Tygacil® Mechanisms of Disease & Action

(two animations)

Overview

These two videos will comprise five – six minutes of 3-D animation. The first video covers the mechanisms of several classes of antimicrobial agents and the development of resistance to these agents. The second video captures the key messaging that Tygacil® is unique because of its structure, expanded broad-spectrum activity and ability to overcome the issue of resistance currently seen in other classes of antimicrobials.

Video I: Mechanism of Disease

In the United States, hospital-acquired infections afflict nearly 2 million patients, and many of these infections show resistance to common antibiotics.[1] **[Klevens *Public Health Rep*. 2007: pg160/¶3; pg163/col2/¶2]** The focus on resistance has increased in recent years as these types of infections are now also originating in the community.[2-4] **[Siegel 2006: pg7/¶2-pg8/¶1] [CDC 2009: pg2/¶4][Klevens JAMA 2007: 1769/Table 7; pg1770/col1/¶2]**

Factors such as overuse and misuse of antibiotics, lapses in infection control and proficiency of bacterial adaptation, have contributed to the prevalence of resistant infections.[3,5] **[Archer 2005: pg 789/col1/¶1] [CDC 2009: pg2/¶5]** When compared to susceptible infections, studies suggest that there is a substantial increase in mortality, morbidity, and cost for patients with antibiotic-resistant infections.[1,2] **[Siegel 2006: pg6/¶2-3] [Klevens *Public Health Rep*. 2007: pg164//c1/¶2]** Accurate diagnosis and appropriate treatment are critical.[2,3,5] **[Siegel 2006: pg6/¶2-3] [CDC 2009: pg2/¶4] [Archer 2005: pg 789/col1/¶1]**

To understand the evolution of bacterial resistance, we turn to the evolution of antibiotics. Over the decades, several classes of antibiotic agents have leveraged the biology of the bacterial cell to arrest or hinder its growth.[5] **[Archer 2005: pg 789/col1/¶2]** Common sites of action in both gram-negative and gram-positive bacteria are the cell wall, DNA, and ribosomes and today we will examine three classes of antibiotics that act on those sites – the beta-lactams, fluoroquinolones and tetracyclines.[5] **[Archer 2005: pg 789/col2/¶2; pg790 table 118-2; pg791/col1/¶2; pg792/col2/¶5]**

The beta-lactams, a class of drugs which include penicillins, carbapenems, cephalosporins, and beta-lactam/beta-lactamase inhibitor combinations (or BLICs), interfere with the synthesis of the bacterial cell wall through two mechanisms.[5,6] **[Archer 2005: pg 790/col1/¶4 –col2/¶1 and table 118-2][Chambers 2005: pg281/col2/¶4]** Beta-lactams inhibit the cell wall enzyme transpeptidase and inhibit penicillin-binding proteins, causing the lysis of the cell wall.[5,6] **[Archer 2005: pg 790/col1/¶4 –col2/¶1,2 and table 118-2][Chambers 2005: pg282/col1/¶1-3]**Some bacteria have adapted to produce enzymes - beta-lactamases and extended spectrum beta-lactamases – which hydrolyze the core beta-lactam ring, inactivating the antibiotic. [5,6] **[Archer 2005: pg 790 table 118-2; pg 793/col1/¶7- col2/¶1] [Chambers 2005: pg282/col2/¶3]**

Fluoroquinolones are synthetic broad spectrum antibiotics which inhibit two enzymes necessary for DNA replication, recombination and repair.[5,7] **[Archer 2005: pg 790 table 118-2; pg 792/col2/¶5][Schentag 1999: pg877/col1/¶3 and col2/¶3]** Inhibition of either enzyme arrests DNA replication, killing the bacteria. [5,7] **[Archer 2005: pg 792/col2/¶5]][Schentag 1999: pg877/col1/¶3]** Resistance to fluoroquinolones arises either as a result of mutations which alter the target enzymes or by creating a decoy protein that binds to the drug so it cannot inhibit the target enzymes.[5,7] **[Archer 2005: pg 790 table 118-2; pg794/col1/¶6][Schentag 1999: pg885/col1/¶5 - col2/¶1]**

Tetracyclines are broad-spectrum antibiotics active against gram-negative and gram-positive bacteria, which bind to bacterial ribosomes and interrupt protein synthesis. [5,8] **[Archer 2005: pg 790 table 118-2 and pg 792/col1/¶6] [Chopra *Microbiol Mol Biol Rev.*2001: pg232/col2/¶1; pg236/col2/¶1]** Bacteria have overcome this mechanism of action through two methods of resistance, efflux pumps and ribosomal protection.[5,8] **[Archer 2005: pg 790 table 118-2; pg794/col1/¶3] [Chopra *Microbiol Mol Biol Rev.* 2001: pg235/col2/¶2]** Efflux pumps remove the antibiotic from the cell.[5,8] **[Archer 2005: pg 794/col1/¶3] [Chopra *Microbiol Mol Biol Rev.* 2001: pg239/col1/¶1,2 – col2/¶1]** Ribosomal protection mechanisms reduce the affinity of the ribosome for tetracyclines, preventing efficient drug binding. [5,8] **[Archer 2005: pg 792/col1/¶6] [Chopra *Microbiol Mol Biol Rev.* 2001: pg240/col2/¶2-4]**

Antibacterial resistance is one of the major limitations to effective antibacterial therapy. As we've shown here today, mechanisms of action and resistance vary greatly from class to class of antibiotics. Effective use of any class of these agents depends on many factors – and an understanding of these mechanisms is key among them. [5]
[Archer 2005: pg 789/col1/¶1; pg 793/col1/¶6]

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Video II: TYGACIL MOA

The emergence of bacterial resistance to existing antibiotics is a serious medical issue that is complicating the effective and appropriate therapy of infectious diseases. An important method of combating this problem is the expansion of known antibiotic classes through synthetic improvement. [1] **[Chopra *Curr Opin Pharmacol.*2001: pg464/col1/¶1**

Tetracycline resistance prompted the development of the glycylcyclines.[2-4] **[Chopra *Microbiol Mol Biol Rev.*2001: pg236/col1/¶1] [Bauer 2004: pg592/col1/¶1] [Zhanel 2004: pg65/col1/¶3]** TYGACIL, or tigecycline, was specifically designed to circumvent key bacterial resistance mechanisms.[1,3-5] **[Bauer 2004: pg592/col1/¶1][Bergeron 1996: pg2226/col1/¶2] [Bradford 2004: pg163/col2/¶2][Chopra *Curr Opin Pharmacol.*2001: pg464/col1/¶1; pg 466/col1/¶1]** TYGACIL is a glycylcycline and is structurally similar to tetracycline, but with a key substitution that enables it to bind to ribosomes in a unique manner. [1,3,5,6] **[Tygacil PI 2010: pg 16/section 12.4/¶1] [Bauer 2004: pg592/col1/¶1; pg 597/col2/¶5][Bergeron 1996: pg2226/col1/¶2][Bradford 2004: pg163/col2/¶2]** Similarly to tetracyclines, TYGACIL binds to and blocks the site on the ribosome that normally accommodates an incoming amino acid. This binding results in the inhibition of protein synthesis needed for growth. [3,5,7] **[Tygacil PI 2010: pg 16/section 12.4/¶1] [Bauer 2004: pg597/col2/¶5 – pg598/col1/¶1][Bergeron 1996: pg2226/col2/¶2]**However, TYGACIL binds to the ribosome at additional sites and with five times greater affinity compared to tetracyclines.[3,5,6] **[Bauer 2004: pg597/col2/¶4][Bergeron 1996: pg2226/col2/¶2][Bradford 2004:pg164/col3/¶2 -pg165/col1/¶1]***In vitro* data suggests that TYGACIL's structure and points of contact on the ribosome may confer the ability to overcome tetracycline resistance mechanisms. [3,6] **[Bauer 2004: pg597/col2/¶5][Bradford pg164/col3/¶2 -pg165/col1/¶1-2]**

TYGACIL is not affected by ribosomal protection, tetracycline efflux pumps, target-site modifications or enzyme target changes.[2-4,6,7] **[text on screen:** In some bacteria, tigecycline resistance has been associated with multi-drug resistant efflux pumps.] Additionally, TYGACIL, as glycylcycline, is not a beta-lactam and therefore is not affected by beta-lactamases, including ESBLs and KPCs.[7] **[Tygacil PI 2010: pg 16/section 12.4/¶2][Bauer2004 pg592/col1/¶12 – col2/¶1][Chopra *Microbiol Mol Biol Rev.* 2001: pg236/col1/¶1][Zhanel 2004: pg65/col2/¶1] [Bradford 2004: pg165/col1/¶2 & Table 1 and pg 167/col1/¶2]**

TYGACIL provides an expanded broad spectrum of *in vitro* activity [**text on screen:** The clinical significance of *in vitro* activity is unknown] and offers a different mechanism of action that, within its indications, represents an alternative therapeutic option to other antibiotic classes.[3-7,9] **[Tygacil PI 2010: pg 16/section 12.4/¶5 through pg18/¶2; pg 16/section 12.4/¶1] [Bauer 2004: pg592/col1/¶1; pg 597/col2/¶5] [Milatovic 2003: pgs401-403/Table 1] [Zhanel 2004: pg70/col1/¶3-col2/¶1; pg71/col1/¶2-col2/¶1 and Table IV; pg73/table V] [Bergeron 1996: pg2226/col1/¶2][Bradford 2004: pg163/col2/¶2]**

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