The “overuse” of antimicrobial agents in hospitals and the wider community has resulted in increasing concern regarding the impact on resistance and the cost of such overuse. It is generally accepted that the inappropriate use and choice of antimicrobials results in increased resistance selection pressure. Anti-infective agents consume a significant proportion of hospital drug expenditure, with figures of 15 – 20% often being quoted. Such agents, as a group, fall within the “top 5” by volume of pharmaceuticals dispensed under the Pharmaceutical Benefits Scheme. Also, in the experience of one of the authors, anti-infective agents are associated with a significant proportion of adverse drug reactions in the paediatric population.

The purpose of this article is to identify the potential roles hospital pharmacists can play in the overall strategy of attempting to ensure the quality use of antimicrobial agents. Like so many other such roles, an efficient and harmonious working relationship with other disciplines within the hospital is an essential element.

Drug education and antibiotic guidelines

Two primary strategies that many hospitals have adopted to achieve rational use of anti-infectives are education and/or guidelines for use. Whilst education alone and thus perhaps “self-initiated” compliance with the principles of good prescribing are desirable, the perpetual demands of operating such a stand alone strategy and the resources needed have been an increasing trend towards guidelines. Various nomenclature is used to describe what is essentially a strategy of control of the prescribing of these agents. Regardless of the real or imaginary implications of antibiotic “guidelines” or antibiotic “policies”, this approach sets out to either define the agents of choice for specific conditions and is usually accompanied by a process of authorisation whereby certain agents can, for example, only be prescribed following approval by an infectious diseases (ID) clinician. The roles of the pharmacist are many-fold in this strategy; there may be involvement at Drug Committee level in the initial addition of a new agent to the formulary and the accompanying criteria for use. Following the introduction of new agents, ongoing and preferably regular monitoring of the agent is required to ensure appropriate use. Together with ID, the pharmacy department is in a prime position through its dispensing and ward services to monitor prescribing of the agent and hopefully initiate a mechanism which results in approved use. Perhaps one of the most desirable examples of a co-operative working relationship between ID and pharmacy is the establishment of an “ID pharmacist”. This achieves an environment of education and mutual “feedback” which has the potential to achieve significant outcomes in the need for the rational use of anti-infective agents. Whilst the contributions of the pharmacist to the overall monitoring role are desirable and relevant, care should also be taken in not becoming the “police-person for antimicrobial use”. Restrictive policies for these agents may place the pharmacist in the unenviable and undesirable position of being “the-watchdog”, leading to conflict with prescribers and patients. We believe that such an approach can cause detriment to the professional standing of the pharmacist and/or cause delays in already crowded outpatient areas. Systems and approaches which minimise such outcomes and yet still contribute to
appropriate monitoring are highly desirable.

Although education alone is often insufficient, it remains a key responsibility of pharmacists and ID clinicians that junior medical staff and health students are exposed to guidelines (both formal and informal) that contribute to better use of anti-infectives both within the hospital and in the general community. The ability of hospital pharmacists to access prescribers and nursing staff is often numerically greater than that of our ID colleagues. This option for promulgating policies is a key role for pharmacists.

**Drug utilisation evaluations / reviews (DUEs)**

Drug utilisation evaluations/reviews (DUEs) are mechanisms which provide data for defined periods of time on the appropriate use of an antimicrobial agent, according to pre-defined criteria. Ideally, this process should be prospective, multidisciplinary, provide feedback to prescribers and be ongoing. One negative of traditional DUEs is that they may require significant resources – the use of relevant information technology such as electronic prescribing and self-funding positions for “DUE pharmacists” are potential mechanisms for overcoming the resource implications. Such processes can provide essential information on the use (and misuse) of the target antimicrobial.

**Adverse drug reactions**

The early recognition of the association between an adverse drug reaction (ADR) and a specific agent often depends on an appropriate structure for detection, analysis and reporting. Spontaneous prescriber-only reporting systems for ADRs are historically deficient in ensuring adequate data. Hospital pharmacists have been and continue to be largely responsible for ADR systems within Australian hospitals. Recognising the relatively poor returns from spontaneous systems alone has seen the use of “reward” systems and various electronic data bases such as ICD coding system. The detection and collation of ADRs to antimicrobial agents is a key element in the quality use of such agents.

**Cost containment**

Antimicrobial agents consume a significant proportion of drug expenditure. Through Drug Committees, Finance Committees and other similar structures, pharmacists are largely responsible for the collation and analysis of cost data. Regular reports may show trends over time that signify changes in the prescribing of a particular agent and are thus yet another mechanism that may lead to the development of guidelines for appropriate use. Furthermore, the pharmacist’s familiarisation with cost data can be utilised as one part of the decision making process which a prescriber goes through when selecting an agent for a particular patient. The purchasing role of the hospital pharmacist contributes to reductions in expenditure on these agents through mechanisms such as contract purchasing and/or individual negotiation. The cost of preparation and administration should also be considered. However, cost should not be the sole factor in product selection – others such as packaging, reconstituted vs powder presentation, associated use of consumables, single dose vs multi-dose, storage needs etc. can all potentially contribute on the quality use of antimicrobials within a particular environment.

“Care should be taken in not becoming the ‘police-person’ for antimicrobial use”

Another important aspect of cost control is to minimize wastage. The hospital pharmacy can contribute to this process in a number of ways. One of the primary examples is the use of centralized intravenous additive services whereby doses of antimicrobial agents can be dispensed for use at the ward and even home level. Not only do such services contribute towards effective final product presentation (eg. sterility), they may also contribute to reducing medication errors such as those associated with wrong drug, wrong dose, inappropriate diluent and/or volume etc. The ability to aseptically use the contents of a vial for more than one patient can provide significant cost savings, some of which can perhaps be diverted to attaining relevant resources to acquire the practice benefits mentioned above.

**Dosing and administration**

The quality use of antimicrobials not only includes the initial selection of an agent, but should extend to the safe administration. Dosing and administration guidelines to minimize adverse events and optimize positive outcomes are key elements. A knowledge of the pharmacokinetics and pharmacodynamics of the various agents can contribute to both of these outcomes. Appropriate dosing regimens utilising prior knowledge and participation in the therapeutic drug monitoring of an agent are important contributions of the pharmacist towards safe and effective therapy.

**Home intravenous antibiotic programs**

The advent of home care services promises much in the way of quality of life and potential (or real) reductions in cross-infection and hospital inpatient costs. The multi-discipline requirements of such programs are such that a number of roles for hospital pharmacists exist. In the case of home intravenous antibiotic programs, this involvement may include educational material (verbal and written) for home use, advice on delivery systems, drawing-up of doses for use at home, advice on storage, safe-handling and discarding of drugs/equipment and close liaison with medical and nursing staff to ensure efficient transition from hospital to home care. Home use of pharmaceuticals has contributed to the demand for better stability data on antibacterials. This type of research and development together with participation in more formal research such as clinical trials are further examples of the roles of hospital pharmacists in this area.

**Conclusion**

The area of infectious disease is one that provides great opportunity for the hospital pharmacist to practice a wide range of skills. It provides, perhaps more than in most other areas of practice, an exciting and rewarding opportunity to work with others in the area of infectious diseases who are likewise committed to achieving the quality use of antimicrobials in our hospitals and in the wider community.
President’s Report

John Turnidge
Adelaide Women’s & Children’s Hospital, SA

ASA is now in its third year and membership has now grown to 250. We are a diverse group with 40% of our members from a medical background, 40% from a scientific background, 10% pharmacists, and 7% from industry. In April, we successfully conducted our second annual scientific meeting. We have spent the last year consolidating our primary aims and establishing ourselves as a credible organisation on the national stage.

Some of the highlights from 2000-01 include:

Discussions with the TGA. Following Antimicrobials 2001, we took Paul Tulkens, one of this years’ international speakers, to the TGA in Canberra. Paul has been actively involved with the process of introducing antimicrobial pharmacodynamics into the drug evaluation process, particularly in Europe. Paul and ASA committee members held talks with the TGA in an effort to get pharmacodynamics included in the Australian drug evaluation agenda.

Submission on JETACAR implementation. As an identified stakeholder, ASA has submitted after request a commentary on the process of implementing JETACAR and Australia’s resistance management strategy. If you want further information, we suggest that you visit the newly established Implementing JETACAR website (http://www.health.gov.au/pubhlth/strateg/jetacar).

Hosting 2002 WPCCID. ASA has accepted the responsibility for conducting the Western Pacific Congress of Chemotherapy and Infectious Diseases (WPCCID) in Perth in December 2002. We are currently drawing up a draft program. We’ll take all the help from members that we can get!

Travel awards. One of our primary aims is to foster research in the study of antimicrobials. Generous grants from industry have been used to establish our travel awards program. We hope to extend our award program in the near future. Our current awards are:

1. Roche Travel Awards. We are very grateful to Roche for their continued support for high quality work to be presented at the ASA meeting. Three awards were made for travel to Antimicrobials 2001, and up to 5 awards (depending on winners’ cities of origin) will be made for travel to Antimicrobials 2002 in Sydney.

2. Amgen Australia Travel Award. Awarded to the best abstract submitted to our annual scientific meeting in any area of antifungal research (laboratory or clinical). The award consists of support to attend a major international mycology meeting relevant to the area of antifungals.

3. AstraZeneca continue to provide support for one individual each year to present their work at the major annual international meeting in antimicrobials, the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). We are currently evaluating submissions for ICAAC in Chicago in September 2001.

Other support for Antimicrobials 2001 meeting. We are grateful to the Australian Society for Infectious Diseases and Bristol-Myers Squibb for providing access to Margaret Hammerschlag to speak at our meeting. We would also like to thank the many companies who have contributed their support to the successful running of our meeting. Our ability to attract high quality speakers is in large part due to their support.

Lecture tours. Three international guests who spoke at Antimicrobials 2001 in Melbourne were able to visit other Australian cities afterwards to speak to those who could not attend the meeting. Fred Tenover and Keiichi Hiramatsu gave lectures in Perth and Adelaide, and Paul Tulkens visited the TGA in Canberra.

Antimicrobials 2002. This will be held in Sydney from 28 February – 2 March 2002. There will be three international speakers, including Fernando Baquero from Madrid and Hendrik Wegener from Copenhagen.

Workshops. ASA has run two very successful susceptibility testing/resistance workshops in Melbourne and Launceston. Our thanks to Nicholas Nuttall in particular for his boundless energy despite very trying circumstances. We also thank Narelle George and Jan Bell for their contributions. There are further workshops planned for 2001, including a workshop during Australian Society for Microbiology (ASM) scientific meeting in Perth in October.

Website. Our web site is still in its infancy (http://www.asainc.net.au/) We hope to expand its content as time passes, including previous newsletters and position statements.

Newsletter. We thank Sue Benson, who has done a wonderful job getting our newsletter on track over the past two years. Sue has had to resign the post due to work commitments. Wendy Munckhof from Princess Alexandra Hospital in Brisbane is the new newsletter editor, commencing this issue. If you are interested in writing an article for the newsletter, please contact her (see contact details at the back of this newsletter).

Financial statement. A financial statement for ASA for the year ended 30 June 2000 has been included with this newsletter.

Aims of ASA

• To facilitate the acquisition and dissemination of knowledge in the field of antimicrobials.
• To encourage the communication and cooperation between those actively engaged in the field of antimicrobials and related disciplines.
• To hold meetings and conferences.
• To demonstrate publicly the need for an educated and considered approach to the use of antimicrobials.
• To encourage research in the study of antimicrobials by grants from funds of the society and by the establishment of scholarships and awards.

ASA Newsletter, June 2001
More than 170 participants attended the 2nd annual scientific meeting of ASA in April at the Carlton Crest Hotel situated by beautiful Albert Park Lake in Melbourne. It is difficult to design a scientific program that appeals to people from the diverse professional backgrounds that make up ASA (medical, scientific, pharmacy and industry) and the program committee should be commended on their efforts. Evaluation forms returned by many of the conference participants particularly commended the high standard of the speakers. After 2 annual meetings, ASA is developing a reputation for the excellent standard of the invited international speakers. After 2 annual meetings, ASA is developing a reputation for the excellent standard of the invited international speakers, and the four who spoke this year gave excellent intellectually stimulating talks. The following are a few highlights from the program:

**MRSA in evolution**

Professor Keiichi Hiramatsu from Tokyo, Japan in this plenary address gave a global account of the rise of MRSA. In his opinion, countries such as Japan that overprescribe broad spectrum cephalosporins and quinolones tend to have problems with MRSA. He described at length his theory that selection pressure from beta-lactam antibiotics converts MSSA to hetero-MRSA, with subsequent pressure from broad-spectrum beta-lactams converting hetero-MRSA to homo-MRSA. Selection pressure from vancomycin then converts homo-MRSA to VISA.

**Vancomycin-intermediate Staphylococcus aureus – your passport to unhappiness**

This session provided a comprehensive overview of the state of play regarding this new organism from two experts in the field, and was certainly one of the highlights of the meeting.

Professor Hiramatsu gave a fascinating lecture on the discovery and mechanisms of VISA. In 1996, he was the first to report vancomycin-intermediate *Staphylococcus aureus* (VISA, defined as vancomycin MIC of 8-16 mg/L) and reported that VISA now occurs in Japan, USA, France, Scotland, Korea, Brazil and Guatemala. Hetero-VISA (defined as vancomycin MIC of 2-4 mg/L) has been described from these countries plus England, Germany, Greece, Spain, Turkey, Hong Kong, Thailand and South Africa. He confirmed that VISA still predominantly develops in MRSA. Keiichi then spoke about his scientific investigations into the resistance mechanism, and reported that VISA strains have thickened cell walls which can either be due to increased cell wall synthesis (in the case of Mu50) or decreased shedding of cell wall (US strains of VISA). He reported that vancomycin MIC correlates well with cell wall thickness, although teicoplanin MIC does not, and hence proposed different mechanisms of resistance for the two drugs. He reported that hetero-VISA and VISA were unstable in laboratory tests and rapidly returned to a vancomycin-susceptible state; in his opinion this could account for the lower incidence of VISA than was originally predicted.

Professor Fred Tenover from the Centres for Disease Control then spoke on the US experience of VISA and laboratory detection issues. He reported difficulties with the definition of VISA due to differing vancomycin breakpoints between the American (NCCLS), British (BSAC), French (CA-SFM) and the Japanese (JSAC) societies. He reported that the current NCCLS definition of VISA requires (1) a broth MIC to vancomycin of 8-16 mg/L, or (2) an MIC by E-test of 6-12 mg/L, or (3) growth of *S. aureus* in 24 hours on brain heart infusion agar containing 6 mg/L vancomycin.

Professor Tenover spoke further on the laboratory detection of VISA. He reported that isolates of VISA often appear mixed with varying colony size on agar plates, but that colonies turned out to be identical on further testing. He suggested that this was a useful laboratory pointer to suspecting the presence of VISA. He reported that disc testing using NCCLS methodology could not detect VISA, as isolates typically had zone sizes of 16-23 mm. He reported that broth microdilution methods were effective, but that full 24-hour incubation was required. He reported that Microscan was a satisfactory screen, but Vitek could overcall vancomycin MICs of *S. aureus* slightly, and that strains with MICs of 4 mg/L by Vitek (or by any other method for that matter) should be subjected to further testing. He reported that E-test was a satisfactory method if Mueller-Hinton agar was used, although endpoints could trail.

Professor Tenover then spoke on results of susceptibility testing of VISA. He reported that strains of VISA were variably susceptible to rifampicin, cotrimoxazole and doxycycline, so these antibiotics should always be tested. For the newer antibiotics, Synercid (quinupristin/dalfopristin) MICs were typically 0.5 – 1 mg/L and linezolid MICs were usually 1-2 mg/L, but that the new glycopeptide oritavancin (formerly known as LY33328) showed cross-resistance with MICs of typically 4-8 mg/L. He also reported that although evenmomycin had low MICs, the compound was no longer being developed for toxicity reasons.

**Can the application of pharmacodynamic principles limit the development of resistance?**

Professor Paul Tulkens from Brussels, Belgium gave an excellent overview of the importance of pharmacokinetics (PK) and pharmacodynamics (PD) to the appropriate usage of antibiotics and to the development of resistance. He commenced at a basic level and then...
expanded, and made a topic which can be difficult to conceptualise clear and easy to understand. He stated that, according to the FDA, the role of PK/PD studies was threefold: (1) in preclinical screening in animal models, to facilitate the early selection of a lead drug candidate; (2) in phase 1 and 2 studies, to select appropriate dosage regimens; and (3) in phase 3 studies, to confirm these regimens. Professor Tulkens voiced concerns that because the goal of beta-lactam dosing is to maximise time of exposure to drug (as time above MIC is the main PD predictor of efficacy for beta-lactams), too low dosages, too long dosage intervals and too high breakpoints could predispose to the selection of resistant subpopulations. He presented data for the quinolones showing that AUC/MIC and peak/MIC are the main PD predictors of efficacy. A peak/MIC ratio of at least 8 is required to prevent development of resistant subpopulations, and he wondered if, for some of the older quinolones, this was the reason for development of resistance, as this ratio has not been achieved for some quinolones with current dosage regimens.

The intracellular environment

Professor Margaret Hammerschlag presented interesting data on the diagnosis and interpretation of tests for the various Chlamydia species. She highlighted the difficulties with serodiagnosis, and therefore the conflicting results obtained with a range of studies. Professor Tulkens spoke again, this time on the current state of knowledge on the intracellular penetration and localisation of antibiotics, compared to the intracellular location of various intracellular pathogens.

Shining a light in dark corners: methods for non standardised susceptibility testing

Professor Tenover presented a range of ideas on how to approach susceptibility testing of the problematic pathogens, including those for which there are no standardised tests, and those for which the standardised tests can be misleading, and additional tests may be required.

Non-human use of antibacterials: antibiotics in the mix

John Turnidge discussed the final JETACAR report and presented evidence linking the development of van A E. faecium with avoparcin, Campylobacter resistance with animal quinolone use, and multi-resistant Salmonellas with animal antibiotic use. He reported that avoparcin has now been withdrawn from sale world-wide, and said that virginiamycin was currently under study. For more information on the final JETACAR report and the government response to it, see the next issue of this newsletter. Also at this session, Mary Barton from Adelaide spoke on prudent use in animals from a veterinary perspective, and Ruth Hall from CSIRO spoke on genetics.

Quiz: Why is this so?

This E. coli isolate was found to be an extended spectrum beta-lactamase (ESBL) producer using NCCLS methodology and the following discs:

1. cefpodoxime (CPD10) and cefpodoxime / clavulanic acid (CD01);
2. ceftazidime (CAZ30) and ceftazidime / clavulanic acid (CD02);
3. cefotaxime (CTX30) and cefotaxime / clavulanic acid (CD03).

Why is this so? Answer page 11.

Conclusion

The meeting was a resounding success and we thank all the industry sponsors without whom we would be unable to run such a high standard meeting. We look forward to Antimicrobials 2002 in Sydney. At this meeting, due to the high standard of local research abstracts submitted to the first two meetings, we plan to introduce a preferred papers session in addition to a poster session. As always, we plan to have at least three international speakers as well.
In Vitro Antifungal Activity of Voriconazole against Moulds

Rosemary Perrie & David Ellis

Voriconazole is a new second-generation triazole developed by Pfizer with the aim of improving the potency and spectrum of fluconazole. Voriconazole has potent activity against yeasts and moulds, including Candida, Cryptococcus, Aspergillus and the dimorphic pathogens Histoplasma capsulatum, Blastomyces dermatitidis, Coccioidioides immitis, Paracoccidioides brasiliensis and Penicillium marneffei. It is also active against fluconazole-resistant yeasts such as Candida krusei and C. glabrata and additional moulds like Pseudallescheria boydii, and species of Fusarium, Acremonium and Trichosporon that are resistant to fluconazole, itraconazole and amphotericin B. Voriconazole is also active against many of the dematiaceous moulds like Cladophialophora and Bipolaris as well as the dermatophytes. Voriconazole has both oral (90% bioavailability) and IV formulations and is widely distributed in body tissue and fluids. We have studied the in vitro activity of voriconazole, amphotericin B and itraconazole against 297 moulds consisting of 44 species belonging to 21 genera.

MIC Microbroth Dilution Method

All isolates were tested by broth microdilution according to the NCCLS M38-P standard i.e. RPMI-1640 medium supplemented with 0.2% glucose and buffered with 0.165 mol/L MOPS, inoculum standardized using a spectrophotometer to approximately 0.4 x 10^4 to 5 x 10^4 CFU/ml, and incubation at 35°C. Microtitre trays were read at 24 and 48 hours for faster growing moulds like Aspergillus and at 72 hours for slower growing moulds like Scedosporium. Inoculum and density checks were done for each test and the following QC stains were used, Candida parapsilosis (ATCC 22019), C. krusei (ATCC 6258) and Paecilomyces variotii (ATCC 22319).

Results

The following fungi had MIC90’s of less than 0.5 µg/ml for Voriconazole; Aspergillus fumigatus, A. flavus, A. nidulans, A. niger, A. terreus, Scedosporium apiospermum (Pseudallescheria boydii), Penicillium marneffei, Paecilomyces sp., Bipolaris sp., Curvularia sp., Exserohilum sp., Exophiala sp., Cladophialophora sp., Phialophora sp., Alternaria sp. and Wangiella sp. However Scedosporium prolificans, Acremonium sp. and most isolates of Fusarium appear to be resistant to all three agents tested; but as with other moulds additional strains need to be tested. Zygomycetous moulds all exhibit poor activity against voriconazole, with MIC90’s in the range 2-8 µg/ml.

Conclusion

The in vitro activity of voriconazole was more potent than or similar to those of itraconazole and amphotericin B for most isolates tested. Voriconazole was more active than amphotericin B against Aspergillus species and Scedosporium apiospermum. All three antifungal agents exhibited poor activity against Fusarium species, Scedosporium prolificans and the zygomycetes. These results are generally consistent with previous comparisons for the in vitro activity of Voriconazole. The proposed indications for voriconazole are invasive aspergillosis; serious Candida infections (including C. krusei), including oesophageal and systemic Candida infections (hepatosplenic candidiasis, disseminated candidiasis, candidaemia); serious fungal infections caused by Scedosporium spp and Fusarium spp. and other serious fungal infections in patients intolerant of, or refractory to, other therapy. It may also be used for the prevention of breakthrough of fungal infections in febrile high-risk patients.

Acknowledgement

This study was supported by a research grant from Pfizer Pharmaceuticals Group.

References

### Susceptibilities [µg/ml] of moulds to Voriconazole, Amphotericin B and Itraconazole

<table>
<thead>
<tr>
<th>Species</th>
<th>No.</th>
<th>Range</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>Voriconazole</th>
<th>Range</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>Itraconazole</th>
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<td><em>Cladophialophora carrionii</em></td>
<td>5</td>
<td>0.03-1.25</td>
<td>0.125</td>
<td>4.0-8.0</td>
<td>8.0</td>
<td>0.06-0.5</td>
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<td>C. bantiana</td>
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<td>0.25</td>
<td>1.0-4.0</td>
<td>4.0</td>
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<td>B. hawaiiensis</td>
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<td>1.0</td>
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<td><em>Exophiala spinifera</em></td>
<td>1</td>
<td>0.125</td>
<td>0.125</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td><em>Curvularia brachyspora</em></td>
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<td><em>C. lunata</em></td>
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<td><em>Exserohilum rostratum</em></td>
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<td>0.125</td>
<td>1.0-2.0</td>
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<td>0.06-0.5</td>
<td>0.5</td>
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<tr>
<td><em>Sporothrix schenckii</em></td>
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<td>0.03-0.25</td>
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<td><em>Absidia corymbifera</em></td>
<td>3#</td>
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<td>4.0</td>
<td>2.0-8.0</td>
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<td>0.25-1.0</td>
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<tr>
<td><em>Mucor racemosus</em></td>
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<td>M. indicus</td>
<td>2#</td>
<td>2.0-4.0</td>
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<td>1.0-2.0</td>
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<td><em>M. ramosissimus</em></td>
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<td>Cunninghamella bertholletiae</td>
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<td><em>Syncephalestrum racemosum</em></td>
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<td>1.0</td>
<td>1.0</td>
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</tbody>
</table>

*Tests read at 72 hours incubation  
#Tests read at 24 hours incubation
Table 1. PAE parameters after 1 h exposure to linezolid

<table>
<thead>
<tr>
<th>Strain</th>
<th>Linezolid MIC (mg/L)</th>
<th>PAE range (0.5-64x MIC) (h)</th>
<th>PAE max a</th>
<th>E50 (mg*h/L)</th>
<th>Corrected r² b</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA ATCC 25923</td>
<td>1.5</td>
<td>0 – 2.2</td>
<td>3.6</td>
<td>37.5</td>
<td>0.926</td>
</tr>
<tr>
<td>MSSA MK803549</td>
<td>0.75</td>
<td>0 – 1.8</td>
<td>1.9</td>
<td>4.8</td>
<td>0.963</td>
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<tr>
<td>MRSA ATCC 49476 c</td>
<td>0.75</td>
<td>0.5 – 2.2</td>
<td>2.2 d</td>
<td>5</td>
<td>0.656</td>
</tr>
<tr>
<td>MRSA MK810545 c</td>
<td>1</td>
<td>-0.5 – 1.3</td>
<td>1.3</td>
<td>10.6</td>
<td>0.688</td>
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<tr>
<td>S. epidermidis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MSSE ATCC 12228</td>
<td>0.375</td>
<td>0.3 - 2</td>
<td>2 d</td>
<td>2.3</td>
<td>0.897</td>
</tr>
<tr>
<td>MSSE M35732</td>
<td>0.5</td>
<td>0 – 1.2</td>
<td>1.2 d</td>
<td>12.3</td>
<td>0.802</td>
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<tr>
<td>MRSE MK506349 c</td>
<td>0.375</td>
<td>0.2 – 1.7</td>
<td>1.8</td>
<td>1.7</td>
<td>0.972</td>
</tr>
<tr>
<td>MRSE MK711617 c</td>
<td>0.25</td>
<td>-0.3 – 1.7</td>
<td>1.8</td>
<td>4.4</td>
<td>0.898</td>
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<tr>
<td>Enterococci</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>E faecalis ATCC29212</td>
<td>1.5</td>
<td>0.3 - 2</td>
<td>2 e</td>
<td>10.2</td>
<td>0.888</td>
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<tr>
<td>VRE faecalis M106009p</td>
<td>1</td>
<td>0.1 – 2.1</td>
<td>3.4</td>
<td>20.3</td>
<td>0.988</td>
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<tr>
<td>VRE faecalis M23304 y</td>
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<td>0.3 – 1.4</td>
<td>1.4 e</td>
<td>3.8</td>
<td>0.839</td>
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<tr>
<td>VRE faecium M31838 e</td>
<td>1</td>
<td>0 - 2</td>
<td>2</td>
<td>5.3</td>
<td>0.997</td>
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<td>S. pneumoniae</td>
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<td></td>
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<tr>
<td>ATCC 49619</td>
<td>0.5</td>
<td>0.1 – 2.3</td>
<td>4.2</td>
<td>13.6</td>
<td>0.981</td>
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<tr>
<td>M48191</td>
<td>0.75</td>
<td>0.5 – 2.3</td>
<td>2.6</td>
<td>1.7</td>
<td>0.99</td>
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<tr>
<td>4G12043</td>
<td>0.75</td>
<td>0 – 2.5</td>
<td>2.7</td>
<td>2.6</td>
<td>0.98</td>
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<tr>
<td>4H02517 e</td>
<td>1.5</td>
<td>0 – 2.5</td>
<td>2.6</td>
<td>4.6</td>
<td>0.903</td>
</tr>
</tbody>
</table>

a PAE max (maximum PAE) and E50 (AUC of linezolid exposure at which 50% of the maximum PAE is reached) were estimated by non-linear least squares regression.
b Corrected r² (defined as the correlation squared between the observed values and the predicted values) shows the degree of fit with the experimental data, using Systat v8.0.
c These isolates are methicillin-resistant.
d These values were fixed in the regression function to enable adequate fit.
e VR, vancomycin-resistant.
f This isolate is relatively penicillin-resistant, with a penicillin MIC of 1.5 mg/L.

The Ability of Mueller Hinton Agar to Detect Low-Expression-Class MRSA

Continued from page 8

Discrepant results for the methicillin 10 mg/L plate:

Isolate 1:
Failed to grow on all 6 MHA.

Isolate 3 and 4:
Failed to grow on 2 MHA.

Isolate 6:
Failed to grow on 1 MHA.

NOTE: Growth characteristics of the isolates varied. Many had minute colonies (haze) making detection of growth difficult.

Conclusions

• The performance of the Kirby-Bauer disc diffusion method and the NCCLS screening plates for the detection of LEC MRSA is dependent on the MHA used.

• Kirby-Bauer Disc Diffusion - LEC MRSA may produce zones of inhibition that may be difficult to interpret.

• NCCLS Screening Plates - Both the 6mg/L oxacillin and the 10mg/L methicillin screening plates may be unreliable for detecting LEC MRSA. Colonies are often minute and therefore difficult to detect.

Recommendations

• Every batch of MHA should be tested for performance before being used for routine susceptibility testing (including batches of MHA that are labelled as having met the NCCLS M6-P standard).

• In addition to the susceptible S aureus control (ATCC 25923) and the LEC MRSA control (ATCC 43300) several locally acquired LEC should also be tested.

Confirmation of ESBLs Using Combination Discs

Recently the National Committee for Clinical Laboratory Standards (NCCLS) recommended using extended spectrum cephalosporin discs with and without clavulanic acid for the confirmation of extended spectrum beta-lactamase (ESBL) positive organisms1.

The combination disc and the equivalent single cephalosporin disc are placed on Mueller Hinton or Iso-Sensitester Agar inoculated with a 0.5 McFarland suspension of the organism to be tested. The discs are spaced to allow the formation of clearly defined inhibition zones. The plate is incubated at 35-37°C for 16-18 hours in ambient air. An organism is interpreted as ESBL-positive if there is an increase of >= 5mm in the inhibition zone of the combination disc when compared to that of the cephalosporin alone.

In the figure the following Oxoid combination discs have been used to confirm an ESBL+ E.coli:

Interpretation

<table>
<thead>
<tr>
<th>Cephalosporin Disc</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime (CTX30)</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefotaxime/clavulanic acid (CDO3)</td>
<td>ESBL NOT DETECTED</td>
</tr>
<tr>
<td>Cefazidime (CAZ30)</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefazidime/clavulanic acid (CD02)</td>
<td>ESBL DETECTED</td>
</tr>
<tr>
<td>Cefpodoxime (CPD10)</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefpodoxime/clavulanic acid (CD01)</td>
<td>ESBL DETECTED</td>
</tr>
</tbody>
</table>

NOTE: CD02 and CD03 combination discs are recommended by NCCLS. CD01 is an Oxoid innovation of the combination disc method which may correctly identify the presence/absence of ESBLs more frequently than the other combination discs2.

1. NCCLS M100-S10 Vol 20, No.1, Jan 2000

Picture quiz provided by Mr Geoff Coombs, Department of Microbiology & Infectious Diseases, Royal Perth Hospital. Phone: 08 9 224 2446. Fax: 08 9 224 1989

Quiz answer (from page 5)
The Ability of Mueller Hinton Agar to Detect Low-Expression-Class MRSA

Geoffrey Coombs, Cheryll McCullough, John Boehm & Keryn Christiansen

Department of Microbiology & Infectious Diseases, Royal Perth Hospital, WA
Email: geoffrey.coombs@health.wa.gov.au

Aim
To assess the performance of six commercially prepared Mueller Hinton agars (MHA) to detect Low-Expression-Class (LEC) methicillin-resistant Staphylococcus aureus (MRSA) by oxacillin and methicillin Kirby-Bauer disk diffusion and the NCCLS 6mg/L oxacillin and 10mg/L methicillin screening plates.

Isolates MICs (mg/L)
- mecA-negative S aureus (n = 1)
  - Isolate 1 0.5
- mecA-positive S aureus (n = 6)
  - Isolate 1 4
  - Isolate 2 8
  - Isolates 3, 4, 5, 6 16

Mueller Hinton Agar
- Acumedia® (batch # 0907-102) (Fig 1)
- Becton Dickinson BBL® (batch # 1500G 2D KUB) (Fig 2)
- Difco (batch # 156255XB) (Fig 3)
- Merck (batch # VK 563235) (Fig 4)
- Oxoid (batch # 213935) (Fig 5)
- Remel (batch # 031221) (Fig 6)

Results
Kirby Bauer Disk Diffusion
- MSSA
  - 4/6 MHA classified the isolate as oxacillin sensitive. A double zone was observed with all MHA.
  - 6/6 MHA classified the isolate as methicillin sensitive. A double zone was observed in 5/6 MHA.

- MRSA
  - 3/6 isolates were classified as oxacillin resistant on all 6 MHA (Figure 1). Discrepant results:
    - Isolate 1
      - Zone diameters ranged from 0–25mm: Sensitive on 4/6 MHA.
    - Isolate 3
      - Zone diameters ranged from 0–14mm: Sensitive on 2/6 MHA.
    - Isolate 6
      - Zone diameters ranged from 0–14mm: Sensitive on 2/6 MHA.

NOTE: Many of the zones of inhibition with both antibiotics had ‘double zones’ or ‘ill defined edges’ making interpretation difficult.

NCCLS Agar Screening Plates
- MSSA
  - Did not grow on all 6 MHA for both the 6mg/L oxacillin and 10 mg/L methicillin screening plates.
- MRSA
  - Only 2/6 MRSA isolates grew on all MHA. Discrepant results for the 6mg/L oxacillin screening plates:
    - Isolate 1 & 6:
      - Did not grow on all 6 MHA.
    - Isolate 3 & 4:
      - Did not grow on 2 MHA.

Continued page 11
Polymerase chain reaction (PCR)-based methods are being used increasingly as the ‘gold standard’ for the detection of methicillin resistance (mecA) in staphylococci. However, additional preparation steps for cell lysis or removal of potential inhibitors from clinical samples increase sample processing time and consequently delay results. In this study a single bacterial colony grown on an agar plate or an aliquot of growth from a positive blood culture bottle, showing gram-positive cocci resembling Staphylococcus spp., was used directly in a multiplex PCR assay, without further subculturing, DNA extraction or enzyme incubation (Fig.1). This procedure simultaneously detected mecA (methicillin resistance), femB (S. aureus) and bacterial 16S rRNA (universal control) genes. Multiple wash cycles with centrifugation were used to remove potential PCR inhibitors.

The assay was evaluated with 41 deposits from positive blood culture bottles, 3 clinical isolates from plate cultures which gave discrepant results on routine susceptibility testing and 40 isolates of staphylococci recovered from a frozen stock collection. To test specificity of the multiplex PCR procedure, 10 negative blood culture bottles and 7 bottles positive for isolates other than staphylococci were examined. Reference strains ATCC 29213 (MSSA) and ATCC 12228 (MSCoNS) were used as a positive controls. The results were compared with the oxacillin susceptibility reports generated by the Vitek 2 GPS-SA cards and with growth on an oxacillin screening plate (6mg/ml, 2% salt).

Results

There was a 100% correlation between Vitek, oxacillin screening plate and PCR results, for S. aureus and coagulase-negative staphylococci (CoNS) isolates obtained directly from blood culture bottles (representative results in Fig. 2). Multiplex PCR assisted in characterising plate cultures of isolates which gave discrepant results on routine testing and distinguished between MRSA and borderline resistant S. aureus (Fig. 2). All 40 frozen stocks (10 MRSA, 10 MSSA, 10 MRCoNS and 10 MSCoNS) were correctly categorised. Seven specimens from blood culture bottles that were positive for isolates other than staphylococci were negative for mecA and/or femB gene. Ten negative blood culture bottles gave negative results for mecA, femB and 16S rRNA genes.

Conclusions

The multiplex PCR direct from blood culture bottles described in this study:

• reliably categorises strains as MRSA, MSSA, MRCoNS and MSCoNS
• is specific
• is simple (no DNA extraction)
• can be completed in 6h compared with 48h for the conventional technique
• may detect of borderline resistant MRSA
• is cost effective (40 cents per isolate for consumables)
• is suitable for routine laboratory work
• more strains need to be tested to confirm these results
Postantibiotic Growth Suppression of Linezolid Against Gram-Positive Bacteria

Wendy J. Munckhof¹, Caroline Giles¹, & John D. Turnidge²

Linezolid has good antibacterial activity against Gram-positive bacteria including methicillin-resistant strains of staphylococci, Enterococcus spp. including vancomycin-resistant strains, and Streptococcus spp. including penicillin-resistant strains¹. Dosing regimens of new antibiotics such as linezolid may be influenced by pharmacodynamic phenomena such as the postantibiotic effect (PAE), defined as “persistent suppression of bacterial growth after brief exposure to an antibiotic”.

Aims of this Study

1. To determine the in vitro PAEs of linezolid against S. aureus, E. epidermidis, E. faecalis, E. faecium and S. pneumoniae.
2. To compare the duration of the PAEs for i. methicillin-resistant and – susceptible strains (staphylococci) ii. vancomycin-resistant and –susceptible strains (enterococci), and iii. penicillin-resistant and –susceptible strains (pneumococci).
3. To analyse the results using the sigmoid E₅₀ mathematical model that has been used to describe the relationship between PAE and AUC of drug exposure²-⁵.

Materials and Methods

Linezolid MICs were determined by E-test, using Mueller-Hinton agar (staphylococci and enterococci) or Mueller-Hinton agar supplemented with 5% sheep blood (pneumococci). MICs for all bacteria tested were less than 2-4 mg/L, tentative breakpoints that have been proposed for linezolid against Gram-positive cocci².

In vitro PAEs were determined according to standard methods using a viable plate counting technique³ previously used by us³-⁵. 10⁶ cfu/ml of organisms in logarithmic phase growth were exposed for 1 hour at 37°C to 8 different concentrations of linezolid ranging from 0.5 - 64 x MIC.

Broths used were Mueller-Hinton broth (staphylococci and enterococci) (BBL) and Brain Heart Infusion broth (pneumococci) (BBL). Subsequent methodology with drug removal by centrifugation and washing and determination of PAE has been described elsewhere³-⁵,¹⁷.

The results were analysed utilising the Hill (sigmoid E₅₀) dose – response equation, a mathematical formula which has been used to describe the relationship between PAE and AUC (area under the concentration – time curve) of drug exposure²-⁵. The Hill dose – response equation is:

\[
P_{AE} = \frac{PAE_{max} \times (AUC)^n}{(E_{50}^n) + (AUC)^n}
\]

where PAE₃₅₀ is the maximum PAE, E₅₀ is the AUC at which 50% of the maximum PAE is reached, and n is a constant associated with the steepness of the exposure-response curve. The parameters PAE₃₅₀, E₅₀ and n were then estimated for each of the bacterial strains using the nonlinear regression module of Systat for Windows v. 8.0 (SPSS Inc., Chicago, IL, USA).

Results

Maximum PAEs for the staphylococci ranged from 1.2 – 2.2 h, and results for the enterococci were similar with maximum PAEs of 1.4 – 2.1 h. Maximum PAEs for the pneumococci were slightly longer and ranged from 2.3 – 2.5 h (Table1).

Table 1 also shows the correlation between the PAEs determined experimentally and those estimated using the Hill (sigmoid E₅₀) equation, with corrected r² ranging from 0.656 – 0.990. For the majority of strains, correlation between experimental results and estimates using the Hill equation was very good, with corrected r² greater than 0.900.

Conclusion

Linezolid exhibits moderate concentration-dependent in vitro PAEs against S. aureus, S. epidermidis, E. faecalis, E. faecium and S. pneumoniae.

Resistance to methicillin (for staphylococci), vancomycin (for enterococci), and penicillin (for pneumococci) had no effect on the duration of the PAE.

Although the presence or absence of in vivo PAE is usually predicted by in vitro studies¹, these results should be confirmed in animal models, as host defence mechanisms, concentrations of drug within the cell, tissue binding of drug, and sub-MIC effects may be important.

Results of PAE testing support twice-daily dosing of linezolid in humans.

Acknowledgements

This work was partly supported by a grant from Pharmacia and Upjohn, Sydney, Australia. We are grateful to Jacqui Schooneveldt and Graeme Nimmo from the Dept. of Microbiology, Princess Alexandra Hospital, Brisbane, for the supply of bacterial isolates.

References


³ ¹ Infection Management Service, Princess Alexandra Hospital, Brisbane;
² Dept of Microbiology & Infectious Diseases, Women’s and Children’s Hospital, Adelaide.
Preliminary announcement

ANTIMICROBIALS 2002

Sydney
Feb 28 – March 2

Invited Speakers

Ferdinand Baquero
Professor of Microbiology,
Ramon y Cajal Hospital, Madrid, Spain

Ferdinand is well known for his work on antimicrobial resis-
tance and is a European and international leader in this field.
He has numerous publications on the selective pressure of
macrolides, beta-lactams and resistant Streptococcus pneu-
moniae, ciprofloxacin-resistant pneumococci, concentration
specific amplification of low level resistant populations and
selection on ESBL’s by beta-lactam use. He also has consid-
erable experience with cystic fibrosis, the 1300 bed Ramon y
Cajal Hospital having a large CF unit. He is active interna-
tionally in the consideration of resistance reduction strategies.

Hendrik Wegener,
Research Professor,
Danish Zoonosis Centre, Danish Veterinary Laboratory,
Copenhagen, Denmark

Hendrik is very active in the area of animal use of antimicro-
bials and has been involved with the World Health
Organisation and their evaluation of the implications of such
use to human health. Denmark has shown major leadership in
tackling the issues around antibiotic use in both humans and
animals. Hendrick has been a key player in the Danish animal
resistance surveillance program and policy development in the
area. He is a speaker who gives a very balanced approach to
all aspects of an area that is of major concern for human health
and of economic significance to agricultural producers.

PRELIMINARY ANNOUNCEMENT

8th Western Pacific Congress on
Chemotherapy & Infectious Diseases
Perth,
1- 5 December, 2002

ASA has accepted responsibility for hosting this meeting. A
brochure was included with this newsletter. For further details
contact:

ICMS Pty Ltd.,
84 Queensbridge St., Southbank, VIC., 3006.
Telephone: (03) 9682 0244 Facsimile: (03) 9682 0288
Email: wpccid@icms.com.au Internet: www.icms.com.au/wpccid

ASA WORKSHOP
during the
2001 AUSTRALIAN SOCIETY FOR MICROBIOLOGY
ANNUAL SCIENTIFIC MEETING
30 Sep – 5 Oct, 2001
Perth

Interactive keypad workshop
“ Reporting practices and interpretative comments: value
adding to susceptibility testing”

Presented by: Keryn Christiansen, Royal Perth Hospital;
Jan Bell, Women’s & Children’s Hospital, Adelaide;
Geoff Coombs, Royal Perth Hospital.

ASA subscriptions

2001/2002 subscriptions are now due. All members have
recently been posted renewal forms.

Subscriptions should be sent to:
Geoffrey Coombs,
ASA Treasurer,
Department of Microbiology & Infectious Diseases,
Royal Perth Hospital,
GPO Box X2213, Perth, WA, 6001.
Telephone: (08) 9224 2446.
Facsimile: (08) 9224 1989
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Newsletter Contributions

Submissions of articles for possible publication or letters to
the editor should be sent to:
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ASA Newsletter Editor,
Infection Management Services Southern Queensland,
Princess Alexandra Hospital,
Ipswich Road, Woolloongabba,
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Telephone: (07) 3240 5920
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Email: wendy_munckhof@health.qld.gov.au