but pharmacokinetics are variable and clinical data on species/isolates with MICs in the range 0.25–1 mg/L are scarce. Non-species-related breakpoints have therefore not been set at this time.

BREAKPOINTS

Breakpoints are summarised in Table 3.

Non-species-related breakpoints

Non-species related breakpoints are determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes. In the case of voriconazole, the pharmacokinetics are variable and the clinical data on species other than C. *albicans, C. parapsilosis* and *C. tropicalis,* and on isolates with higher MICs, are scarce. Therefore non-species related breakpoints have not been set for voriconazole.

Species-related breakpoints

A clinical response of 76% has been achieved for infections due to the species listed in Table 3 when MICs were lower than, or equal to, the epidemiological cut-offs. Wild-type populations of *C. albicans*, *C. tropicalis* and *C. parapsilosis* were therefore considered to be susceptible to voriconazole. Monte Carlo simulations showed that a target attainment of 24 would encompass more than 99% of the population for an MIC of ≤0.125 mg/L. There is insufficient information on the response to voriconazole treatment in infections caused by *Candida* isolates with higher MICs.

Strains with MIC values above the S/I breakpoint are rare and the identification and antimicrobial susceptibility testing of any such isolate must be repeated and, if the result is confirmed, the isolate should be sent to a reference laboratory for further investigation.

Species without breakpoints

Clinical studies of invasive candidosis caused by *C. glabrata*, have shown a 21% lower response to voriconazole compared with the response of infections caused by *C. albicans*, *C. parapsilosis* or *C. tropicalis.* CART analysis of outcome versus MIC did not find higher MICs to be the explanation for the lower response. Consequently, clinical breakpoints for *C. glabrata* will not be set unless more data become available. The clinical response of infections caused by *C. krusei* is similar to that of infections caused by *C. albicans, C. parapsilosis* and *C. tropicalis.* However, as there were only nine cases available for analysis, clinical breakpoints have not been set for *C. krusei*.

© 2008 The Authors
Journal Compilation © 2008 European Society of Clinical Microbiology and Infectious Diseases, *CMI*, **12**, 985–987