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UK BACTERIAL ENDOCARDITIS WORKSHOPS

October/November 1998

The British Society for Antimicrobial Chemotherapy (BSAC), in collaboration with the Association of Medical Microbiologists (AMM) and the Hospital Infection Society (HIS), is holding a series of educational workshops focusing on bacterial endocarditis.

Dulwich – Monday 19 October

Darlington – Wednesday 21 October

Chester – Thursday 22 October

Bristol – Friday 23 October

Derby – Wednesday 28 October

Peterborough – Thursday 5 November

Reading – Tuesday 10 November

Dublin – Date to be advised

Stirling – Date to be advised

Registration Fee: £25.00 (BSAC/AMM/HIS members), £100.00 (non-members)

The meetings will commence with a buffet lunch at 12 noon. The workshops will begin at 1.00pm and will close at approximately 4.30pm.

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Contents

Leading articles

- Antibiotic resistance
R. G. Finch **125**
- Extended-spectrum β -lactamases in *Pseudomonas aeruginosa*
P. Nordmann and M. Guibert **128**

Original articles

- Interactions of plaunotol with bacterial membranes
T. Koga, H. Watanabe, H. Kawada, K. Takahashi, Y. Utsui, H. Doman, C. Ishii, T. Narita and H. Yasuda **133**
- In-vitro activity of lytic peptides, inhibitors of ion transport systems and ionophorous antibiotics against *Pneumocystis carinii*
O. Cirioni, A. Giacometti, F. Barchiesi and G. Scalise **141**
- Influence of ciprofloxacin and other antimicrobial drugs on different *Escherichia coli* strains in continuous-flow cultures under aerobic and anaerobic conditions
H. Bernhardt, K. Schulz, K. Zimmermann and M. Knoke **147**
- Increasing resistance of planktonic and biofilm cultures of *Burkholderia cepacia* to ciprofloxacin and ceftazidime during exponential growth
M. Desai, T. Bühler, P. H. Weller and M. R. W. Brown **153**
- Comparison of the modified Stokes' method of susceptibility testing with results obtained using MIC methods and British Society of Antimicrobial Chemotherapy breakpoints
P. E. Gosden, J. M. Andrews, K. E. Bowker, H. A. Holt, A. P. MacGowan, D. S. Reeves, J. Sunderland and R. Wise **161**
- In-vitro investigation of the antibacterial activity of agents which may be used for the oral treatment of lung infections in CF patients
R. M. E. Richards, V. E. S. Hamilton and M. R. Thomas **171**
- The effects of increasing levels of quinolone resistance on in-vitro activity of four quinolones
K. S. Thomson and C. C. Sanders **179**
- Glycopeptide tolerance in *Staphylococcus aureus*
J. May, K. Shannon, A. King and G. French **189**
- Activated cell-wall synthesis is associated with vancomycin resistance in methicillin-resistant *Staphylococcus aureus* clinical strains Mu3 and Mu50
H. Hanaki, K. Kuwahara-Arai, S. Boyle-Vavra, R. S. Daum, H. Labischinski and K. Hiramatsu **199**
- The effect of a component of tea (*Camellia sinensis*) on methicillin resistance, PBP2' synthesis, and β -lactamase production in *Staphylococcus aureus*
T. S. Yam, J. M. T. Hamilton-Miller and S. Shah **211**
- In-vitro susceptibility of *Cryptococcus neoformans* isolates to fluconazole and itraconazole
K. G. Davey, E. M. Johnson, A. D. Holmes, A. Szekely and D. W. Warnock **217**

The effect of dicloxacillin and fusidic acid on the extracellular and intracellular killing of <i>Staphylococcus aureus</i> S. L. Nielsen and F. T. Black	221
Bacterial concentrations in pus and infected peritoneal fluid—implications for bactericidal activity of antibiotics C. König, H.-P. Simmen and J. Blaser	227
Efficacy and safety of teicoplanin plus rifampicin in the treatment of bacteraemic infections caused by <i>Staphylococcus aureus</i> E. P. F. Yzerman, H. A. M. Boelens, M. Vogel and H. A. Verbrugh	233
<hr/>	
Brief reports	
Diethylcarbazine-related antimicrobial activity in <i>Mycobacterium tuberculosis</i> -infected blood L. W. Kitchen, C. M. Weston and S. P. Day	241
In-vitro antibiotic susceptibility and molecular analysis of anaerobic bacteria isolated in Cape Town, South Africa C. L. Koch, P. Derby and V. R. Abratt	245
Sub-MICs of sanfetrinem promote the interaction of human polymorphonuclear granulocytes with a multiply resistant strain of <i>Klebsiella pneumoniae</i> A. M. Cuffini, V. Tullio, A. I. Palarchio, A. Bonino and N. A. Carlone	249
Voriconazole against fluconazole-susceptible and resistant candida isolates: in-vitro efficacy compared with that of itraconazole and ketoconazole M. H. Nguyen and C. Y. Yu	253
Comparison of four antibiotics in a murine model of necrotizing cutaneous infections caused by toxigenic <i>Streptococcus pyogenes</i> and <i>Staphylococcus aureus</i> N. Barg	257
Comparative grepafloxacin phototoxicity in mouse skin K. Owen	261
<hr/>	
Correspondence	
Current MIC breakpoints may understate the potential efficacies of carbapenems for treatment of patients with infections caused by strains of <i>Streptococcus pneumoniae</i> that are resistant or of intermediate susceptibility to penicillin J. R. Edwards, J. S. Bradley and K. P. Klugman	265
Study on the in-vitro activity of LY333328 against Gram-positive cocci M. L. Mezzatesta, G. Bonfiglio, L. De Angelis, S. Stefani and G. Russo	266
Activities of cefepime and five other antibiotics against nosocomial PER-1-type and/or OXA-10-type β -lactamase-producing <i>Pseudomonas aeruginosa</i> and <i>Acinetobacter</i> spp. H. Vahaboglu, S. Saribaş, H. Akbal, R. Ozturk and A. Yuçel	269
Evaluation of the activities of two-drug combinations of rifampicin, polymyxin B and ampicillin/sulbactam against <i>Acinetobacter baumannii</i> C. Tascini, F. Menichetti, S. Bozza, A. Del Favero and F. Bistoni	270
A study of the mechanisms involved in imipenem resistance in <i>Pseudomonas aeruginosa</i> isolates from Japan R. A. Stunt, C. J. Thomson, D. J. Payne and S. G. B. Amyes	272
Emergence of resistance to third-generation cephalosporins amongst <i>Salmonella typhimurium</i> isolates in Greece: report of the first three cases L. S. Tzouvelekis, M. Gazouli, A. Markogiannakis, E. Paraskaki, N. J. Legakis and E. Tzelepi	273
Isolation of glycopeptide resistant <i>Streptococcus gallolyticus</i> strains with <i>vanA</i> , <i>vanB</i> , and both <i>vanA</i> and <i>vanB</i> genotypes from faecal samples of veal calves in The Netherlands D. Mevius, L. Devriese, P. Butaye, P. Vandamme, M. Verschure and K. Veldman	275

Activity of nisin against <i>Streptococcus pneumoniae</i> , <i>in vitro</i> , and in a mouse infection model <i>B. P. Goldstein, J. Wei, K. Greenberg and R. Novick</i>	277
An isocratic high performance liquid chromatography (HPLC) assay for moxifloxacin, a new 8-methoxyquinolone <i>C. M. Tobin, J. Sunderland, L. O. White, A. P. MacGowan and D. S. Reeves</i>	278
Book reviews	281

287 05/03 38
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ANACOR EX. 2096 - 5/9

Voriconazole against fluconazole-susceptible and resistant candida isolates: in-vitro efficacy compared with that of itraconazole and ketoconazole

M. Hong Nguyen^{a,b*} and Christine Y. Yu^a

^aDepartment of Medicine, Division of Infectious Disease, University of Florida College of Medicine, PO Box 100277, JHMHC, Gainesville, FL 32610; ^bVA Medical Center, Gainesville, FL, USA

We compared the in-vitro activity of fluconazole, itraconazole, ketoconazole and voriconazole against 67 blood isolates of *Candida* spp. exhibiting a wide range of fluconazole MICs (0.125 to >64 mg/L). Voriconazole was the most potent *in vitro*, followed by itraconazole, ketoconazole and fluconazole. Itraconazole and voriconazole had in-vitro activity against fluconazole-susceptible and -resistant candida isolates. Higher itraconazole and voriconazole MICs were observed in isolates exhibiting higher fluconazole MICs, suggesting cross-resistance. Itraconazole and voriconazole MICs of ≥ 16 mg/L were observed only in *Candida albicans* and *Candida tropicalis*. *Candida krusei* and *Candida glabrata* exhibited itraconazole MICs of 0.5–1 mg/L and voriconazole MICs of 0.25–0.5 mg/L.

Introduction

Voriconazole is a new triazole antifungal agent which acts by inhibiting cytochrome P450 sterol 14 α -demethylase, an enzyme involved in ergosterol biosynthesis. Voriconazole has potent in-vitro and in-vivo activity against *Aspergillus* spp. and other moulds.^{1–3} Although voriconazole has in-vitro activity against fluconazole-resistant *Candida albicans*, *Candida krusei* and *Candida glabrata*,^{4,5} its activity against other *Candida* spp. that are fluconazole-resistant *in vitro* is unknown. Furthermore, the in-vitro activity of voriconazole has not been compared with that of itraconazole and ketoconazole. The goal of this study was to compare the in-vitro activity of fluconazole, itraconazole, ketoconazole and voriconazole against a large number of candida isolates; the isolates studied exhibited a wide range of fluconazole MICs.

Materials and methods

Sixty-seven blood isolates of *Candida* spp. collected during a prospective study of candidaemia were tested.⁶ These isolates exhibited fluconazole MICs ranging from 0.125 to >64 mg/L. These included *C. albicans* (24 isolates), *Candida tropicalis* (17), *C. glabrata* (12), *Candida parapsilosis* (8), *C. krusei* (3) and *Candida lusitanae* (3). *C.*

parapsilosis ATCC 90018, *C. albicans* ATCC 90028 and 90029 and *C. glabrata* ATCC 90030 were incorporated into each set of experiments as quality control isolates.

The susceptibility testing was performed by a macro-dilution method adhering to the National Committee for Clinical Laboratory Standards (NCCLS) protocol.⁷ Fluconazole (Pfizer Central Research, Groton, CN, USA) stock solutions of 2000 mg/L were prepared with sterile distilled water. Voriconazole (Pfizer Central Research, Groton, CN, USA) stock solutions of 4000 mg/L were prepared with dimethylsulphoxide (DMSO); subsequent dilutions were performed in water. Stock solutions of ketoconazole and itraconazole (Janssen Research Foundation, Beerse, Belgium) were prepared with 0.2 N HCl and DMSO, respectively; subsequent drug dilutions were performed according to the manufacturer's protocol. The concentrations of drugs tested were: 0.125–64 mg/L for fluconazole; 0.015–16 mg/L for itraconazole and voriconazole; and 0.03–16 mg/L for ketoconazole. Each *Candida* sp. was tested simultaneously against fluconazole, itraconazole, ketoconazole and voriconazole.

Results and discussion

The fluconazole, itraconazole, ketoconazole and voriconazole MICs for the ATCC isolates were: 0.5, 0.125, 0.06

*Tel: +1-352-3794027; Fax: +1-352-3794015; E-mail: nguyemt@medicine.ufl.edu

and 0.015 mg/L, respectively, for ATCC 90018; 0.5, 0.125, 0.06 and 0.03 mg/L, respectively for ATCC 90028; 0.5, 0.125, 0.03 and 0.03 mg/L, respectively, for ATCC 90029; 16, 0.125, 0.03 and 0.03 mg/L, respectively, for ATCC 90030.

The MIC ranges, MIC₅₀s, MIC₉₀s and geometric mean MICs of ketoconazole, fluconazole, itraconazole and voriconazole for specific *Candida* spp. are presented in Table I. Using the fluconazole breakpoint values proposed by the NCCLS,⁸ 69% (46/67) of *Candida* spp. were susceptible, 9% (6/67) dose-dependently susceptible and 22% (15/67) resistant to fluconazole *in vitro*. Using the itraconazole breakpoints,⁸ 40% (27/67) were susceptible, 40% (27/67) dose-dependently susceptible and 20% (13/67) resistant to itraconazole *in vitro*.

To our knowledge, this is the first published study to compare the in-vitro efficacy of voriconazole, itraconazole and ketoconazole against a large number of *Candida* spp. with a wide range of fluconazole MICs. We included in our study not only fluconazole-resistant *C. albicans* and *C. krusei*, but also *C. tropicalis*, *C. parapsilosis* and *C. lusitaniae*. We demonstrated that voriconazole was the most potent of the azole agents against the *Candida* spp.

tested (geometric mean of 0.12 mg/L), followed by itraconazole (geometric mean of 0.30 mg/L) and ketoconazole (geometric mean of 0.75 mg/L).

Voriconazole had in-vitro activity against both fluconazole-susceptible and -resistant *Candida* spp. For fluconazole-susceptible isolates, voriconazole was significantly more potent than itraconazole and ketoconazole: the geometric mean MIC of voriconazole (0.04 mg/L) was significantly lower than that of itraconazole (0.17 mg/L; $P < 0.001$) and that of ketoconazole (0.43 mg/L; $P < 0.001$) (Table II). Moreover, 91% (42/46) of the fluconazole-susceptible *Candida* spp. exhibited voriconazole MICs of ≤ 0.125 mg/L, whereas only 52% (24/46) exhibited itraconazole MICs ≤ 0.125 mg/L, and 48% (21/46) exhibited ketoconazole MICs ≤ 0.125 mg/L.

For fluconazole-resistant or dose-dependently susceptible isolates, voriconazole also demonstrated good in-vitro activity. Sixty-two percent (13/21) of these isolates exhibited voriconazole MICs of ≤ 0.5 mg/L, whereas only 43% (9/21) exhibited itraconazole MICs of ≤ 0.5 mg/L, and 19% (4/21) exhibited ketoconazole MICs of ≤ 0.5 mg/L. As previously noted, *C. krusei* and *C. glabrata*, species often associated with fluconazole resistance, were sus-

Table I. In-vitro activity of ketoconazole, fluconazole, itraconazole and voriconazole against *Candida* spp.

Species	n	Antimicrobial agent	48 h MIC (mg/L)			
			range	50%	90%	geometric mean
<i>C. albicans</i>	24	ketoconazole	0.03->16	8	>16	1.10
		fluconazole	0.125->64	0.5	>64	1.30
		itraconazole	0.06->16	0.125	0.5	0.22
		voriconazole	≤ 0.015 ->16	≤ 0.015	0.25	0.06
<i>C. tropicalis</i>	17	ketoconazole	0.03->16	4	>16	1.75
		fluconazole	0.5->64	8	>64	9.02
		itraconazole	0.015->16	0.25	>16	0.54
		voriconazole	≤ 0.015 ->16	0.125	>16	0.33
<i>C. glabrata</i>	12	ketoconazole	0.03-1	1	1	0.47
		fluconazole	2-32	8	32	8.00
		itraconazole	0.25-1	0.5	1	0.56
		voriconazole	0.06-0.5	0.125	0.25	0.16
<i>C. parapsilosis</i>	8	ketoconazole	0.03-1	0.125	1	0.19
		fluconazole	0.5->64	2	32	3.35
		itraconazole	0.125-0.5	0.125	0.25	0.19
		voriconazole	0.015-1	0.03	0.25	0.06
<i>C. krusei</i>	3	ketoconazole	0.5-1	0.5	0.5	0.63
		fluconazole	>64	>64	>64	64.07
		itraconazole	0.25-0.5	0.5	0.5	0.40
		voriconazole	0.5	0.5	0.5	0.50
<i>C. lusitaniae</i>	3	ketoconazole	0.03-0.5	0.03	0.5	0.08
		fluconazole	0.125-32	2	32	1.99
		itraconazole	0.125-0.5	0.125	0.5	0.20
		voriconazole	0.015-0.5	0.015	0.5	0.06

Table II. Geometric means, MIC₅₀ and MIC₉₀ for fluconazole-susceptible and -resistant *Candida* species against itraconazole, ketoconazole and voriconazole

Azole agent	Geometric mean MIC (range) for fluconazole:			MIC ₅₀ /MIC ₉₀ (mg/L) for fluconazole:	
	susceptible isolates	resistant isolates	<i>P</i> value	susceptible isolates	resistant isolates
Itraconazole					
all <i>Candida</i> spp.	0.17	1.39	<0.001	0.125/0.5	1/16
<i>C. albicans</i>	0.13	3.97	<0.001	0.125/0.25	16/16
<i>C. tropicalis</i>	0.13	2.51	0.001	0.125/0.25	1/16
<i>C. glabrata</i>	0.46	1.00	0.01	0.5/0.5	1/1
<i>C. parapsilosis</i>	0.18	0.25	NS	0.125/0.25	0.125/0.5
<i>C. krusei</i>	–	0.40	–	–	0.5/0.5
Ketoconazole					
all <i>Candida</i> spp.	0.43	2.51	0.003	0.25/16	4/16
<i>C. albicans</i>	0.70	11.36	0.06	0.5/16	8/16
<i>C. tropicalis</i>	1.06	3.06	NS	0.5/16	8/16
<i>C. glabrata</i>	0.37	1.00	NS	0.5/1	1/1
<i>C. parapsilosis</i>	0.11	1.00	0.01	0.125/0.25	1/1
<i>C. krusei</i>	–	0.63	–	–	0.5/0.5
Voriconazole					
all <i>Candida</i> spp.	0.04	1.14	<0.001	0.03/0.125	0.5/16
<i>C. albicans</i>	0.02	5.64	<0.001	0.015/0.06	16/16
<i>C. tropicalis</i>	0.08	1.68	0.003	0.06/0.125	0.25/16
<i>C. glabrata</i>	0.13	0.25	NS	0.125/0.25	0.25/0.5
<i>C. parapsilosis</i>	0.03	0.50	0.002	0.03/0.06	0.25/1
<i>C. krusei</i>	–	0.50	–	–	0.5/0.5

NS, not significant.

ceptible *in vitro* to itraconazole,⁹⁻¹⁰ to voriconazole⁴ with MICs of 0.25–0.5 mg/L, and to ketoconazole with MICs of 0.5–1 mg/L (Table II).

Despite these promising results, there was cross-resistance between fluconazole and voriconazole for some *Candida* spp. For example, isolates with higher fluconazole MICs were associated with higher voriconazole MICs ($P < 0.001$, linear regression). There was also cross-resistance between fluconazole, itraconazole and ketoconazole: the higher fluconazole MICs were associated with higher itraconazole and ketoconazole MICs ($P < 0.001$, and 0.003, respectively). This pattern of cross-resistance has been previously described, and may result from the similar mechanisms of actions of these agents.^{9,10}

Six (38%) of the 16 *Candida* spp. with fluconazole MICs of ≥ 64 mg/L displayed itraconazole MICs of ≥ 16 mg/L and ketoconazole MICs of ≥ 8 mg/L. All of these isolates had voriconazole MICs of ≥ 16 mg/L. In our study, these high levels of resistance to multiple azole agents (MICs ≥ 8 mg/L) were seen only for *C. albicans* and *C. tropicalis* isolates. Fluconazole-resistant *C. krusei*, *C. glabrata*, *C. parapsilosis* and *C. lusitanae* isolates, on the other hand, did not display high-level resistance to itraconazole, ketoconazole and voriconazole.

In conclusion, voriconazole has potent *in-vitro* activity against *Candida* spp., including those that were dose-dependently fluconazole-susceptible or fluconazole-resistant. This finding suggests that voriconazole might be effective in the treatment of refractory candidosis caused by fluconazole-resistant strains. However, cross-resistance with fluconazole exists in a small subset of *Candida* spp. Given the high oral bioavailability and the well tolerated nature of voriconazole, this drug may become an important addition to the armamentarium of systemic antifungal agents. This promise, however, requires to be confirmed in the clinical setting.

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