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Antimicrobials and Drug Interactions

Louis Roller

Department of Pharmacy Practice, Victorian College of Pharmacy (Faculty of Pharmacy) Monash University, VIC

"EVERYTHING IS A DANGEROUS DRUG EXCEPT REALITY, WHICH IS UNENDURABLE"
CYRIL CONNOLLY, THE UNQUIET GRAVE, 1945

INTRODUCTION

It has been estimated that, on average, a hospitalised patient may receive as many as six to ten different drugs during their admission. Ambulatory patients may be taking a comparable number of medications, and these estimations do not give any indication of the usage of home and/or over-the-counter remedies and complementary medicines. It is not uncommon for older persons to be taking 15-25 medications for various chronic conditions.[1-4]

It is an accepted rule of prescribing that whenever possible one medication should be used for one condition. However, this is not always possible. For example, in chronic disease states, such as epilepsy, diabetes, heart disease, asthma, hypertension, HIV/AIDS and cancer the conjoint administration of several drugs may be beneficial and even necessary. Multiple drug therapy may constitute good practice but unfortunately, this may lead to adverse drug reactions and/or drug-drug interactions.[1-4]

Commonly, two or more drugs given together for the same condition act quite independently of each other, (eg aspirin and a penicillin for a streptococcal throat infection). However, the concurrent use of two drugs can change the effects of both, which may be beneficial (as in the case of penicillins with probenecid), or detrimental, (as in the case of simvastatin and clarithromycin leading to elevated serum levels of simvastatin and toxicities such as myopathy and rhabdomyolysis).[5-8]

MECHANISMS OF DRUG INTERACTIONS

A drug interaction might be defined as *"a measurable modification (in magnitude or duration) of the action of one drug by prior or concomitant administration of another substance, including prescription and non-prescription drugs, food, alcohol, cigarette smoking or diagnostic tests"*.[5-8]

Drug interactions generally to fall into two major categories: **pharmacokinetic interactions** or **pharmacodynamic interactions.**

PHARMACOKINETIC INTERACTIONS

Pharmacokinetic interactions are those in which the absorption, distribution, metabolism or excretion of a drug is altered and these are certainly the most commonly seen with antimicrobial interactions.[6-13]

ABSORPTION

Since most drugs are given orally, drug interactions resulting in altered absorption of an agent in the upper gastrointestinal tract are the most important example of this kind of interaction. One common example is the formation of poorly-soluble complexes between tetracycline group of antibiotics with antacids containing divalent or trivalent ions such as magnesium, calcium, aluminium and bismuth. Similarly, iron and zinc-containing preparations will markedly reduce the absorption of tetracyclines. Antacids may also drastically reduce the bioavailability of ketoconazole, fluoroquinolone antibiotics, digoxin, iron compounds, nitrofurantoin, phenothiazine tranquillisers, and propranolol. Generally, these interactions may be prevented by advising the patient to take the two drugs at a suitable time-interval apart.[6-13]

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Antimicrobials and Drug Interactions... Cont

Distribution

Once a drug has been administered parenterally or has been absorbed via the gastro-intestinal tract it is rapidly distributed around the body by the circulation. Many drugs will become protein bound, particularly to plasma albumin. The extent of protein binding varies greatly, but some drugs are very highly protein bound (eg. warfarin is 99.6 percent bound to plasma albumin). It should be remembered that although only the *unbound* form of the drug is available for pharmacological action, the bound fraction of drug is relatively protected from the effects of metabolism and excretion. Antimicrobial agents that are highly protein-bound include amprenavir (90%), atovaquone (99.9%) ceftriaxone (85-95%), daptomycin (92%), doxycycline (93%), dicloxacillin (95-98%), efavirenz (99%), itraconazole (99.8%), mefloquine (98%) and the sulfonamides. When one highly protein bound drug competes with another highly bound drug (eg warfarin, phenylbutazone, methotrexate, phenytoin) for the limited binding sites that exist on the protein, a change in either agent's pharmacokinetics can occur[6-13].

Metabolism (biotransformation)

Some drugs are excreted unchanged, however, most drugs are chemically altered within the liver microsomes into smaller, more water soluble molecules, or combined with glucuronic acid or sulphate to form larger, but again more water soluble compounds which are then excreted. Most drugs must be *biotransformed* or *metabolised* in this way before they can be excreted. In pharmacokinetics, the word "metabolism' often refers to the process of making the drug more polar and hence water soluble. In most cases, metabolism leads to termination of drug action via inactivation and excretion. On some occasions, metabolism may yield a more active species. This latter principle can be used therapeutically to create prodrugs (such as many anti-HIV reverse transcriptase inhibitors which are activated inside cells). Drug metabolism reactions are commonly classified as either Phase I or Phase II reactions[6-13].

Phase I (nonsynthetic) reactions generally involve relatively minor structural modifications of the parent drug via oxidation, reduction or hydrolysis in order to produce a more water soluble (more polar) metabolite. Frequently, Phase I reactions provide a 'handle' for further modification of a compound by subsequent Phase II reactions.

Phase II reactions (synthetic) involve the coupling of a water soluble endogenous molecule such as glucuronic acid, sulfate, glutathione to a chemical (parent chemical or Phase I metabolite) to facilitate excretion. Phase II reactions are frequently termed 'conjugation' reactions.

Collectively, these enzymes are generally referred to as drug metabolising enzymes. Although the major organ of metabolism is the liver, the levels of some drug metabolising enzymes are quite high in the gastrointestinal tract, lung, brain, and kidney. The cytochrome P450 enzyme system is the most important and well-studied of the drug-metabolising enzymes. In terms of drug interactions, the most important of these are CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. The activity of drug metabolising enzymes such as the cytochromes P450 is influenced to a significant degree by such factors as: genetic polymorphism, enzyme inhibition, enzyme induction, diet, health status, gender and age[6-13]. The clinical significance of these alterations depend largely on the therapeutic index of the drug in question[6].

Pharmacogenetic polymorphisms

Genetic differences in the metabolism of various drugs and environmental chemicals have been known for more than four decades. These differences are frequently referred to as pharmacogenetic polymorphisms. These polymorphisms represent variations in the genes encoding drug metabolising enzymes including the cytochromes P450. Historically, such polymorphisms were identified following unexpected responses to therapeutic agents. More recently, advances in nucleic acid amplification and detection techniques have enabled identification of the precise alterations in genes that are responsible for some of these polymorphisms. As more polymorphisms are identified, it is becoming apparent that each individual possesses a distinct complement of drug metabolising enzymes. This diversity might be described as a 'metabolic fingerprint'[6-13].

Enzyme inhibition

Inhibition is reduced enzyme activity due to direct interaction with a drug. This process usually begins with the first dose of the inhibitor, and the duration of inhibitions correlate with the half-lives of the drugs involved. There are three basic types of enzyme inhibition:

(i) *competitive:* between the substrate and the inhibitor for the same binding site on an enzyme, eg, fluoxetine and desipramine (CYP2D6), omeprazole and diazepam (CYP2C19);

(ii) *non-competitive:* eg drugs such as carbamazepine, midazolam and cyclosporin are catalysed by CYP3A, and hence their plasma concentrations are increased when their metabolism is inhibited by use with such drugs as erythromycin, clarithromycin, and ketoconazole;

(iii) *uncompetitive:* eg cimetidine (competitor) binds at a site on the enzyme distinct from the substrate and hence will tend to interact with many drugs.

Enzyme induction

The effect of induction is to increase the amount of P450 isoenzyme(s) present, thereby increasing the metabolism and clearance of a drug. A additional factor in the time-course of induction is the time required for enzyme degradation and new enzyme production. The short half-life of rifampicin results in enzyme induction (CYP3A4, CYP2C) which is usually apparent within 24 hours, whereas phenobarbitone, which has a half-life of 3-5 days, requires about one week for induction (CYP3A4, CYP1A2, CYP2C) to become apparent.

Figure 1 illustrates the potential effects of an enzyme inhibitor or an enzyme inducer on a substrate drug.

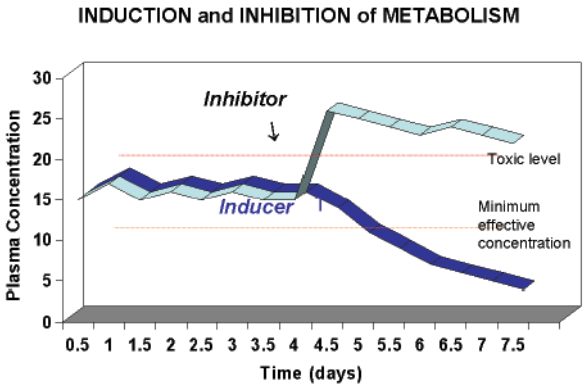

Figure 1: Potential effects of an enzyme inhibitor on a substrate drug (light shading) and the effects of an enzyme inducer (dark shading) of the same substrate drug. Note that the plasma levels of the substrate drug are represented by troughs and peaks and up until the introduction of either the inhibitory agent (increases plasma levels of the substrate drug to toxic levels) or the inducing agent (decreases plasma levels of the substrate drug to sub-therapeutic levels) the drug is within its appropriate therapeutic range.

Interactions at excretory sites

Any factor which either enhances or reduces excretion of a drug will have an effect on the serum level of that drug. This is most commonly seen with drugs that are excreted via the urine. Antibiotics that are eliminated primarily via the kidneys unchanged include the penicillins, cephalosporins and the fluoroquinolones.

Tubular secretion: Probenecid can increase serum levels of penicillins and cephalosporins by blocking their excretion, and this interaction is commonly utilised to therapeutic advantage. However, competition for tubular secretory sites can also occur with other combinations where the consequences are not as beneficial.

Changes in urinary pH: The renal clearance of weak organic bases with pKa values of 7.5 to 10 is increased if the urine is rendered acidic (eg with ammonium chloride, hexamine, megadoses of ascorbic acid) and decreased in alkaline urine (sodium bicarbonate & citrate, potassium bicarbonate & citrate, vegetarians, etc.). Conversely, the clearance of weak organic acids (pKa, 3.0 to 7.5) is higher in alkaline than acid urine. Nitrofurantoin and hexamine hippurate, which are frequently used in the prophylaxis or treatment of urinary tract infections, are examples of antimicrobial agents that require an acidic urine for activity. The concomitant use of urinary alkalinisers with these agents significantly reduces their antimicrobial effects[6-9,13].

Table 1 shows some common and potentially serious drug or drug class interactions with antimicrobial agents, the likely effect and mechanism of action where known.

Pharmacodynamic interactions

Pharmacodynamic interactions are those that involve the actions or effects of drugs at receptor sites, and include situations such as concurrent administration of two drugs having similar (potentiating) or opposing (antagonistic) effects. In many situations, there may be more than one mechanism involved. This may lead to either an increase in concentration or activity of one drug in the presence of another, leading to potential toxic reaction or conversely, a reduction in activity or reduction in plasma levels of that drug in the presence of another and therefore a diminution of clinical effect.

Oral contraceptives and antimicrobials

There are no good data to support anecdotal reports that the use of oral contraceptives with most antimicrobial agents reduces contraceptive efficacy. There is a very low level of risk (about 1%) of interactions between oral contraceptives and antimicrobials. Interactions may occur in a small subset of women with extensive enterohepatic circulation. However, there is no way of identifying this subgroup. There have been numerous reports of women becoming pregnant while taking oral contraceptives and rifampicin together. For other antimicrobials, data are conflicting and prospective studies are lacking or inconclusive. A practical approach to antimicrobial treatment in women taking oral contraceptives is that women should be given information about the use of barrier methods or avoidance of intercourse until their next menses if they are concerned about the risk, or have had previous contraceptive pill failure or developed breakthrough bleeding during antimicrobial use. A change to older, higher oestrogen dose contraceptives might provide a margin of safety in preventing contraceptive failure due to possible drug interactions. However, the increased risk of thromboembolic disease associated with the use of higher oestrogen dose contraceptives precludes their routine use. As both infections and antimicrobial agents not infrequently cause gastrointestinal symptoms, if an individual experiences vomiting or severe diarrhoea (as either an adverse effect of the medication or as a result of infection), additional contraceptive precautions should be taken[14,18].

Antimicrobials and Drug Interactions... Cont

Over-the-counter and herbal medicines

The Australian Pharmaceutical Formulary (APF)[13] has an extra-warning label[5] which is required to be applied to dispensed medicines which states:

"Ask your doctor or pharmacist before using any other medicine including over-the-counter medicines and herbal products."

This label is used for those medicines that are known to either have a low therapeutic index and/or cause multiple interactions usually via the inhibition of the metabolism of a range of medicines. It is designed to assist consumers and pharmacists to be aware of potential interactions. Certain complementary medicines can cause significant interactions with antimicrobials (eg St Johns Wort with ritonavir) and patients must be warned of this potential when taking these products.

Summary

The occurrence of a particular drug interaction in a given individual is a unique event, and as such, will best be addressed by an individualised approach that is unique to the circumstances. From the pharmacists' perspective, if an interaction of a type that is potentially dangerous is anticipated or detected, the patient should be informed that a consultation with the prescriber will occur and that a change in the medication(s) may be required [19]. Given the complex and often unpredictable nature of drug interactions involving antimicrobial agents, PC-or PDA-based drug interaction software programs (eg MIMS, MicroMedex, Epocrates) can be invaluable aids for the busy pharmacist or clinician to ensure that their patients are not placed at unnecessary risk of morbidity or mortality.

Table 1: Common drugs or drug class interactions with antimicrobial agents[6-17]

Drug	Interacting Drug	Effects	Mechanism
amiodarone	quinolones	↑QTc interval	similar action
	saquinavir	↑amiodarone	CYP3A4 inhibition
amoxycillin /ampicillin	allopurinol	↑incidence of rash	unknown
azole antifungals	antacids/ H2 RAs /	↓azole	↓absorption
	proton pump inhibitors		
	benzodiazepines	↑benzodiazepine	CYP3A4 inhibition
	cisapride	↑cisapride	CYP3A4 inhibition
	cyclosporin	↑cyclosporin	CYP3A4 inhibition
	tacrolimus	↑tacrolimus	CYP3A4inhibition
	didanosine	↓azole	↓absorption
	indinavir/saquinivir	↑indinavir/saquinivir	CYP3A4 inhibition
	quinine/quinidine	↑quinine/quinidine	CYP3A4 inhibition
	rifamycins	↓azole	CYP3A4 induction
	theophylline	↓theophylline	↓absorption?
	warfarin	↑warfarin	CYP3A4 inhibition
buspirone	azole antifungals	↑buspirone	CYP3A4 inhibition
	clarithromycin	↑buspirone	CYP3A4 inhibition
	erythromycin	↑buspirone	CYP3A4 inhibition
	rifamycins	↓buspirone	CYP3A4 induction
	verapamil	↑buspirone	CYP3A4 inhibition
carbamazepine	azole antifungals	↑carbamazepine	CYP3A4 inhibition
	clarithromycin	↑carbamazepine	CYP3A4 inhibition
	erythromycin	↑carbamazepine	CYP3A4 inhibition
	isoniazid	↑carbamazepine	mutual metabolism
		isoniazid toxicity	mutual metabolism
	ritonavir	↑carbamazepine	CYP3A4 inhibition
	doxycycline	↓doxycycline	enzyme induction
	phenytoin	↓carbamazepine	enzyme induction
	rifamycins	↓carbamazepine	enzyme induction
cisapride	azole antifungals	↑cisapride	CYP3A4 inhibition
	clarithromycin	↑cisapride	CYP3A4 inhibition
	erythromycin	↑cisapride	CYP3A4 inhibition
	fluconazole	↑cisapride	CYP3A4 inhibition
	indinavir	↑cisapride	CYP3A4 inhibition
	ritonavir	↑cisapride	CYP3A4 inhibition
	saquinavir	↑cisapride	CYP3A4 inhibition
clarithromycin/erythromycin	bromocriptine	↑bromocriptine	CYP3A4 inhibition
	buspirone	↑buspirone	CYP3A4 inhibition
	carbamazepine	↑carbamazepine	CYP3A4 inhibition

Table 1: Common drugs or drug class interactions with antimicrobial agents[6-17] Continued.....

	cisapride	↑cisapride	CYP3A4 inhibition
	pimozide	↑pimozide	CYP3A4 inhibition
	cyclosporin	↑cyclosporin	CYP3A4 inhibition
	ergot alkaloids	↑ergot	CYP3A4 inhibition
	midazolam	↑midazolam	CYP3A4 inhibition
	pimozide	↑pimozide	CYP3A4 inhibition
	quinolones	↑QTc interval	additive effects
	rifamycin	↑rifamycin↓macrolide	mutual metabolism
	triazolam	↑triazolam	CYP3A4 inhibition
	tacrolimus	↑tacrolimus	CYP3A4 inhibition
	theophylline	↑theophylline	CYP3A4 inhibition
	warfarin	↑warfarin	CYP3A4 inhibition
cyclosporin/tacrolimus	azole antifungals	↑cyclosporin/tacrolimus	CYP3A4 inhibition
	macrolides	↑cyclosporin/tacrolimus	CYP3A4 inhibition
	quinolones	↑cyclosporin/tacrolimus	enzyme inhibition
	rifamycins	↓cyclosporin/tacrolimus	CYP3A4 induction
felodipine	erythromycin	↑felodipine	CYP3A4 inhibition
	itraconazole	↑felodipine	CYP3A4 inhibition
indinavir	amiodarone	↑amiodarone	CYP3A4 inhibition
	antacids	↓indinavir	↓absorption
	azole antifungals	↑indinavir	CYP3A4 inhibition
	benzodiazepines	↑benzodiazepine	CYP3A4 inhibition
	carbamazepine/	↓indinavir	CYP3A4 induction
	cisapride	↑cisapride	CYP3A4 inhibition
	ergot alkaloids	↑ergot	CYP3A4 inhibition
	fentanyl	↑fentanyl	CYP3A4 inhibition
	phenytoin	↓indinavir	CYP3A4 induction
	other antiretrovirals	↑↓	inhibition/induction
	sildenafil	↑sildenafil	CYP3A4 inhibition
	St John's Wort	↓indinavir	CYP3A4 induction
phenytoin	azole antifungals	↑phenytoin↓azole	mutual metabolism
	isoniazid	↑phenytoin	enzyme inhibition
	rifamycins	↓phenytoin	CYP3A4 induction
	sulfonamides	↑phenytoin	enzyme inhibition
protease inhibitors	azole antifungals	↑saquinavir	CYP3A4 inhibition
sucralfate	ketoconazole	↓digoxin	↓absorption
	quinolones	↓digoxin	↓absorption
theophylline	macrolides	↑theophylline	enzyme inhibition
	quinolones	↑theophylline	enzyme inhibition

Table 1: Common drugs or drug class interactions with antimicrobial agents[6-17] Continued.....

warfarin	azole antifungals	↑warfarin activity	enzyme inhibition
	cotrimoxazole	↑warfarin activity	enzyme inhibition
	griseofulvin	↓warfarin activity	unknown
	macrolides	↑warfarin activity	enzyme inhibition
	metronidazole	↑warfarin activity	enzyme inhibition
	quinolones	↑warfarin activity	enzyme inhibition
	rifamycins	↓warfarin activity	enzyme induction
	sulfonamides	↑warfarin activity	enzyme inhibition
	tetracyclines	↑warfarin activity	↓synthesis vitamin K

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Responses to the ASA June 2005 picture quiz

1) What does this test demonstrate?

The test demonstrates metallo-β-lactamase (MβL) production in the organism. This is evidenced by: 1) imipenem resistance; 2) imipenem-EDTA susceptibility and 3) aztreonam susceptibility. In this organism, the approximation of the EDTA disc and the imipenem disc did **not** result in a zone of synergy between the two discs. This problem was highlighted by Clare Franklin in her excellent presentation on phenotypic detection of metallo-β lactamases at Antimicrobials 2005 (which is available to members on the ASA website) and emphasises the need to use more than one method for phenotypic identification of MβL production.

MβLs will hydrolyse all β-lactam agents with the exception of aztreonam, for which the enzyme has a low affinity (it should be noted however that aztreonam has been shown to be clinically inefficacious when used to treat infections caused by MβL-producing organisms). Resistance to ceftazidime and imipenem in a Gram-negative rod is suggestive of the presence of an MβL, and such isolates should be further investigated. Unlike other β-lactamases, which are serine proteases, the metallo-β-lactamases require divalent metal cations to catalyse their hydrolysis of the β-lactam ring. Zinc is the preferred ion, although cadmium may also be an effective catalyst. The zinc requirement of these enzymes may be utilised in a screening test for their presence. Upon the addition of EDTA to an imipenem disc, any zinc ions in the vicinity are chelated, inhibiting the action of the MβL and resulting in a zone of inhibition around the imipenem + EDTA disc. False positives may be seen in strains of *P. aeruginosa* possessing a mutant OprD porin (which results in imipenem resistance), and further testing should always be carried out prior to reporting the isolation of an MβL.

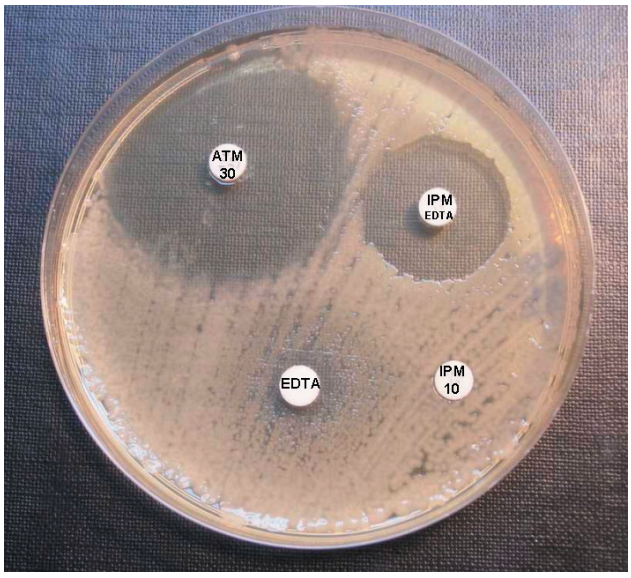
2) What might be the identity of this organism?

Metallo-β-lactamase enzymes can be found in a range of gram-positive and negative-bacteria. Oxidase positive gram-negative rods known to carry MBL enzymes include *Pseudomonas aeruginosa, Aeromonas* spp, *Flavobacterium* spp and *Cryseobacterium* spp.

This organism was identified as *Aeromonas hydrophila.* By the time the organism had been isolated, the patients diarrhoeal illness had resolved and the patient has been discharged.

3) Are there any potential infection control implications of isolating this organism with this susceptibility profile?

Apart from the chromosomal MβLs of some organisms (eg: *Stenotrophomonas maltophilia* and *Chryseobacterium meningosepticum*), genes coding for MβLs will be found on gene cassettes within class 1 or class 3 integrons. These are mobile genetic elements, and thus may be transferred from one Gram negative rod to another. The same integrons often carry partially deleted *qac* genes fused to *sul* genes, as well as gene cassettes coding for *aac* and *aad* class aminoglycoside hydrolysing enzymes. Such isolates will



display resistance to, and be selected by, the use of not only β-lactams, but quarternary ammonia disinfectants, sulfonamides and a variety of aminoglycosides. Thus there is great potential for the transfer of this remarkable degree of multi-drug resistance between gram-negative rods within a hospital setting..

Any isolation of an MβL producer by a hospital laboratory should be immediately reported to the infection control department. As MβLs are commonly found in *Aeromonas* spp (although they may not be detected by routine susceptibility testing methods)[1], and nosocomial patient – to patient transmission of this organism is not considered epidemiologically important, no added infection control precautions were instituted. If the organism had proven to be a *Pseudomonas aeruginosa* (which can be cultured from XLD media), then additional precautions would have been indicated to restrict the spread of the organism.

References

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PARTIAL CREDIT TO:

Richard Bradbury, Medical Scientist, Microbiology Department, Royal Hobart Hospital

CORRECTION

Picture Quiz June 2005 Question:

The "XLD" in XLD agar stands for "xylose –lysine desoxycholate, not "xylose – lysine decarboxylase" as stated originally.

Tigecycline: A New Glycylcycline

Sharmila Melvani

Infectious Diseases Pharmacist, Austin Health, Victoria

Introduction

Tigecycline (Tygacil; Wyeth) is the first of a new class of antibiotics called the glycylcyclines and has recently received approval from the US Food and Drug Administration for the treatment of complicated skin, skin structure and intra-abdominal infections. Glycylcyclines are semi-synthetic analogues of earlier tetracyclines and have been developed to circumvent common mechanisms of resistance (drug efflux and ribosomal protection) which have limited the use of tetracyclines in the past.[1] Structurally, tigecycline is a derivative of minocycline.[2]

Mechanism of action

Tetracyclines bind to the 30S ribosome within the bacterial cell, inhibiting protein synthesis.[3] It is thought that the glycylcyclines bind 5-fold more strongly to the 30S ribosome compared to tetracyclines, which overcomes the ribosomal protection mechanism of resistance.[4] In addition, glycylcyclines are unable to induce tetracycline efflux proteins[2] and have demonstrated activity against organisms that display efflux-based resistance and ribosomal protection.[4] Tigecycline is primarily bacteriostatic, although it is reportedly bactericidal for S. *pneumoniae*.[5, 6]

Spectrum of activity

In vitro activities of tigecycline against clinical isolates obtained between 1997 and 2004 are presented in table 1.[7] Tigecycline is active against a broad range of gram-positive organisms including methicillin-resistant S. *aureus* (including community-acquired strains), vancomycin-resistant enterococci, and penicillin-resistant S. *pneumoniae*, gram-negative organisms including extended-spectrum beta lactamase-producing strains of *E.coli* and *K. pneumoniae*. It is also active against most strains of anaerobic bacteria. Tigecycline has poor *in vitro* activity against *P. aeruginosa* (MIC_{90} = 16mg/L) and limited activity against *Proteus mirabilis, Providencia species* and *Burkholderia cepacia*. Activity has been reported against organisms that cause "atypical pneumonia" (eg *Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Mycoplasma hominis*) and nontuberculous mycobacteria.[8, 9]

Pharmacokinetics & pharmacodynamics

Unlike tetracyclines, tigecycline is only available in a parenteral form: oral bioavailability is poor.[10] It is administered as a 30 to 60 minute infusion twice daily. It has a high volume of distribution (>10 L/kg) indicating extensive distribution into the tissues, and protein binding is approximately 68%. It is eliminated primarily by the liver via biliary excretion of unchanged drug, and via glucuronidation with <30% of drug excreted unchanged in the urine.[10] It has a long half life (36 hours) which is prolonged in patients with renal dysfunction, but dose reduction is not required.[11] The maintenance dose should be halved in patients with severe (Child Pugh C) hepatic dysfunction. The AUC:MIC ratio is the pharmacodynamic parameter that appears to best correlate with bacteriologic eradication of infections caused by gram-negative and gram-positive bacteria.[12]

Clinical data

Tigecycline is active in a number of animal infection models. The animal data has recently been reviewed and summarised.[13] Two Phase II trials and four Phase III trials of tigecycline in the clinical setting have been completed. All trials assessed the safety and efficacy of tigecycline in the treatment of either complicated skin and skin structure infections (cSSSI) or complicated intra-abdominal infections (cIAI).

Phase II trials

A randomised, open label, dose ranging study of tigecycline in 160 hospitalised patients with cSSSI was performed.[14] Patients were randomised to receive either 25mg (initial 50mg loading dose) or 50mg (initial 100mg loading dose) of tigecycline every 12-hours. In the test-of-cure (TOC), clinical and microbiological cure rates were higher in the 50mg dose group (74% and 69%, respectively).

An open-label study of 111 patients with cIAI who received 50mg of tigecycline every 12-hours has been reported.[15] Diagnoses included perforated and gangrenous appendicitis, complicated cholecystitis, or perforated diverticulitis and peritonitis. Clinical cure rates at the TOC and end-of-treatment were 67% and 76% respectively, and in the intent-to-treat analyses corresponding cure rates were 55% and 72% respectively.

Tigecycline: A New Glycylcycline Continued....

In both trials, nausea (22% [25mg dose group], 35% [50mg dose group] and 42.3% [50mg cIAI group]) and vomiting (13% [25mg dose group], 19% [50mg dose group] and 27% [50mg cIAI group]) were the most common adverse effects reported. There was one episode of moderately severe *C. difficile* infection, deemed possibly tigecycline-induced by the investigators of the cIAI Phase II trial.

Phase III trials

Tigecycline was evaluated for the treatment of cSSSI in adults in two separate multinational, randomised, double-blind, active-controlled phase III trials.[16,17] Combined results were recently published.[18] These trials compared tigecycline (100mg load followed by 50mg 12-hourly) with vancomycin (1g IV 12-hourly) plus aztreonam (2g IV 12-hourly) for up to 14 days. The most common diagnosis was deep soft tissue infection with cellulitis. The primary efficacy endpoint was the clinical response at the TOC visit in the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. The pooled analysis demonstrated that tigecycline was as effective as vancomycin plus aztreonam therapy (CE: 86.5% [95% CI, 82.9% - 89.6%] versus 88.6% [95% CI, 85.1%-91.5%], P<0.001 for noninferiority, c-mITT: 79.7% [95% CI, 76.1% - 83.1%] versus 81.9% [95% CI, 78.3% - 85.1%], P<0.001 for noninferiority - refer to table 2). With respect to safety, nausea (34.5% versus 8.2%) and vomiting (19.6% versus 3.6%) were the most common adverse events in the tigecycline group.

Tigecycline has also been evaluated for the treatment of cIAI in hospitalised patients in two multinational, randomised, double-blind, phase III trials.[19,20] Again, combined results were recently published.[21] In both studies, patients were randomised to receive either tigecycline (100mg load followed by 50mg IV 12-hourly) or imipenem-cilastatin (500mg/500mg IV 6-hourly) for up to 14 days. The most common diagnoses included complicated appendicitis and cholecystitis. The primary efficacy endpoint was the clinical response at the TOC visit in the microbiologically evaluable (ME) and microbiological modified intent-to-treat (m-mITT) patients. Pooled analysis demonstrated that the clinical efficacy in the ME group was 81.6% for tigecycline, versus 86.2% for imipenem-cilastatin (95% CI for the difference, -4.5% to 4.4%; P<0.0001 for noninferiority) and in the m-ITT group was 80.2% for tigecycline versus 81.5% for imipenem-cilastatin (95% CI for the difference, -5.8% to 3.2%; P<0.0001 for noninferiority - refer to table 3). Again, nausea (24.4% versus 19%) and vomiting (19.2% versus 14.3%) were the most frequent adverse events associated with tigecycline.

Place in therapy

Is tigecycline a welcomed addition to the antibiotic therapy armamentarium? It is an expanded broad-spectrum antibiotic with activity against gram-positive, gram-negative, anaerobic, and atypical pathogens including clinically important drug resistant pathogens, which makes it an attractive agent. At this stage there is limited published clinical experience, however there is a potential role for tigecycline in the treatment of complicated skin and skin structure infections and intra-abdominal infections (as demonstrated in overseas trials) especially in patients with beta-lactam, quinolone or carbapenem allergy. However, its use in the Australian setting is yet to be established, and microbiological and clinical data for important emerging pathogens such as heteroresistant vancomycin intermediate *S. aureus* (hVISA) and community-acquired MRSA are lacking. The role of tigecycline in hospital practice will be better defined when there are clinical data in immunocompromised patients and patients with deep-seated infections such as osteomyelitis and endocarditis (tigecycline has been investigated in a rat model of endocarditis and a rabbit model of osteomyelitis and has demonstrated possible therapeutic potential).[22,23]

It should be noted that existing data regarding the efficacy of tigecycline in cSSSI and cIAI does not show superiority to currently available agents, and rates of some adverse effects (eg nausea and vomiting) are higher than those reported with comparative agents. There is no information about the safety or efficacy of tigecycline in children or pregnant women. Tigecycline is not contraindicated in patients with an existing tetracycline allergy, but caution is required given structural similarities. Tigecycline may have similar adverse effects as the tetracyclines (e.g. discolouration of teeth).[24]

A TGA approval application has been submitted for tigecycline in Australia. However, tigecycline may currently be acquired through the Special Access Scheme (SAS). At this point in time, use of tigecycline has been evaluated in a limited number of patients and no routine monitoring is required, however, as with any new medication, post marketing surveillance will be important to establish safety (especially with use beyond two weeks) and efficacy of tigecycline compared to currently marketed antibiotics.

Table 1 - *In vitro* activity of tigecycline against isolates obtained between 1997 and 2004 [7]

organism	no of isolates	MIC (µg/ml)	
		range	90%
gram-positive organisms			
Staphylococcus aureus			
methicillin-susceptible	160	0.03 – 0.25	0.12
methicillin-resistant	170	0.03 - 2	0.25
community-acquired, methicillin resistant	10	0.12 - 0.25	0.25
glycopeptide intermediate	19	0.06 - 1	0.25
Staphylococcus epidermidis			
methicillin susceptible	159	0.03 - 2	0.5
methicillin resistant	155	0.03 - 1	0.5
Staphylococcus haemolyticus	166	≤0.016 – 2	0.5
Streptococcus pneumoniae			
penicillin susceptible	176	≤0.03 – 0.12	0.06
penicillin intermediate	305	≤0.03 – 0.03	0.06
penicillin resistant	270	≤0.03 – 0.25	0.06
Streptococcus pyogenes	176	≤0.03 – 0.06	0.06
Streptococcus agalacticae	115	≤0.03 – 0.06	0.06
Enterococcus faecalis			
vancomycin susceptible	159	0.03 – 0.25	0.12
vancomycin resistant	147	≤0.016 – 0.5	0.12
Enterococcus faecium			
vancomycin susceptible	171	≤0.03 – 0.25	0.12
vancomycin resistant	155	≤0.03 – 0.25	0.12

Table 1 - *In vitro* activity of tigecycline against isolates obtained between 1997 and 2004 [7] Continued....

gram-negative organisms			
Citrobacter freundii	160	≤0.06 – 8	0.5
Enterobacter aerogenes	161	≤0.06 – 4	1
Enterobacter cloacae	160	0.25 – 8	0.5
Escherichia coli			
non ESBL producing	208	0.06 – 1	0.5
ESBL-producing	170	0.06 – 4	0.5
Klebsiella pneumoniae			
non-ESBL, non-AmpC producing	180	0.25 – 4	1
ESBL producing	171	0.12 – 4	2
AmpC producing	89	0.25 – 4	0.5
Klebsiella oxytoca	140	0.12 – 2	0.5
Morganella morganii	145	0.12 – 8	4
Proteus mirabilis	160	0.5 – 16	8
Serratia marcescens	160	0.25 – 8	2
Salmonella Enteritidis	229	0.12 – 2	1
Shigella sonnei	274	0.06 – 1	0.5
Pseudomonas aeruginosa	160	0.25 – 32	16
Acinetobacter baumannii	158	0.03 – 4	2
Aeromonas hydrophila	142	0.06 – 1	0.5
Burkholderia cepacia	183	≤0.06 – >32	16
Stenotrophomonas maltophilia	160	0.06 – 16	2
Haemophilus influenzae	204	0.06 – 1	0.5
Haemophilus parainfluenzae	157	0.06 – 2	1
Moraxella catarrhalis	240	≤0.03 – 0.25	0.12
Pasteurella multocida	126	≤0.015 – 0.25	0.12

Table 1 - *In vitro* activity of tigecycline against isolates obtained between 1997 and 2004 [7] Continued....

anaerobes			
Bacteroides fragilis group	425	0.015 – 32	4
Prevotella spp.	81	0.015 – 1	0.5
Clostridium difficile	63	≤0.06 – 0.25	0.5
Clostridium perfringens	70	0.03 – 4	0.5
Eubacterium lentum	30	≤0.06 – 1	0.25
Peptostreptococcus spp	99	0.015 – 0.25	0.25

Table 2 - Clinical cure rates from two pivotal studies in complicated skin and skin structure infections after 5 to 14 days of therapy (based on table included in Tygacil Product Information[24])

	tigecycline[a]	vancomycin/aztreonam[b]	Difference (tigecycline – vancomycin/aztreonam) % (95% CI)	Tests for noninferiority *P*
	n/N (%)	n/N (%)		
Integrated				
CE	365/422 (86.5%)	364/411 (88.6%)	-2.1 (-6.8 to 2.7)	<0.001
c-mITT	429/538 (79.7%)	425/519 (81.9%)	-2.1 (-7.1 to 2.8)	<0.001
Study 300[17]				
CE	165/199 (82.9%)	163/198 (82.3%)		
c-mITT	209/277 (75.5%)	200/260 (76.9%)		
Study 305[16]				
CE	200/223 (89.7%)	201/213 (94.4%)		
c-mITT	220/261 (84.3%)	225/259 (86.9%)		

[a] 100 mg initially, followed by 50mg every 12 hours

[b] vancomycin (1g IV every 12 hours) / aztreonam (2g IV every 12 hours)

Table 3 - Clinical cure rates from two studies of tigecycline in complicated intra-abdominal infections after 5 to 14 days of therapy (based on table included in Tygacil Product Information24)

	tigecycline[a]	Imipenem/Cilastatin	Difference (Tigecycline – imipenem/cilastatin) Percentage (95% CI)	Tests for noninferiority *P*
	n/N (%)	n/N (%)		
Integrated				
ME	441/512 (86.1%)	442/513 (86.2%)	0.0 (-4.5 to 4.4)	<0.0001
m-mITT	506/631 (80.2%)	514/631 (81.5%)	-1.3 (-5.8 to 3.2)	<0.0001
Study 301[20]				
ME	199/247 (80.6%)	210/255 (82.4%)		
m-mITT	227/309 (73.5%)	244/312 (78.2%)		
Study 306[19]				
ME	242/265 (91.3%)	232/258 (89.9%)		
m-mITT	279/322 (86.6%)	270/319 (84.6%)		

[a] 100 mg initially, followed by 50mg every 12 hours

[b] Imipenem/cilastatin (500mg every 6 hours)

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Tigecycline: A New Glycylcycline Continued....

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Antimicrobials 2005 Presentations

PDFs of presentations from the recent ASA annual scientific meeting

"Antimicrobials 2005" are now available in the members' area of the ASA website.

PDFs include the plenary, symposia, proffered and poster sessions. If you are not a member of ASA, membership applications forms can be downloaded from this website.

ASA AstraZeneca 2005 Travel Award

Congratulations to Jian Li from the Department of Pharmacy Practice at Monash University for being awarded the 2005 ASA AstraZeneca Travel Award. This award will assist Jian to attend the 45th ICAAC meeting to be held in Washington DC, USA in December 2005.

ANTIMICROBIALS IN ESTABLISHED CORONARY ARTERY DISEASE

Articles reviewed:

Azithromycin for the secondary prevention of coronary events.

Grayston JT, Kronmal RA, Jackson LA, Parisi AF, et al.

New England Journal of Medicine 2005; 352: 1637-45.

Antibiotic treatment of *Chlamydia pneumoniae* after acute coronary syndrome.

Cannon CP, Braunwals E, McCabe CH, Grayston JT et al.

New England Journal of Medicine 2005; 352: 1646-54.

Atherosclerotic vascular disease is the leading cause of morbidity and mortality in Western societies. Despite this dismal statistic, improved survival has been achieved through primary and secondary prevention strategies. In the search for new risk factors, infection, in particular with *Chlamydophila pneumoniae* has been identified as a possible cause or promoter of coronary artery disease. Several epidemiological and pathological studies have suggested that *C pnemoniae* infection increases the risk of coronary artery disease in those infected by 3-15%. Animal models have also suggested a pathogenic role for *C pneumoniae*.

In the study reported by Grayston and colleagues (the ACES trial), 4012 patients with stable coronary artery disease were randomised to a weekly therapy with oral azithromycin 600mg or placebo for one year. Patients were followed for a mean of 3.9 years. There was no significant difference in all-cause or cardiac mortality, nor cardiovascular morbidity between the two groups. A subgroup analysis of those patients who positive for *C pneumoniae* antibodies on study entry did not show a benefit from antibiotic therapy. Unfortunately, data on high sensitivity-CRP (hs-CRP) levels or other markers of inflammation was not presented, which may have shed some light on any possible anti-inflammatory effect of azithromycin.

Another large study was reported by Cannon and colleagues in the same issue of the NEJM (the PROVE-IT/TIMI 22 trial), 4162 patients with established coronary artery disease with a recent hospitalisation for acute coronary syndrome were randomised to receive gatifloxacin (400mg daily for two weeks, then 400mg for 10 days of every month) or placebo for a mean duration of 2 years. This trial also showed no reduction in the rate of cardiovascular events in the group that received gatifloxacin. A sub-analysis of this trial did show a benefit from pravastatin, in particular in those with a raised hs-CRP. Other large studies (eg WIZARD/ACADEMIC), and a well-constructed meta-analysis also have shown no therapeutic benefit from antimicrobial therapy in those with established coronary artery disease.

Comment

The above trials provide compelling evidence that anti-chlamydial antimicrobial therapy does not reduce the incidence of cardiovascular disease events in patients with established coronary artery disease. Coronary artery disease is a multi-factorial interaction between the environment and possibly hundreds of genes; *C pneumoniae* would appear to have only a minor role in the establishment of athersclerosis, and may have little or no role in the progression of coronary artery disease. To reduce the incidence of objective end-points of cardiac morbidity and mortality, a therapy has to either reduce plaque progression, or reduce plaque rupture. Thus far, the most successful treatment has been with statin drugs, where plaque regression has been shown with intravascular ultrasound. Other agents (eg ACE inhibitors, ARBs and glitazones) are also thought to have plaque and endothelium-stabilising properties. The data from these and other studies suggests that macrolides and fluoroquinolones, whilst active against *C. pneumoniae*, do not alter outcomes in established coronary artery disease. However, the possibility that these agents may be able to prevent atherogenesis or benefit those patients who have early atherosclerosis has not been excluded.

Timothy Bates

General Physician

Royal Perth Hospital, Perth WA

HOME IV TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Home management of mild to moderately severe community-acquired pneumonia: a randomised control trial.

Richards DA, Toop LJ, Epton MJ, McGeogh GRB, Town GU, Wynn-Thomas SMH, Dawson RD, Hlavac MC, Werno AM, Abernethy PD.

Medical Journal of Australia 2005; 183: 235-8.

Support continues to grow for home management of a number of infectious diseases. Evidence of safety and efficacy of home treatment of PSI class II and III community-acquired pneumonia (CAP) with oral antibiotics already exists.[1] Adding further evidence to the home-based treatment of CAP is this randomised controlled trial by Richards and colleagues conducted to determine whether community management of mild to moderately severe CAP was as effective and acceptable as standard hospital management.

Between July 2002 and October 2003, 49 of the 146 eligible patients presenting with mild to moderately severe CAP (CURB-65[2] scoring system 0-2) to the ED of Christchurch Hospital were randomised to receive home treatment (24) or standard hospital treatment (25). Other exclusion criteria included serious comorbidity requiring admission, immunocompromised patients, those with pleural effusion or pulse oximetry oxygen saturation of <92% on air and those living alone or outside the metropolitan area. Both groups were well matched apart from significantly more in the home group having had tertiary education.

Both groups received an initial IV dose of antibiotic according to the physician's choice but identical treatment guidelines were provided to both groups. Subsequent care in the home group consisted of daily GP visits and at least twice daily nurse visits.

Primary outcome measures were duration to discharge, duration of IV and subsequent oral antibiotics, self-rated symptom severity and general functioning. Secondary outcome measures included complications and patient satisfaction.

Median number of days to discharge was higher in the home care group (4 vs 2), however there was no difference in the number of days on IV or oral antibiotics. There was also no difference in patient-rated symptom scores or general functioning. Complications were similar in both groups while patient satisfaction was higher in the home care group. Finally, the estimated cost difference of home management was about $400 less per patient.

Comment:

The main strength of this study is its prospective, randomised controlled design involving the careful selection of a subset of patients that were predicted and subsequently found to be suitable for home treatment of CAP. However, the small study population including significant patient differences in the two groups and variation in treatment regimens call for further larger and more treatment concordant studies to be performed before home management of mild to moderately severe CAP gains universal acceptance as an effective alternative to hospital treatment.

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Michael Wehrhahn

Hospital in the Home (IVAB) Registrar

Royal Perth Hospital, Perth WA

MICROARRAY BASED DETECTION OF ANTIMICROBIAL RESISTANCE: A BRAVE NEW WORLD IN THE DIAGNOSTIC LABORATORY?

Microarray-based detection of 90 antibiotic resistance genes of gram-positive bacteria.

Perreten V, Vorlet-Fawer L, Slickers P, Ehricht R, Kunhert P, Frey J.

Journal of Clinical Microbiology 2005; 43: 2291 – 2302

Determination of bacterial antimicrobial resistance by nucleic acid amplification and detection is now routine in many Australian clinical microbiology laboratories. The range of resistance determinants that can be detected by current PCR-based methods is limited by a number of factors, including the requirement for numerous separate PCR reactions or complex multiplex PCR to detect more than one resistance gene in an organism of interest. Microarray technology allows the detection of numerous genes (or gene function) simultaneously, and is widely used in genome research laboratories. The authors of this paper (which include employees of the company that manufactures the microarray chips and readers used in the study) report on a microarray-based method of detecting multiple antibiotic resistance genes in a range of gram-positive bacteria that are commonly identified in the clinical microbiology laboratory.

36 strains of gram-positive bacteria (obtained mostly from reference collections) containing a wide range of resistance determinants were examined. 137 oligonucleotides (26-33-mers) representing sequences from 90 genes known to encode resistance in gram-positive bacteria were spotted onto a microarray incorporated into a specially-designed microreaction tube. Bacterial DNA was amplified and labelled with biotinylated nucleotides, then hybridised to the chip. A streptavidin-peroxidase conjugate was added to the tube and hybridisation detected using an array tube reader. Results were compared to standard PCR-based gene detection and phenotypic antimicrobial resistance to a wide range of agents was determined by broth microdilution (NCCLS/CLSI methodology).

The microarray-based method detected all but one of the numerous antimicrobial resistance genes known to be present in the 29 previously well-characterised bacteria (which included eight different genera of gram-positive bacteria commonly found in the clinical laboratory, and gram-positive resistance genes cloned into an *E. coli* vector). In addition, the microarray-based method detected many other antimicrobial resistance genes that were not previously known to be present in these strains. The microarray was also able to detect multiple resistance genes on a conjugative plasmid (pRE25) inserted into *Enterococcus faecalis* and *Bacillus anthracis*, and in addition identified multiple resistance genes in clinical strains of *Staphylococcus haemolyticus, Clostridium perfringens, Lactococcus lactis* and *vanA* vancomycin-resistant *Enterococcus faecium*, the presence of which were confirmed genotypically by PCR and phenotypically by broth microdilution.

Comment

Is microarray-based detection of antimicrobial resistance determinants feasible in a busy clinical microbiology laboratory? Possibly. The authors did not comment on the cost of the method in terms of equipment and consumables, which is likely to be very significant even when compared to standard nucleic acid amplification/detection methods. They did note that the entire process can be completed in less than 24h. Genes that have a high degree of sequence homology (eg *vanB* and *vanB2*) could not be differentiated on this chip, and resistance conferred by genes with single base mutations (eg *rpoB* gene polymorphisms) were not targeted, as this would require more stringent annealing conditions than used in this study. This promising data needs to be reproduced on a larger set of clinical isolates with a diverse range of resistance determinants, and also should be evaluated for gram-negative organisms (eg for the detection of ESBL and MBL genes).

Ronan Murray

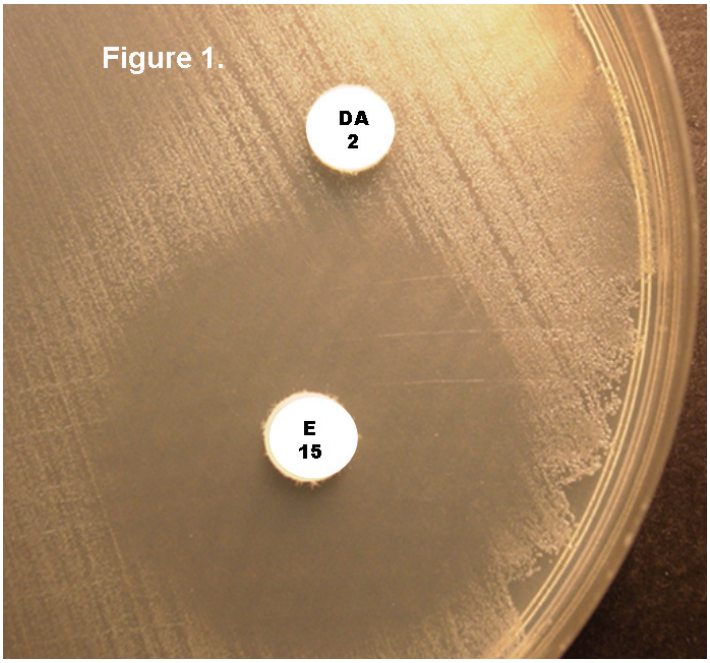
Infectious Diseases Physician and Clinical Microbiologist

PathWest Laboratory Services WA, Royal Perth Hospital, Perth WA

Picture Quiz September 2005

Staphylococcus aureus was isolated from a specimen of pus collected from a soft tissue abscess. The patient denied having received any recent antimicrobial therapy.

Figure 1 shows disc susceptibility testing results for erythromycin 15μg (E15) and clindamycin 2μg (DA2) using CLSI methodology. The discs are spaced 20mm apart.



1) What is the likely mechanism of resistance to clindamycin?

2) How would you report susceptibility to erythromycin?

Please email your responses to Dr Ronan Murray at ronan.murray@health.wa.gov.au or info@asainc.net.au

Answers will be published in the next issue and correct responses will be acknowledged.

Picture quiz provided by Cheryll McCullough and Ronan Murray from the Department of Microbiology and Infectious Diseases, Royal Perth Hospital, Perth WA

Newsletter Contributions

Submission of articles for possible publication or letters to the editor should be sent to:

Dr Ronan Murray
ASA Newsletter Editor
Department of Microbiology and Infectious Diseases
Royal Perth Hospital
GPO Box X2213
Perth WA 6847

Telephone: (08) 9224 2444
Facsimile: (08) 9224 1989
Email: ronan.murray@health.wa.gov.au

ASA Subscriptions

Subscriptions should be sent to:

Geoffrey Coombs
ASA Treasurer
Dept. of Microbiology & Infectious Disease
Royal Perth Hospital
GPO Box X2213
Perth WA 6847

Telephone: (08) 9224 2446
Facsimile: (08) 9224 1989
Email: geoffrey.coombs@health.wa.gov.au

Meeting Calendar

Appropriate use of Antimicrobials in Hospitals and the Community (International Society of Chemotherapy and Slovenian Society of Chemotherapy)

13th –15th October 2005

Bled, Slovenia

website: http://www.albatros-bled.com/dms-2005

9th International Union against Sexually Transmitted Infections: World Congress

15th to 18th November 2005

Bangkok, Thailand

The 45th Annual Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC) 2005 (American Society for Microbiology) (rescheduled)

16th-19th December 2005

Washington DC Convention Center
Washington DC, USA

website: http://www.ICAAC.org

8th International Symposium on Febrile Neutropenia

26th to 28th January 2006

Athens, Greece

website: http://www.imedex.com

International Conference on Emerging Infectious Diseases (National Center for Infectious Diseases, Centers for Disease Control)

19th – 22nd March 2006

Marriott Marquis
Atlanta, Georgia USA

website: http://www.iceid.org/

16th European Congress of Clinical Microbiology and Infectious Diseases (European Society for Clinical Microbiology and Infectious Diseases)

1st – 4th April 2006

Nice, France

website: http://www.akm.ch/eccmid2006/

Australasian Society for Infectious Diseases Annual Scientific Meeting

1st- 4th April 2006

Wellington Convention Centre/ Town Hall
Wellington, New Zealand

Meeting Information/Assistance:
Dart Associates:
Tel: 02 9418.9396/97
Fax: 02 9418 9398

Email: dartconv@mpx.com.au

International Society for Human & Animal Mycology (ISHAM) 2006

25th to 29th June 2006

Paris, France

website: http://www.isham.org

Australian Society for Antimicrobials 7th Annual Scientific Meeting

23rd - 25th February 2006

Crowne Plaza, Coogee Beach
Sydney, Australia

website:
http://www.icms.com.au/asa2006/