Synthetic antimicrobial agents&drug combinations

By:

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SULFONAMIDES

- Sulfonamides were the first antimicrobial agents (AMAs) effective against pyogenic bacterial infections.

- Because of rapid emergence of bacterial resistance and the availability of many safer and more effective antibiotics, their current utility is limited, except in combination with trimethoprim (as cotrimoxazole) or pyrimethamine (for malaria).

SULFONAMIDES

ADVERSE EFFECTS

- Nausea, vomiting and epigastric pain.
- Crystalluria
- Hypersensitivity reactions
- Hepatitis

Uses

- *Pneumocystis pneumonia*
- *Urinary tract infections*
- *Respiratory tract infections*
- *Bacterial diarrhoeas and dysentery*

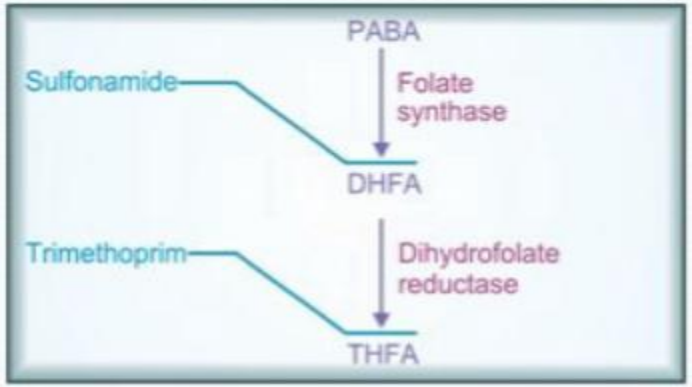
SULFONAMIDES

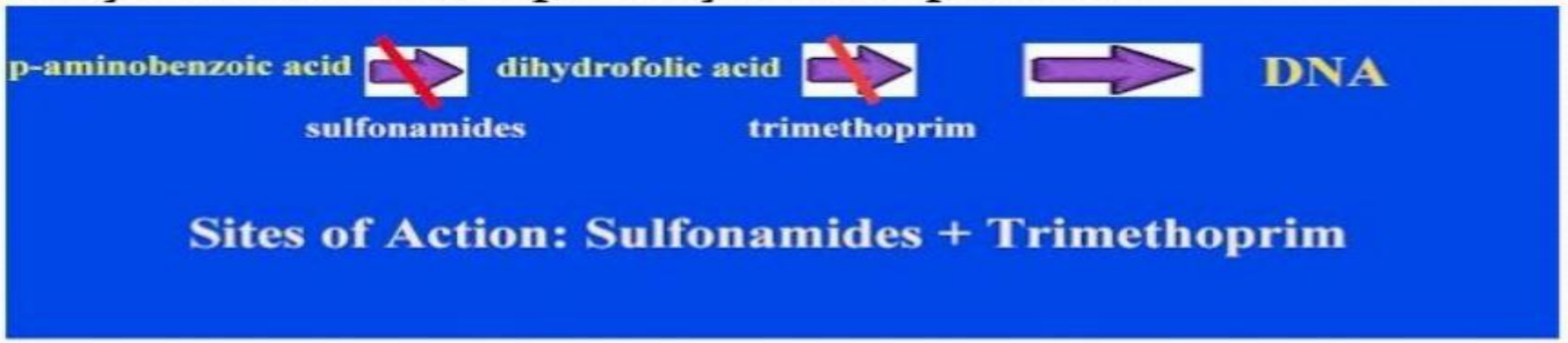
- **Action:** bacteriostatic

- **Action:**
- Gr+ (S. aureus, S. pneumoniae, etc.)
- Gr- (gonococci, meningococci, H. influenzae, E. coli, Proteus spp., Salmonella, Shigella, etc.) bacteria + chlamydia, Pneumocystis, actinomycetes, Plasmodium falciparum, Toxoplasma.

- No effect on Pseudomonas aeruginosa and most anaerobes.

- **Co-trimoxazole (sulfamethoxazole+trimethoprim)**- in contrast to all other drugs, has a bactericidal action! Currently, the most widely used for the treatment of Pneumocystis infection, especially in HIV-patients.





- Note: in recent years, the use of sulfonamides in clinical practice has decreased significantly (highly toxic, most microorganisms have developed resistance to them).

SULFONAMIDES

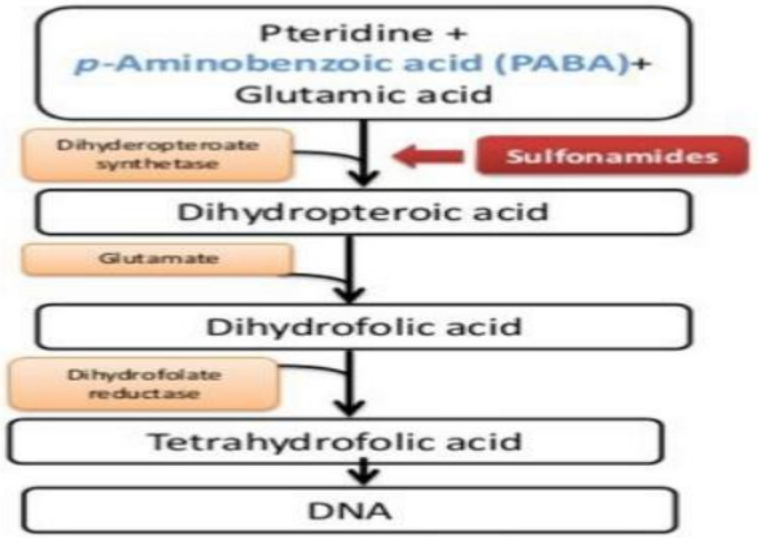
Mechanism of action:

- They are chemical analogues of p-aminobenzoic acid (PABA) → they competitively inhibit bacterial enzyme, which is responsible for the synthesis of folic acid → inhibit bacterial folic acid, which is the most important factor of microbial life.

In environments containing large amounts of PABA, such as pus or tissue breakdown products, antimicrobial action of sulfonamides is significantly weakened.

Mechanism of action

- Bacteria synthesize their own folic acid (FA) of which *p*-aminobenzoic acid (PABA) is a constituent, and is taken up from the medium.
- Sulfonamides, are structural analogues of PABA, inhibit bacterial folate synthase and formation of folate get inhibited.
- Sulfonamides competitively inhibit the PABA with pteridine residue to form dihydropteroic acid which conjugates with glutamic acid to produce dihydrofolic acid.
- Sulfonamide altered folate an which is metabolically injurious



Quinolones/Fluoroquinolones

Classification:

- **I gen- (mostly for urinary tract infections):**
  - **Nalidixic acid**
  - **Oxolinic acid**

  Only Gr-: Proteus, E. coli, Enterobacter, Klebsiella.

- **IIgen (a broad spectrum antimicrobial action):**
  - **Lomefloxacin**
  - **Norfloxacin**
  - **Ofloxacin**
  - **Pefloxacin**
  - **Ciprofloxacin**
  - **Enoxacin**

- Gr-; Escherichia coli, Klebsiella (including K. pneumoniae), Salmonella spp., Shigella spp. Proteus spp. Serratia spp. Enterobacter spp. P. aeruginosa, Haemophilus influezae
  Slightly Gr+, eg. Staph. spp. Mycobacterium tuberculosis

- **III gen (respiratory):**
  - **Levofloxacin**
  - **Sparfloxacin**

  Gr-:Haemophilus influezae, Klebsiella, Helicobacter pylori, Neisseria, Serrata etc+Mycobacterium tuberculosis, M. leprae.
  A higher activity against Gr+ bacteria (pneumococci, Staph., Str., Entrococcus spp. Corynebacterium diphtheriae, etc.) intracellular pathogens (chlamydia, Legionella, Mycoplasma).

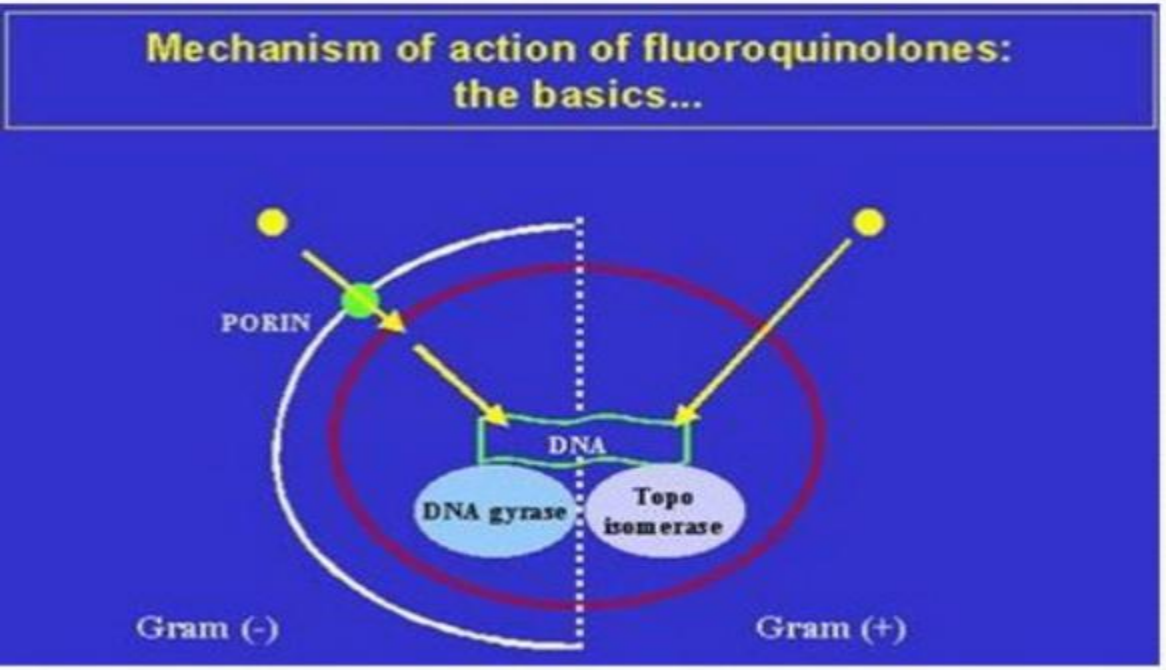
- **IVgen (respiratory+ antianaerob):**
  - **Moxifloxacin**

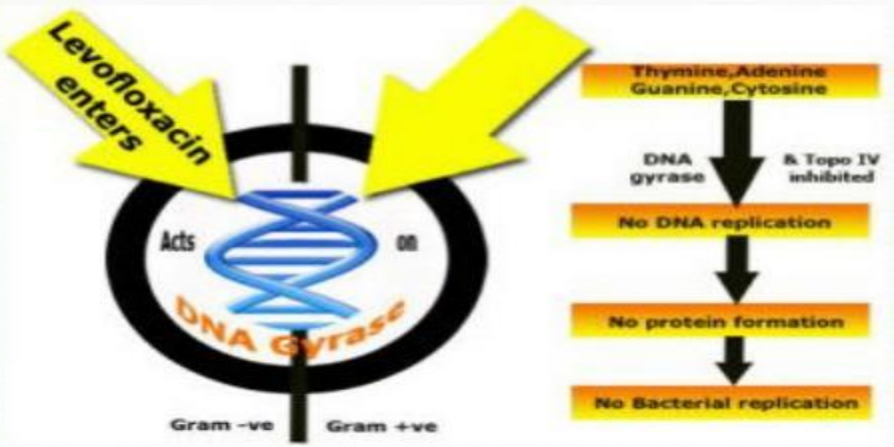
  As the group III + anaerobes.

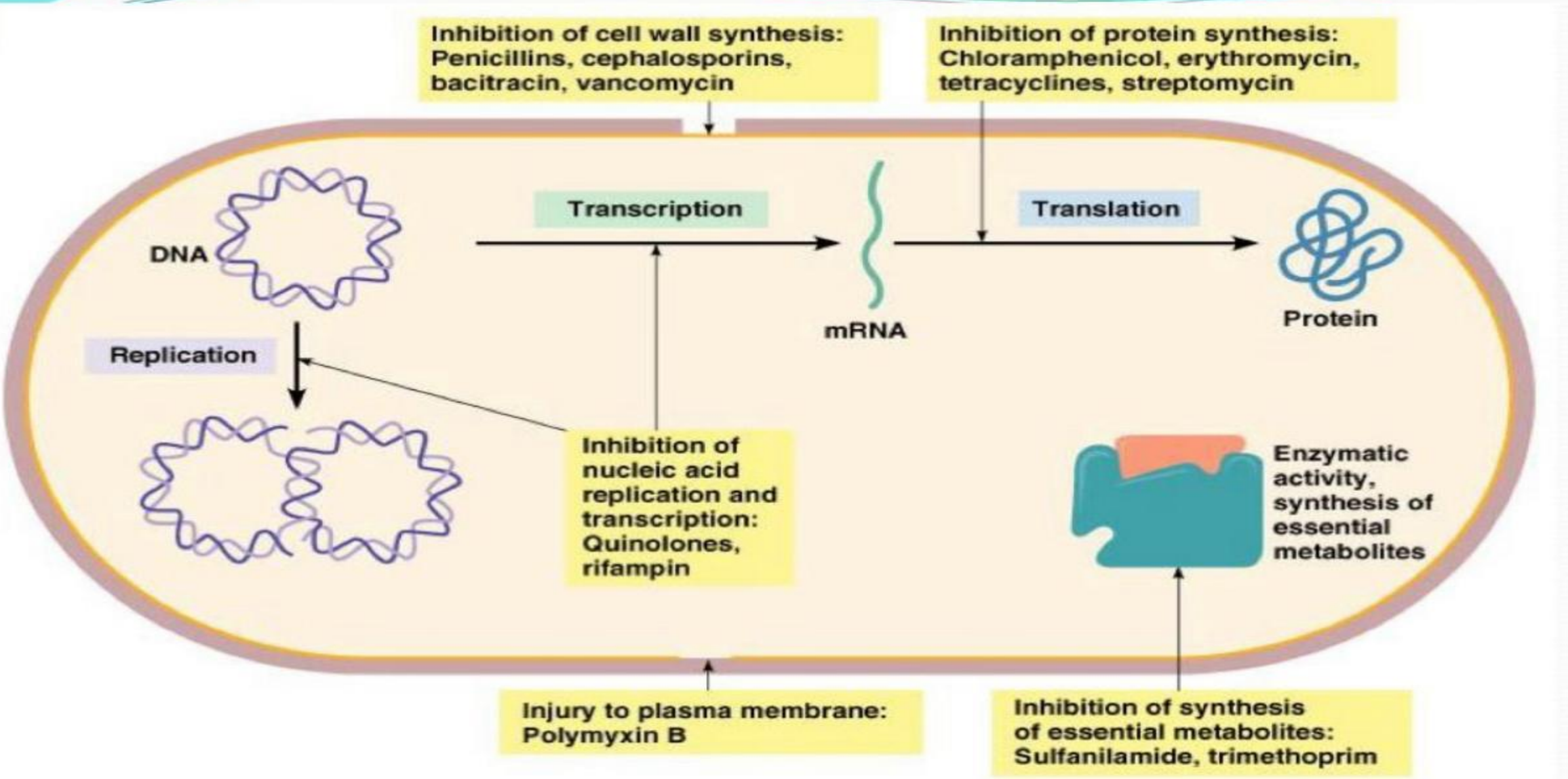
- **They are recommend to use these drugs as a reserve, primarily because of hepatotoxicity+ cardiotoxicity**

Quinolones/Fluoroquinolones

- **Mechanism of action:** violation of DNA synthesis by inhibiting DNA gyrase (topoisomerase II) and topoisomerase IV
- **Action:** bactericidal







Nitrofurans

Nifuroxazide, nitrofurantoin, furazidin, furazolidone

- **Mechanism of action:** as acceptors of oxygen, nitrofurans hinder the process of cellular respiration of the bacteria,also- inhibit the biosynthesis of nucleic acids.
- **Action:** depending on the concentration of the bacteriostatic or bactericidal effect.
- **Activity:** broad spectrum(Gr- and Gr+ bacteria, some anaerobes, fungi /Candida).
- In addition, furazolidone and nifuratel active against some protozoa (Giardia, Trichomonas)

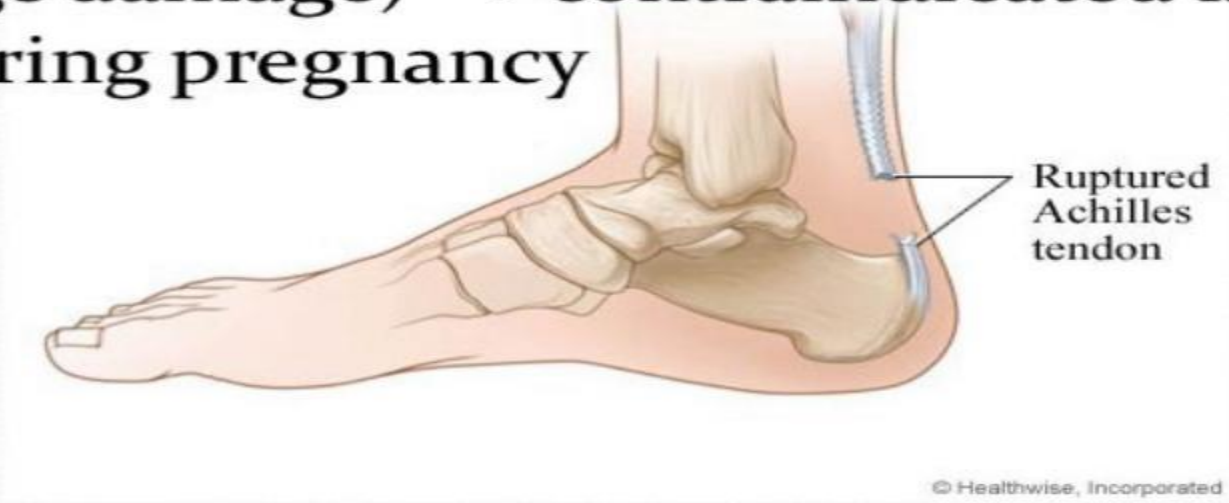
- ***Nitrofurantoin* is the drug of choice for uncomplicated infections of the lower urinary tract.**
- ADR - neuropathy, pneumonitis and hepatitis.

Uses

- *Urinary tract infections*
- *Bacterial gastroenteritis*
- *Typhoid* (Ciprofloxacin is one of the first choice drugs in typhoid fever)
- *Bone, soft tissue, gynaecological and wound infections*
- *Respiratory infections* (*Mycoplasma, Legionella, H. Influenzae* pneumonias)
- ***Tuberculosis*** - fluoroquinolones – 2nd line drugs for the treatment of tuberculosis! (reserve drugs, with an average efficiency)

Adverse reactions

- Tendinitis and tendon rupture (Achilles tendon rupture, cartilage damage) → contraindicated in children and during pregnancy

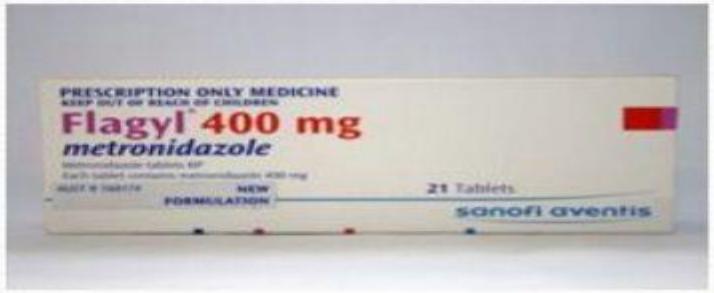


- Phototoxicity
- Cardiotoxicity (*Prolongation of QT interval)*
- Neurotoxicity (seizures, headaches, hallucinations).

Nitroimidazoles

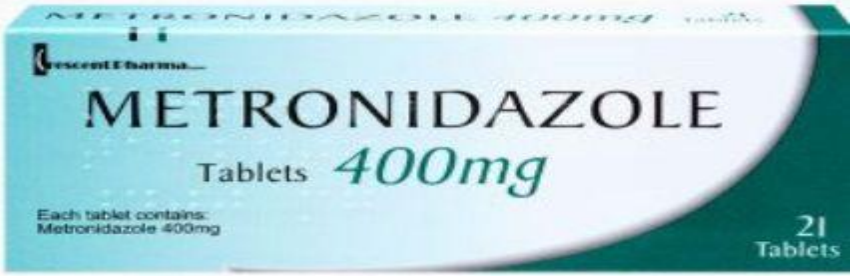
Metronidazole, Tinidazole, Ornidazole

- **Mechanism of action**: violation of DNA replication and protein synthesis in microbial cells, by inhibiting tissue respiration.
- **Action:** bactericidal
- **Activity:** anaerobes (G+ and G-): Bacteroides, Clostridium (including C. difficile), Protozoa (T. vaginalis, E. histolytica, G. lamblia, L. intestinalis, E. coli, Leishmania spp.), as well as **H. pylori**.



Medical uses

- Bacterial vaginosis
- Pelvic inflammatory disease
- Pseudomembranous colitis (*C. difficile* colitis)
- *C. difficile* diarrhea
- Amoebiasis
- Trichomoniasis
- To eradicate Helicobacter pylori



ADR:

- nausea, diarrhea, abdominal pain, vomiting
- headache, dizziness
- metallic taste in the mouth

- hypersensitivity reactions (rash, itch, flushing, fever)
- leucopenia, neutropenia
- increased risk of peripheral neuropathy and central nervous system toxicity

drug combinations

A combination of two antibacterial agents may produce the following responses 1
1.Synergism, where the joint effect is greater than the sum of the effects of each drug acting alone. 2.Additive effect, in which the combined effect is equal to the arithmetic sum of the effects of the tow individual

3 Antagonism (interference), in which there is a lesser effect of the mixture than that of the more potent drug action alone.

There are four possible justifications as to the use of antibacterial agents in combination

1 ..theconcept of clinical synergism, which may be extremely difficult to demonstrate convincingly. Even with trimethoprim plus sulphamethoxazole, where true synergism occurs in vitro, the optimum ratio of the two components may not always be present in vivo, i.e. at the site of infection in a particular tissue..

2. A wider spectrum of cover may be obtained, which may be (a) desirable as an emergency measure in life-threatening situations; or (b) of use in treating mixed infections.

3 ..The emergence of resistant organisms may be prevented. A classical example here occurs in combined antitubercular therapy (see earlier).

4 ,,A possible reduction in dosage of a toxic drug may be achieved.Indications for combined therapy are now considered to be much fewer than originally thought. There is also the problem of a chemical or physical incompatibility between two drugs. Examples where combinations have an important role to play in antibacterial chemotherapy