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AMINOGLYCOSIDES

amikacin, gentamicin, neomycin, streptomycin, tobramycin

inhibitors of bacterial protein synthesis; bactericidal

Mechanism of action:

binding to the 30S subunit of the ribosome, where they: 1.interfere with the initiation of complex of peptide formation 2. cause breakup of polysomes into nonfunctional monosomes 3. cause misreading of mRNA

Pharmacokinetics:

- poorly absorbed from the GI tract (highly ionized nature)
- binding to albumins - negligible (exc. of streptomycin),
- volume of distribution=volume of extracellular fluid,
- penetration to CSF - inadequate,
- high concentration – renal cortex, endolymph and perilymph of the inner ear
- eliminated generally by glomerular filtration, in large fraction as unchanged drugs

Effectiveness related to the peak of serum concentration = **concentration-dependent killing**

Postantibiotic effect – antibacterial activity persists beyond the time during which measurable drug is present

Spectrum of activity

Aerobic Gram-negative bacilli

Streptomycin - less active than other aminogl.; drug-resistant tuberculosis, tularemia, plague

Gentamicin, tobramycin – preferred (low costs, long experience with use); UTI – seriously ill patients, pneumonia – nosocomial + cell wall inhibitors, infective endocarditis + cell wall inhibitors

Amikacin - broadest spectrum; resistance to inactivating enzymes; hospital acquired infections

Neomycin – prophylaxis of hepatic coma, preparation of the bowel for surgery, topical application in the skin infections

Mechanisms of resistance

1. **adenylation, acetylation, phosphorylation by bacterial enzymes**
2. impaired entry into the cell:
   a. mutation or deletion of a porin proteins
   b. oxygen-dependent transport blocked by divalent cations, hyperosmolality, low pH, anaerobic conditions
3. mutation of receptor protein on the 30S ribosomal subunit

Adverse effects:

Risk of toxicity related to the dosage and duration of the treatment

ototoxicity – hair cells – vestibular or auditory dysfunction**; irreversible**

nephrotoxicity – neomycin>>>streptomycin - **reversible**

neuromuscular blockade – neo>kana>ami>genta>tobramycin - **do not use in patients with myasthenia gravis**

dysfunction of the optic nerve

Dosage:

Once-daily dose regimen – preferred

Multiple-daily dose regimen: pregnancy, children, low creatinine clearance

GLYCOPEPTIDES

Vancomycin, teicoplanin, telavancin, dalbavancin

inhibitors of cell wall synthesis; bactericidal

Vancomycin

Mechanism of action: bind to the D-Ala-D-Ala terminus of nascent peptidoglycan pentapeptide = inhibition of tranglycosylase = further elongation of peptidoglycan and cross-linking

Pharmacokinetics:

- poorly absorb from the GI
- to achieve systemic effects - only iv. administration
- widely distributed in the body inc. CSF
- renal elimination

Spectrum of activity:

Gram-positive bacteria- Staph. including strains resistant to methicillin, Streptococcus pyogenes, pneumoniae, viridans streptococci, most strains of Enterococcus spp., Corynebacterium spp., Clostridium spp.

Mechanism of resistance

modification of the binding site

Therapeutic uses:

- pseudomembranous colitis (orally)
- pneumonia, empyema, endocarditis, osteomyelitis, soft tissue abscesses CAUSED BY METHICILLIN-RESISTANT STAPHYLOCOCCI (iv)
- severe staphylococcal infections in patients who are allergic to penicillin and cephalosporin and in these patients - endocarditis caused by viridians streptococci (iv)

Untoward effects:

- hypersensitivity reactions, chills, fever, infusion related erythematous, urticariae reaction, flushing, tachycardia, hypotension
- „red-men" or „red-neck" syndrome – rapid iv infusion; direct toxic effect on mast cells
- ototoxicity
- nephrotoxicity.

Teicoplanin
Spectrum of activity and mechanism of action - like vancomycin
Could be given i.m.; once-daily dose regimen – long half-life
Side effects: hypersensitivity

Telavancin, dalbavancin – semisynthetic lipoglycopeptides derivatives of teicoplanin and vancomycin respectively

Telavancin – gram-positive bacteria including strains resistant to vancomycin; used in the therapy of complicated skin and soft tissue infection; iv

Dalbavancin – gram-positive bacteria including MRSA and vancomycin resistant; long half-life; iv once/week

BACITRACIN – inhibitor of cell wall synthesis
Gram positive aerobic bacteria, Actinomyces, Fusobacterium
Used topically – ophtalmic and dermatologic indications

MUPIROCIN – proteins synthesis inhibitor
Gram positive bacteria and selected Gram negative
Dermatologic indications - topically

POLYMYXINS
Basic peptides
Mechanism of action – disruption of the bacterial cell membranes (interaction with phospholipids)
Pharmacokinetics:
not absorbed from GI tract, from any mucosa and surface of lesions,
excreted by the kidneys
Spectrum of activity – restricted to gram-negative bacteria Enterobacter, E. coli, Klebsiella, Salmonella, Pasteurella, Bordetella, Shigella, most strains of Pseudomonas aer.
Therapeutic uses:

- ophtalmic, otic infections - topical use (external otitis due to Pseudomonas, corneal ulcers)
- severe Pseudomonas pneumonia (inhalation of the parenteral preparations - as adjuvant therapy)
- severe infections of urinary tract, sepsis, peritonitis -iv

Untoward effects

- nausea, vomiting, diarrhea, when taken orally
- nephrotoxicity (renal tubules) - when given parenterally
- neurotoxicity (peripheral)

DAPTOMYCIN
an acidic cyclic lipopeptide antibiotic produced in fermentation by *Streptomyces roseosporus*
It is a 13-membered amino-acid cyclic lipopeptide with a hydrophilic core and hydrophobic tail
Mechanism of action
The hydrophobic tail of daptomycin binds irreversibly to the cell membrane of Gram (+) bacteria via a calcium-dependent process. A channel is formed, causing rapid depolarization of the cell membrane due to efflux of potassium, and possibly other cytoplasmic ions. Bacterial cell death results from the widespread dysfunction of macromolecular synthesis
Therapeutic use

- treatment of skin and skin structure infections caused by Gram-positive pathogens,
- treatment of bacteremia and right-sided endocarditis (pulmonary surfactant antagonizes daptomycin) caused by *S. aureus*, including strains resistant to methicillin (MRSA)

Untoward effects
Myopathy
Allergic pneumonia – prolonged therapy (>2 weeks)