

Drugs Used in 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*, *Mobilinicus spp*, *Megasphaera spp*, *Sneathia spp* and mixed vaginal anaerobs replacing the beneficial lactobacilli in the vagina
- Many gram positive cocci (streptococci, staphylococci and pneumococci) are sensitive.
- **Enterococci and aerobic gram negative organisms are resistant.**

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

- **$t_{1/2}$ ~ 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.**
- 5. Infections resulting from fecal spillage (penetrating wounds, surgery on GIT, perforation of a viscus).**
- 6. 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:

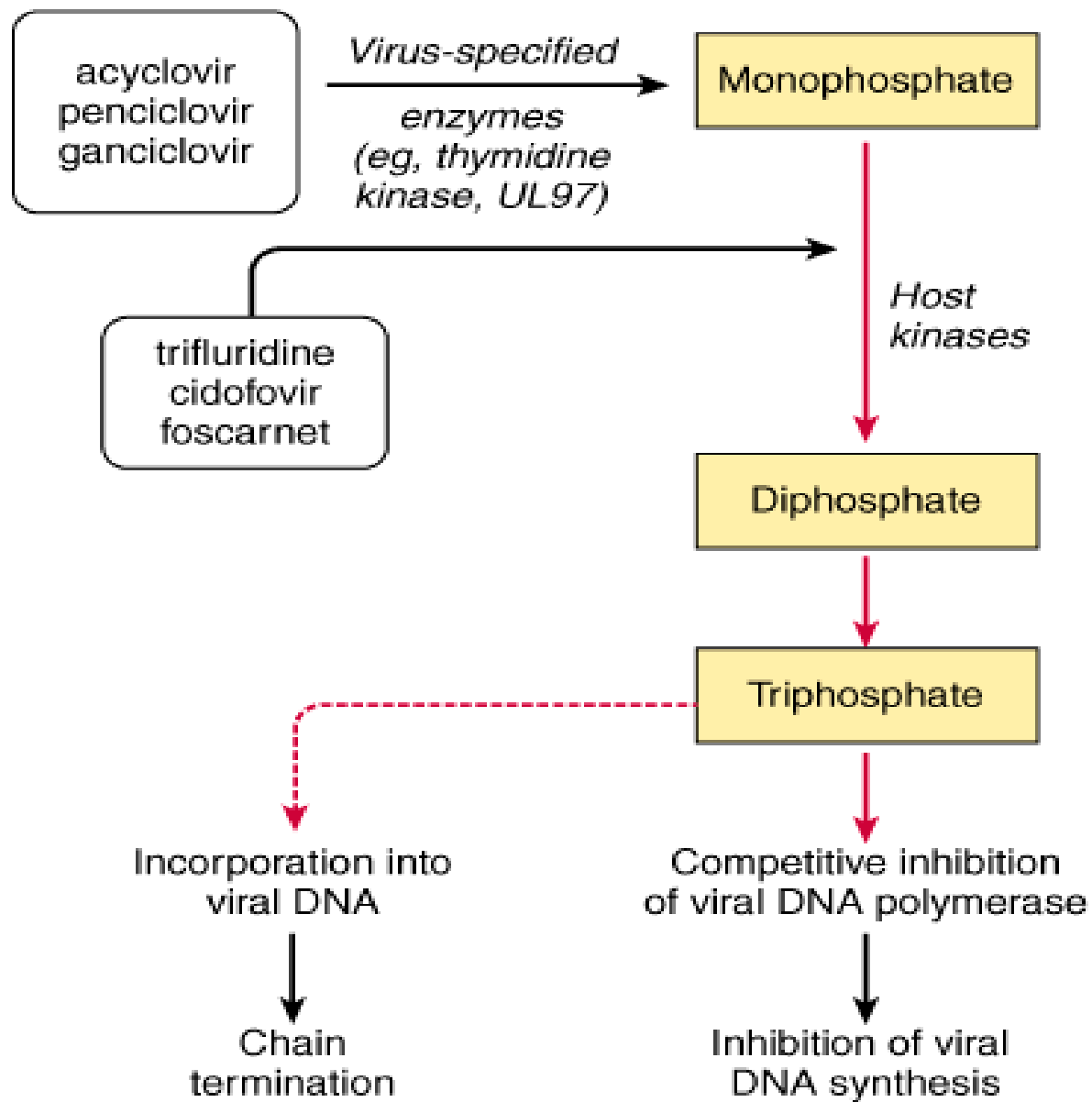
- **Requires 3 phosphorylation steps for activation: It is first converted to the monophosphate derivative by viral thymidine kinase and then to the di- and triphosphate by host cell enzymes.**
- **Because it requires virus enzymes first for activation, it is selectively activated, and the active metabolites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

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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:
 - a) reversible crystalline nephropathy
 - b) interstitial nephritis
 - c) 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.