Cell Wall Inhibitors

Introduction

Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall—a structure that mammalian cells do not possess. The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links.

To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms. They have little or no effect on bacteria that are not growing and dividing. The most important members of this group of drugs are the βlactam antibiotics (named after the β-lactam ring that is essential to their activity), vancomycin, and daptomycin.

PENICILLINS

The penicillins share features of chemistry, mechanism of action, pharmacology, and immunologic characteristics with cephalosporins, monobactams, carbapenems, and βlactamase inhibitors. All are β-lactam compounds, so named because of their four membered lactam ring (**Figure1**).

Chemistry

All penicillins have the basic structure shown in Figure 1. A thiazolidine ring (A) is attached to a β-lactam ring (B) that carries a secondary amino group (RNH–). Substituents (R) can be attached to the amino group. Structural integrity of the 6 aminopenicillanic acid nucleus (rings A plus B) is essential for the biologic activity of these compounds. Hydrolysis of the β -lactam ring by bacterial β-lactamases yields penicilloic acid, which lacks antibacterial activity.

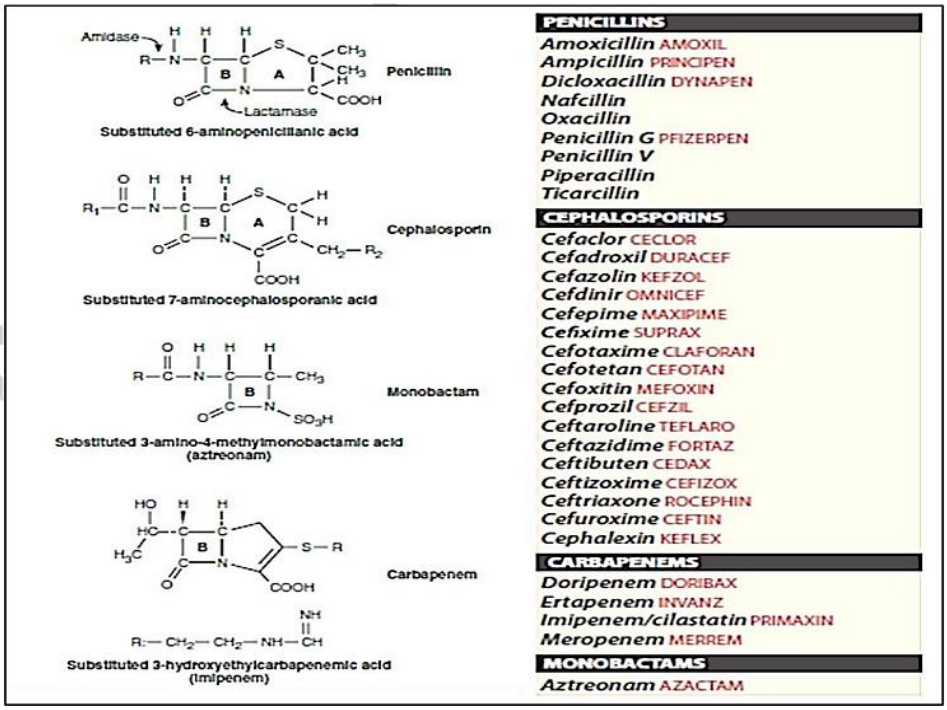

Figure 1: Core structures of four β-lactam antibiotic families.

Classification

Substituents of the 6-aminopenicillanic acid moiety determine the essential pharmacologic and antibacterial properties of the resulting molecules. Penicillins can be assigned to one of three groups (below). Within each of these groups are compounds that are relatively stable to gastric acid and suitable for oral administration, eg, penicillin V, dicloxacillin, and amoxicillin.

1. Penicillins (eg, penicillin G): These have greatest activity against Gram-positive organisms, Gram-negative cocci, and non-β-lactamase-producing anaerobes. However, they have little activity against Gram-negative rods, and they are susceptible to hydrolysis by β-lactamases.

2. **Antistaphylococcal penicillins (eg, nafcillin):** These penicillins are resistant to staphylococcal β-lactamases. They are active against staphylococci and streptococci but not against enterococci, anaerobic bacteria, and Gram-negative cocci and rods.

3. **Extended-spectrum penicillins (aminopenicillins and antipseudomonal penicillins):** These drugs retain the antibacterial spectrum of penicillin and have improved activity against Gram-negative rods. Like penicillin, however, they are relatively susceptible to hydrolysis by β-lactamases.

Mechanism

of Action The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane. Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins. These drugs are bactericidal and work in a time-dependent fashion. Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall. Consequently, they are inactive against organisms devoid of this structure, such as mycobacteria, protozoa, fungi, and viruses.

Resistance

Resistance to penicillins and other β-lactams is due to one of four general mechanisms: (1) inactivation of antibiotic by β-lactamase, (2) modification of target PBPs (penicillin-binding protein), (3) impaired penetration of drug to target PBPs, and (4) antibiotic efflux.

1- **Beta-lactamase production** is the most common mechanism of resistance. Hundreds of different β -lactamases have been identified. Some, such as those produced by Staphylococcus aureus, Haemophilus influenzae, and Escherichia coli, are relatively narrow in substrate specificity, preferring penicillins to cephalosporins.

a. Other β-lactamases, eg, AmpC β-lactamase produced by Pseudomonas aeruginosa and Enterobacter sp and extended-spectrum β -lactamases (ESBLs) in Enterobacteriaceae, hydrolyze both cephalosporins and penicillins.

b. Carbapenems are highly resistant to hydrolysis by penicillinases and cephalosporinases, but they are hydrolysed by metallo- β -lactamases and carbapenemases.

2- Altered target PBPs (penicillin-binding protein) are the basis of methicillin resistance in staphylococci and of penicillin resistance in pneumococci and most resistant enterococci. These resistant organisms produce PBPs that have low affinity for binding β-lactam antibiotics, and they are not inhibited except at relatively high, often clinically unachievable, drug concentrations.

3- Resistance due to impaired penetration of antibiotic occurs only in Gram negative species because of the impermeable outer membrane of their cell wall, which is absent in Gram-positive bacteria.

Beta-lactam antibiotics cross the outer membrane and enter Gram-negative organisms via outer membrane protein channels called porins. Absence of the proper channel or down-regulation of its production can greatly impair drug entry into the cell.

Poor penetration alone is usually not sufficient to confer resistance because enough antibiotic eventually enters the cell to inhibit growth. However, this barrier can become important in the presence of a β -lactamase, even a relatively inefficient one, as long as it can hydrolyze drug faster than it enters the cell. Gram-negative organisms also may produce an **efflux pump**, which consists of cytoplasmic and periplasmic protein components that efficiently transport some βlactam antibiotics from the periplasm back across the cell wall outer membrane.

Pharmacokinetics

- The route of administration of a β-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.

- The combination of ampicillin with sulbactam, ticarcillin with clavulanic acid and the antistaphylococcal penicillins nafcillin and oxacillin must be administered intravenously (IV) or intramuscularly (IM).

- Penicillin V, amoxicillin, and dicloxacillin are available only as oral preparations. Others are effective by the oral, IV, or IM routes.

- **Depot preperation**: Procaine penicillin G and benzathine penicillin G are administered IM and serve as depot forms. They are slowly absorbed into the circulation and persist at low levels over a long time period.

- Most of the penicillins are incompletely absorbed after oral administration, and they reach the intestine in sufficient amounts to affect the composition of the intestinal flora. Food decreases the absorption of all the penicillinase-resistant penicillins because as gastric emptying time increases, the drugs are destroyed by stomach acid. Therefore, they should be taken on an empty stomach.

- All the penicillins cross the placental barrier, but none have been shown to have teratogenic effects. However, penetration into bone or cerebrospinal fluid (CSF) is insufficient for therapy unless these sites are inflamed. [Note: Inflamed meninges are more permeable to the penicillins, resulting in an increased ratio of the drug in the CSF compared to the serum.]

- The primary route of excretion is by kidneys. So, patients with impaired renal function must have dosage regimens adjusted. Nafcillin and oxacillin are exceptions to the rule.

They are primarily metabolized in the liver and do not require dose adjustment for renal insufficiency. The penicillins are also excreted in breast milk.

Clinical Uses

- Except for amoxicillin, oral penicillins should be given 1–2 hours before or after a meal; they should not be given with food to minimize binding to food proteins and acid inactivation.

- Amoxicillin may be given without regard to meals.

- Blood levels of all penicillins can be raised by simultaneous administration of probenecid, 0.5 g every 6 hours orally, which impairs renal tubular secretion of weak acids such as β-lactam compounds.

- Penicillins, like all antibacterial antibiotics, should never be used for viral infections and should be prescribed only when there is reasonable suspicion of, or documented infection with, susceptible organisms.

A. Penicillin

- Penicillin G is a drug of choice for infections caused by streptococci, some enterococci, penicillin-susceptible pneumococci, staphylococci confirmed to be non β-lactamase producing, and certain other Gm+ve rods, and non-β-lactamase producing Gm-ve anaerobic organisms.

- Depending on the organism, the site, and the severity of infection, effective doses range between 4 and 24 million units per day administered intravenously in four to six divided doses. High-dose penicillin G can also be given as a continuous intravenous infusion.
- Penicillin V, the oral form of penicillin, is indicated only in minor infections because of its relatively poor bioavailability, the need for dosing four times a day, and its narrow antibacterial spectrum. Amoxicillin is often used instead.

B. Penicillins Resistant to Staphylococcal Beta- Lactamase (Methicillin, Nafcillin, and Isoxazolyl Penicillins)

- These semisynthetic penicillins are indicated for infections caused by β-lactamase producing staphylococci, although penicillin susceptible strains of streptococci and pneumococci are also susceptible to these agents. Enterococci, and methicillin-resistant strains of staphylococci are resistant. In recent years the empirical use of these drugs has decreased substantially because of increasing rates of methicillin resistance in staphylococci. However, for infections caused by methicillin-susceptible and penicillin resistant strains of staphylococci, these are considered drugs of choice.
- These drugs are relatively acid-stable and have reasonable bioavailability. However, food interferes with absorption, and the drugs should be administered 1 hour before or after meals.

C- Extended-Spectrum Penicillins (Amoxicillin, Aminopenicillins, Carboxypenicillins, and Ureidopenicillins)

- These drugs have greater activity than penicillin against Gm-ve bacteria because of their enhanced ability to penetrate the Gm-ve outer membrane.
- Like penicillin G, they are inactivated by many β-lactamases.
- The aminopenicillins, ampicillin and amoxicillin, have very similar spectrums of activity, but amoxicillin is better absorbed orally. Amoxicillin, 250–500 mg three times daily, is equivalent to the same amount of ampicillin given four times daily.
- Amoxicillin is given orally to treat bacterial sinusitis, otitis, and lower respiratory tract infections. Ampicillin and amoxicillin are the most active of the oral β-lactam antibiotics against pneumococci with elevated MICs to penicillin and are the preferred β-lactam antibiotics for treating infections suspected to be caused by these strains.

- Ampicillin (but not amoxicillin) is effective for shigellosis. Ampicillin, at dosages of 4 12 g/d intravenously, is useful for treating serious infections caused by susceptible organisms like anaerobes and enterococci.

- Ampicillin is not active against Klebsiella sp, Enterobacter sp, P aeruginosa and other Gm-ve aerobes that are commonly encountered in hospital-acquired infections. These organisms intrinsically produce β-lactamases that inactivate ampicillin.

- The carboxypenicillins, carbenicillin and ticarcillin, were developed to broaden the spectrum of penicillins against Gram negative pathogens, including P aeruginosa. The piperacillin is also active against many Gm-ve bacilli, such as Klebsiella pneumoniae and P aeruginosa.

- Ampicillin and amoxicillin are available in combination with one of several β-lactamase inhibitors: clavulanic acid and sulbactam. The addition of a β-lactamase inhibitor extends the activity of these penicillins to include β-lactamase-producing strains of S aureus as well as some β -lactamase-producing Gm-ve bacteria.

Adverse reactions

Penicillins are among the safest drugs, and blood levels are not monitored. However, adverse reactions may occur, such as:

1. **Hypersensitivity:** Approximately 5% percent of patients have some kind of reaction, ranging from rashes to angioedema and anaphylaxis. Cross-allergic reactions occur among the β-lactam antibiotics.

2. **Diarrhea:** is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. Pseudomembranous colitis from Clostridium difficile and other organisms may occur with penicillin use.

3. **Nephritis**: Penicillins, particularly methicillin, have the potential to cause acute interstitial nephritis. Methicillin is therefore no longer used clinically.

4. **Neurotoxicity:** The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

5. Hematologic toxicities: Decreased coagulation may be observed with high doses of some penicillins like piperacillin and ticarcillin (and, to some extent, with penicillin G). Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts should be monitored weekly for such patients.

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.