Drugs for Genital Infections

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Metronidazole

- **Metronidazole and tinidazole are nitroimidazoles.**

Mechanism of Action:

- **The nitro group of metronidazole is chemically reduced in anaerobic bacteria and sensitive protozoans.**
- **Reactive reduction products appear to be responsible for antimicrobial activity.**

Metronidazole

Pharmacokinetics:

- Oral metronidazole and tinidazole are readily absorbed and permeate all tissues by simple diffusion.
- Intracellular concentrations rapidly approach extracellular levels.
- Peak plasma concentrations are reached in 1–3 hours.
- The half-life of unchanged drug is 7.5 hours for metronidazole and 12–14 hours for tinidazole.

Metronidazole

- **Can be given PO, PR, Topical & IV**
- **Metronidazole and its metabolites are excreted mainly in the urine.**
- **Plasma clearance of metronidazole is decreased in patients with impaired liver function.**

Metronidazole

Therapeutic Uses:

1. **Bacterial vaginosis: caused by anaerobic bacteria, *Gardnerella vaginalis, Prevotella spp, Mobilinincus spp, Megaspahera spp, Sneathea spp* and mixed vaginal anaerobs replacing the beneficial lactobacilli in the vagina.**
2. **Trichomoniasis – in the vagina and other places.**

Metronidazole

Other therapeutic uses:

A. **Invasive amebiasis in the intestine and liver, but less effective against organisms in the lumen of the gut. They kill the trophozoites of *Entameba histolytica* with no effect on cysts.**

B. **Giardiasis**

C. **Anaerobic bacteria: *Bacteroides fragilis, Clostridium spp &* some streptococci. Intraabdominal infections, Antibiotic-associated enterocolitis and brain abscess.**

Metronidazole

Adverse Effects:

1. Metallic, bitter taste, nausea & dry mouth
2. GIT irritation: vomiting, diarrhea
3. Irritation of mucous membranes – dysuria, dark urine
4. Rash and neutropenia
5. Alcohol intolerance: disulfiram-like reaction
6. Pancreatitis
7. IV infusion may be associated with seizures and peripheral neuropathy

Metronidazole

8. **CNS: dizziness, insomnia, weakness, headache, sensory neuropathies, parasthesia, ataxia, encephalopathy, seizures. Use with caution in CNS disease**
9. **Needs dose adjustment in severe hepatic or renal disease**
10. **Better avoided during pregnancy and lactation**

Metronidazole

Drug Interactions:

1. It potentiates the anticoagulant effect of warfarin
2. Elimination is accelerated by phenobarbital and phenytoin and inhibited by cimetidine
3. May increase lithium toxicity

Clindamycin

Mechanism of Action:

- **Inhibits microbial protein synthesis, by interfering with the formation of initiation complexes, and with aminoacyl translocation reactions.**
- **The binding site is the 50S ribosomal subunit and is identical to that of erythromycin.**

Clindamycin

Mechanisms of Resistance:

1. **Mutation in the ribosomal receptor site.**
2. **Modification of the receptor by a constitutively expressed methylase.**
3. **Enzymatic inactivation of clindamycin.**
4. **Gram positive aerobes are constitutively resistant because of poor permeability of the outer membrane.**

- **Resistance to clindamycin generally confers resistance to macrolides.**

Clindamycin

Antibacterial spectrum:

- **Anaerobic bacteria both gram positive and gram negative, including *Bacteroides* sp.**
- ***Gardnerella spp, Prevotella spp, Mobilinincus spp, Megaspahera spp, Sneathea spp* and mixed vaginal anaerobs replacing the beneficial lactobacilli in the vagina**
- **Many gram positive cocci (streptococci, staphylococci and pneumococci).**
- **Enterococci and aerobic gram negative organisms are <u>resistant</u>.**

Clindamycin

Clindamycin-resistant bacteria:

- **Enterococci**
- **Aerobic gram negative organisms**
- **GBS strains (group B Streptococci)**
- **Gram-negative anaerobes such as B. fragilis**

Clindamycin

Pharmacokinetics:

- **Widely distributed into body fluids and tissues, including bone and placenta and breast milk, except brain and CSF.**
- **It penetrates well into abscesses.**
- **It is actively taken up and concentrated by phagocytic cells.**
- **It is about 90% bound to plasma proteins.**
- **It is metabolized in the liver, and both active drug and metabolite are excreted in bile and urine.**

Clindamycin

- **t½ ~ 2.5 hours in normal individuals and 6 hours in patients with anuria, but no dosage adjustment is needed in renal failure.**
- **Accumulates in severe hepatic dysfunction.**

Clindamycin

Therapeutic uses:

1. **Infections of the female genital tract (bacterial vaginosis, septic abortion and pelvic abscesses)**
2. **Anaerobic infections**
3. **Osteomyelitis** **4. Lung abscess.**
4. **Infections resulting from fecal spillage (penetrating wounds, surgery on GIT, perforation of a viscus).**
5. **Aspiration pneumonia, in combination with an aminoglycoside or cephalosporin.**

Clindamycin

Adverse Effects:

1. **GIT irritation: nausea, vomiting, diarrhea.**
2. **Superinfection: diarrhea & pseudomembranous colitis due to *Clostridium difficile*.**
3. **Thrombophlebitis.**
4. **Thrombocytopenia and neutropenia.**
5. **Allergic reactions.**

Antiherpes Agents

- **Used to treat herpes simplex virus (HSV) & Varicella-zoster virus (VZV) infections.**
- **Include: Acyclovir, (and others)**
- **Is an acyclic guanosine derivative.**
- **It is 10 times more potent against HSV-1 and HSV-2 than VZV.**

Acyclovir

Mechanism of Action:

- **Requires 3 phosphorylation steps for activation: It is first converted to the monophosphate derivative by viral thymidine kinase and then to the di- and triphosphate by host cell enzymes.**
- **Because it requires virus enzymes first for activation, it is selectively activated, and the active metabolites accumulate in infected cells.**

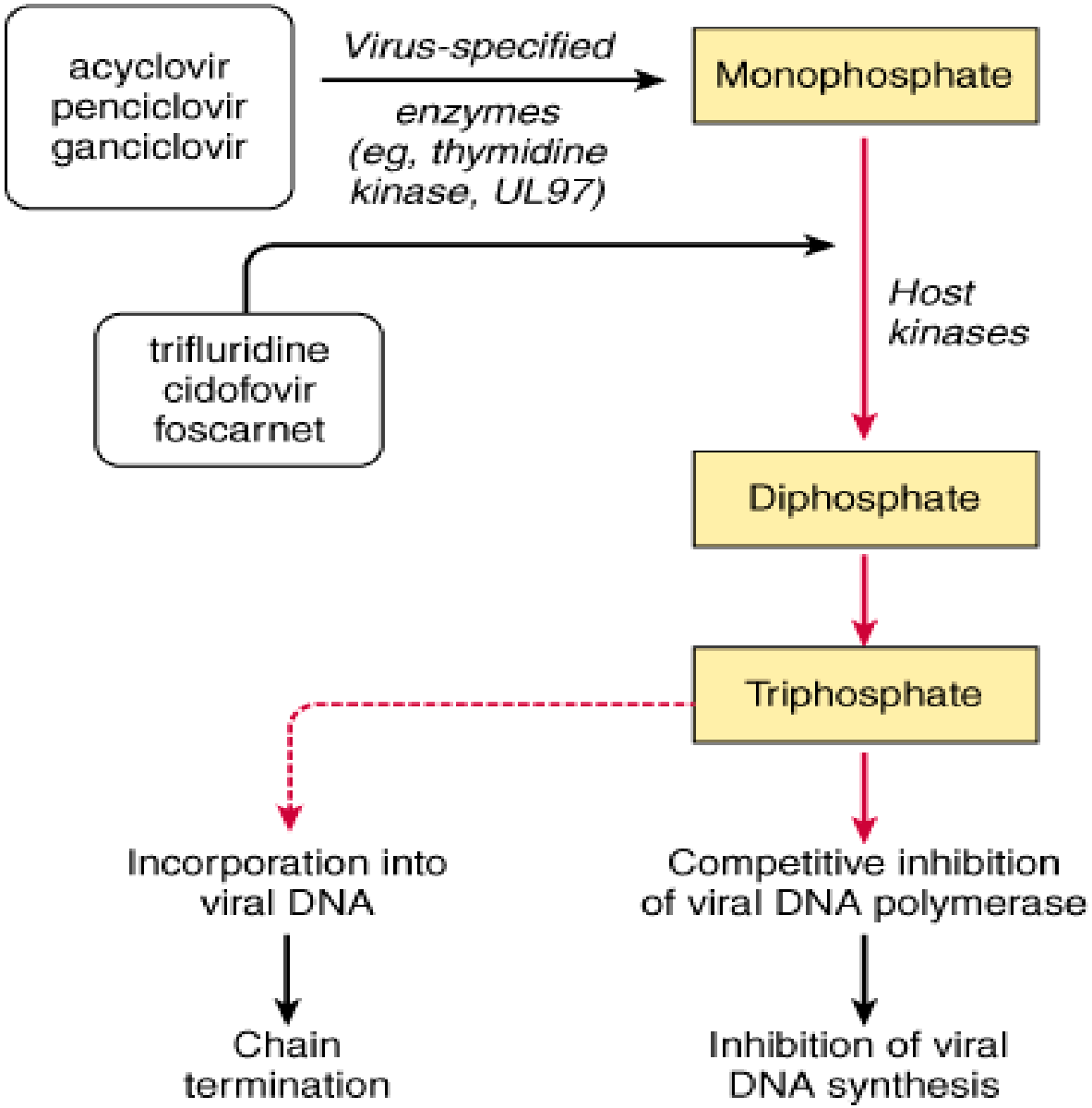
Acyclovir

- **Acyclovir triphosphate inhibits viral DNA synthesis by 2 mechanisms:**

1. **Competition with deoxy-GTP for viral DNA polymerase → binds irreversibly to DNA template.**
2. **Chain termination following incorporation into the viral DNA.**

Mechanism of resistance:

- **Due to alteration of either viral thymidine kinase or DNA polymerase.**



Mechanism of action of antiherpes agents.

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Acyclovir

Pharmacokinetics:

- Bioavailability is low (15-20%), and is unaffected by food.
- Available in oral, intravenous, and topical formulations.
- Cleared primarily by glomerular filtration and tubular secretion.
- Half-life of elimination is ~ 3 hours in patients with normal renal function, and 20 hours in patients with anuria.
- Diffuses readily into most tissues and body fluids.

Acyclovir

Therapeutic uses:

1. **Genital herpes: caused mainly by HSV-2 (although HSV-1 can also be responsible).**
2. **Herpes labialis.**
3. **Herpes zoster.**
4. **Herpes encephalitis.**
5. **Neonatal herpes.**

Acyclovir

Adverse Effects:

1. Nausea, diarrhea, headache – occasional.
2. IV administration may be associated with reversible crystalline nephropathy or interstitial nephritis; or neurologic toxicity (tremors, delirium, seizures). These are uncommon with adequate hydration and avoidance of rapid infusion rates.

Drug Interactions:

- Probenecid and cimetidine decrease acyclovir clearance and increase exposure.