48 Bacitracin, Glycopeptide Antibiotics, and the Polymyxins

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DRUG LIST

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Bacitracin and the polymyxins are polypeptide antibiotics. They are relatively toxic drugs and have had only limited use in chemotherapy until recently. Vancomycin, a glycopeptide, although not without side effects, is widely used. Teicoplanin is a new glycopeptide antibiotic that may be beneficial against certain infections caused by gram-positive organisms. The mechanisms of action of this group vary. Bacitracin and the glycopeptides affect cell wall synthesis, whereas the polymyxins affect the cell membrane. Bacitracin and the glycopeptides are used for the treatment of infections caused by gram-positive bacteria; the polymyxins are used for treating gram-negative infections and are active against *Pseudomonas aeruginosa.*

BACITRACIN

Structure and Mechanism of Action

Bacitracin is a mixture of polypeptide antibiotics produced by *Bacillus subtilis.* As with penicillin, it contains a thiazolidine nucleus attached through L-leucine to a peptide composed of both D- and L-amino acids. However, it does not contain a β-lactam ring. *Bacitracin prevents cell wall synthesis by binding to a lipid pyrophosphate carrier that transports cell wall precursors to the growing cell wall.* Bacitracin inhibits the dephosphorylation of this lipid carrier, a step essential to the carrier molecule's ability to accept cell wall constituents for transport.

Antimicrobial Spectrum

Bacitracin inhibits gram-positive cocci, including *Staphylococcus aureus,* streptococci, a few gram-negative organisms, and one anaerobe, *Clostridium difficile.*

Absorption, Distribution, and Excretion

Bacitracin is primarily a *topical* antibiotic. Previously, it was administered intramuscularly, but the toxicity associated with its parenteral administration has precluded systemic use. The bacitracins are not absorbed from the gastrointestinal tract following oral administration.

Clinical Uses

Bacitracin is highly active against staphylococci, *Streptococcus pyogenes,* and *C. difficile.* Its high degree of activity against the group A streptococci is used in the laboratory as a means of differentiating between the Lancefield group A streptococci and other streptococci.

Bacitracin is well tolerated topically and orally and is frequently used in combination with other agents (no-

tably polymyxin B and neomycin) in the form of creams, ointments, and aerosol preparations. Hydrocortisone has been added to the combination for its antiinflammatory effects. Bacitracin preparations are effective in the treatment of impetigo and other superficial skin infections. However, poststreptococcal nephritis has followed the topical treatment of impetigo, and therefore oral penicillin therapy is preferred. Bacitracin has been used with limited success for eradication of *S. aureus* in the nares. Because of the risk of serious nephrotoxicity, the *parenteral use of bacitracin is not justified.*

GLYCOPEPTIDES: VANCOMYCIN AND TEICOPLANIN

Structure and Mechanism of Action

Vancomycin (*Vancocin*) is a complex tricyclic glycopeptide antibiotic produced by *Streptomyces orientalis,* while teicoplanin (*Targocid*) is derived from *Actinoplanes* (*Actinomyces*) *teichomyceticus.* Teicoplanin has two major components: a phosphoglycolipid (A_1) and five chlorine-containing glycopeptides (A_2). It is available as an investigational drug.

The glycopeptides are inhibitors of cell wall synthesis. They bind to the terminal carboxyl group on the D-alanyl-D-alanine terminus of the *N*-acetylglucosamine-*N*-acetylmuramic acid peptide and *prevent polymerization* of the linear peptidoglycan by peptidoglycan synthase. They are bactericidal in vitro.

Antimicrobial Spectrum

The glycopeptides are narrow-spectrum agents that are active against gram-positive organisms. Like vancomycin, teicoplanin is bacteriostatic against staphylococci, streptococci, and enterococci. Gram-positive rods, such as *Bacillus anthracis, Corynebacterium diphtheriae, Clostridium tetani,* and *Clostridium perfringens,* are also sensitive to the glycopeptides. The glycopeptides are not effective against gram-negative rods, mycobacteria, or fungi.

Absorption, Distribution, and Excretion

Vancomycin is poorly absorbed from the gastrointestinal tract, resulting in high concentrations in the feces. In neutropenic patients and others with altered gastrointestinal mucosa with denudation, significant oral absorption of vancomycin may occur and may be accompanied by additive toxicity if rapid infusion or large parenteral doses of the drug are given concomitantly. Except for the treatment of staphylococcal enterocolitis and pseudomembranous colitis, it is administered intravenously. Peak serum levels are achieved 2 hours after intravenous (IV) administration, and about 55% is bound to serum protein. The therapeutic range is a trough concentration between 5 and 15 μg/mL, and the peak should stay below 60 μg/mL to avoid side effects. In normal adults the serum half-life is 5 to 11 hours. With impaired renal function, the half-life is 7 to 9 days. The dose of vancomycin must be carefully adjusted to avoid toxicity or ineffective treatment, especially in patients undergoing hemodialysis. Pediatric oncology patients with normal renal function may require vancomycin dosage regimens that are substantially greater than predicted. Similar studies in adult patients with hematological malignancies have suggested a larger dosage requirement as well, owing to an increased volume of distribution.

After IV administration, vancomycin diffuses into serous cavities and across inflamed but not normal meninges. It can be used in the treatment of meningitis with susceptible organisms. It is also given via ventriculoatrial or ventriculoperitoneal shunts when these become infected.

Renal excretion is predominant, with 80 to 90% of an administered dose eliminated in 24 hours. Only small amounts appear in the stool and bile after intravenous administration.

Teicoplanin, like vancomycin, is not absorbed from the intestinal tract. Peak plasma levels are achieved about 2 hours after intramuscular administration. The drug distributes widely in tissues; plasma protein binding is about 90%. The half-life approximates 50 hours, which is considerably longer than that of vancomycin, and may make it useful for outpatient administration. Like vancomycin, teicoplanin is excreted by the kidneys.

Clinical Uses

Vancomycin and teicoplanin display excellent activity against staphylococci and streptococci, but because of the wide availability of equally effective and less toxic drugs, they are *second-line drugs in the treatment of most infections.* As antistaphylococcal agents they are less effective than β-lactam cephalosporin antibiotics, such as nafcillin and cefazolin. They have attained much wider use in recent years as a consequence of the emergence of methicillin-resistant *S. aureus* (MRSA) infections, in particular the growing importance of *Staphylococcus epidermidis* infections associated with the use of intravascular catheters and in patients with peritonitis who are on continuous ambulatory peritoneal dialysis.

Vancomycin is also an effective alternative therapy for the treatment of staphylococcal enterocolitis and endocarditis. The combination of vancomycin and either streptomycin or gentamicin acts synergistically against enterococci and is used effectively for the treatment or

prevention of enterococcal endocarditis. Teicoplanin demonstrates similar synergy.

Staphylococcal vascular shunt infections in persons undergoing renal dialysis have been successfully treated with vancomycin. Vancomycin in oral form can also be used in patients in whom *C. difficile* colitis is not responding to metronidazole.

Teicoplanin, although not available in the United States, has been used to treat a wide range of gram-positive infections, including endocarditis and peritonitis. It is not as effective as the β-lactams, but its actions are similar to those of vancomycin against staphylococcal infections.

An increased prevalence of MRSA has resulted in a greater use of vancomycin for this disorder. High-grade resistance of pneumococci to penicillin may also necessitate vancomycin therapy. Enterococci that are resistant to vancomycin are emerging as major nosocomial pathogens. These strains are generally resistant to a number of other antibiotics, such as penicillin, ampicillin, and gentamicin, which limits treatment options. The possibility of transferring these resistance determinants to other gram-positive organisms, like *S. aureus,* is a valid concern. It is therefore necessary to limit the use of vancomycin to treatment of serious infections caused by methicillin-resistant staphylococci and situations in which allergies preclude the use of other antibiotics.

Adverse Effects

The major adverse effect associated with vancomycin therapy is ototoxicity, which may result in tinnitus, high-tone hearing loss, and deafness in extreme instances. More commonly, the intravenous infusion of vancomycin can result in chills, fever, and a maculopapular skin rash often involving the head and upper thorax (red man syndrome). Red man syndrome is associated with increased levels of serum histamine. Vancomycin is rarely nephrotoxic when used alone. Teicoplanin rarely causes red man syndrome or nephrotoxicity.

THE POLYMYXINS

The polymyxins are a group of antibiotics produced by *Bacillus polymyxa.* Polymyxin B (*Aerosporin*) and colistin (polymyxin E, *Coly-Mycin*) are used in the treatment of bacterial diseases.

Structure and Mechanism of Action

The polymyxins are polypeptide antibiotics that contain both hydrophilic and lipophilic regions. These antibiotics accumulate in the cell membrane and probably interact with membrane phospholipids. Most likely the fatty acid portion of the antibiotic penetrates the hydrophobic portion of the membrane phospholipid and the polypeptide ring binds to the exposed phosphate groups of the membrane. Such an interaction would distort the membrane, impair its selective permeability, produce leakage of metabolites, and inhibit cellular processes. In the laboratory polymyxin B can neutralize the effects of bacterial lipopolysaccharide (LPS) of gram-negative organisms and may stimulate the biosynthesis of complement component C_3, factor B, interleukin (IL) 6, and granulocyte-macrophage colony stimulating factor (GM-CSF). Its clinical use in gram-negative sepsis has not been established. These antibiotics also are toxic to mammalian cells.

Antimicrobial Spectrum

The polymyxins are active against facultative gram-negative bacteria, *P. aeruginosa* in particular.

Absorption, Distribution, and Excretion

Polymyxin B and colistin are not well absorbed from the gastrointestinal tract. An intramuscular injection of the polymyxins results in high drug concentrations in the liver and kidneys, but the antibiotic does not enter the cerebrospinal fluid (CSF), even in the presence of inflammation.

The polymyxins are slowly excreted by glomerular filtration; the slow elimination rate is due to binding in tissues. Elimination is decreased in patients with renal disease, and drug accumulation can lead to toxicity. Sodium colistimethate, the parenteral preparation, binds less to tissue and is excreted faster than the free base.

Clinical Uses

With the advent of potent broad-spectrum antibiotics, such as the quinolones and third-generation cephalosporins, *the indications for the use of the polymyxins, with their serious potential for toxicity, are few.* Their only justifiable use may be as topical agents.

In combination with neomycin, polymyxin B can be used as a bladder irrigant to reduce the risk of catheter-associated infections, although this use remains controversial. It also can be used as topical therapy in external otitis caused by *P. aeruginosa.*

Adverse Effects

Colistin and polymyxin B can cause extreme nephrotoxicity when used parenterally, and any preexisting renal insufficiency will potentiate the nephrotoxicity caused by these antibiotics.

Neurotoxicity is a rare adverse reaction that can be recognized by perioral paresthesia, numbness, weakness, ataxia, and blurred vision. These drugs may precipitate respiratory arrest both in patients given muscle relaxants during anesthesia and in persons with myasthenia gravis.

Study Questions

1. A pediatric nurse is found to be colonized with MRSA in her nares during an outbreak investigation in the pediatric intensive care unit. The best strategies to eradicate her nasal carriage could be
   (A) Parenteral therapy with IV vancomycin
   (B) Oral vancomycin
   (C) Bacitracin ointment application to her nasal passages
   (D) Polymyxins
   (E) A month-long furlough from patient care
2. In the treatment of uncomplicated urinary tract infection caused by gram-negative bacteria, the therapy of choice would be
   (A) Teicoplanin
   (B) Bacitracin
   (C) IV vancomycin
   (D) IV polymyxin B
   (E) Trimethoprim-sulfamethoxazole
3. Effective interventions for treating a minor surgical suture site infection should definitely include one of the following choices:
   (A) Polymyxins
   (B) Bacitracin
   (C) Triple antibiotics (bacitracin, Polymyxin B, and neomycin) ointment
   (D) IV vancomycin
   (E) Observation
4. A urine culture in an asymptomatic female patient with an indwelling Foley catheter comes back with more than 50,000 colonies of enterococci. The urinalysis is unremarkable. The best course of action would be to
   (A) Start IV vancomycin to cover enterococci
   (B) Seek the newly approved drug linezolid for possibility of vancomycin-resistant enterococci (VRE)
   (C) Initiate a quinolone like levofloxacin with broad-spectrum coverage for UTIs
   (D) Discontinue use of the Foley catheter if possible and obtain follow-up cultures if she develops symptoms
   (E) Watchful waiting
5. Which glycopeptide or polypeptide antibiotic is still investigational and not used in the United States for parenteral therapy?
   (A) Polymyxins
   (B) Vancomycin
   (C) Teicoplanin
   (D) Bacitracin
   (E) Linezolid

ANSWERS

1. **C.** In an outbreak setting, involved hospital staff may undergo culture investigation of their skin flora and orifices to determine the source of infection. Oral vancomycin is not usually absorbed from the GI tract to be effective, and IV vancomycin is not indicated to eradicate colonization. Bacitracin ointment has been used with limited success and may be an option, along with strict handwashing and isolation precautions. Polymyxins are effective topical agents for gram-negative infections. A furlough from patient care responsibilities is unlikely to eradicate her nasal colony.
2. **E.** Trimethoprim, which exhibits broad-spectrum activity, with sulfamethoxazole is active against most aerobic and facultative gram-positive and gram-negative organisms. It is very effective in UTIs caused by gram-negative bacteria. Teicoplanin, bacitracin, and vancomycin are antibiotics with limited spectra of gram-positive coverage. Although polymyxins are active against gram-negative organisms, their only use is topical because of severe nephrotoxicity associated with IV therapy. Alternative therapy would be to use quinolone.
3. **C.** Minor suture irritation and superficial infection can be treated topically. Effective agents in the absence of culture results would be an ointment such as triple antibiotic, which has gram-positive and gram-negative spectra. Generally, polymyxins are active only against gram-negative organisms, and bacitracin works only against gram-positive organisms. Intravenous antibiotics are not indicated unless this evolves into a deeper soft tissue infection. Observation without any active management is unlikely to be successful.
4. **D.** It is not unusual to get colonized by hospital flora, especially with an indwelling Foley catheter. If the patient does not have any clinical evidence of infection, it is not necessary to start therapy with vancomycin or for that matter, any antibiotic. Enterococcal UTI can still be treated with penicillins, but they are increasingly resistant to penicillins and even vancomycin. Since susceptibility data are still pending, neither vancomycin nor the new drug linezolid is yet indicated. Levofloxacin, although a good drug for UTIs, does not have enterococcal coverage. Discontinuation of the Foley catheter if possible and follow-up appear to be the best option. Watchful waiting may not be effective because these patients may go on to develop complicated UTIs.

5. C. Teicoplanin, although used in Europe, is not approved for use in the United States. It can be used to treat a variety of gram-positive infections and should be considered in resistant gram-positive infections as well. Bacitracin and polymyxins are topical agents with potential for serious nephrotoxicity when used parenterally. Linezolid is recently approved for resistant gram-positive infections (VRE and MRSA) and is available in the United States.

SUPPLEMENTAL READING

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CASE Study Endovascular Infection

A 72-year-old male nursing home resident is brought to the emergency department with change in mental status, fever, and shortness of breath. Last year he underwent partial resection of his colon to treat ischemic bowel disease. He receives total parenteral nutrition (TPN) via a central line. His examination revealed temperature 104°F (40°C), heart rate 110 beats/minute, respiratory rate 32/minute, blood pressure 90/50 mm Hg. He was lethargic but arousable. He denied any cough or headache, abdominal pain, or change in bowel or bladder function except that his urinary output has fallen over the past few shifts. Pertinent points in his examination included a supple neck and a central venous catheter in place without any evidence of infection. Heart sounds were normal, without any murmurs, and he reported diffuse nonspecific vague abdominal discomfort without any localization or rebound tenderness. His laboratory findings were WBC 29,000/mm^2, hemoglobin 13 g/dL, platelets 300,000.

Urinalysis showed 2 to 5 WBC with a negative-gram stain and nitrite test. He had clear lung fields with a few old calcific deposits. An abdominal series showed no evidence of obstruction or perforation. You get a call from the nursing home that three of four bottles of blood cultures drawn the day before were positive for gram-positive cocci in clusters. A correct statement with regard to his management is

Because of recent surgery, perforation of the bowels should be considered and an emergency laparotomy performed.

With a chronic indwelling Foley catheter, he most likely has urosepsis.

His central line should be immediately discontinued, and specific therapy with vancomycin should be initiated.

He has aspiration pneumonia. The lung fields were clear because findings on chest radiographs take time to evolve, and film may remain negative at initial presentation.

Discontinue his central line and initiate treatment with IV nafcillin.

ANSWER: This patient has line sepsis. The causation of his infection is not clear initially, and his presentation, without any localizing features, gives rise to the possibility of a line infection. The catheter sites frequently do not reveal any evidence of infection, but high-grade bacteremia (3 of 4 bottles) with gram-positive cocci strongly suggests an endovascular infection. With a high prevalence of methicillin resistance in staphylococcal infections in hospital and nursing home settings, vancomycin therapy should be initiated along with discontinuation of the line. Indeed, the organisms later prove to be MRSA, and neither nafcillin nor any other β-lactam or cephalosporin would be effective in management of his infection.