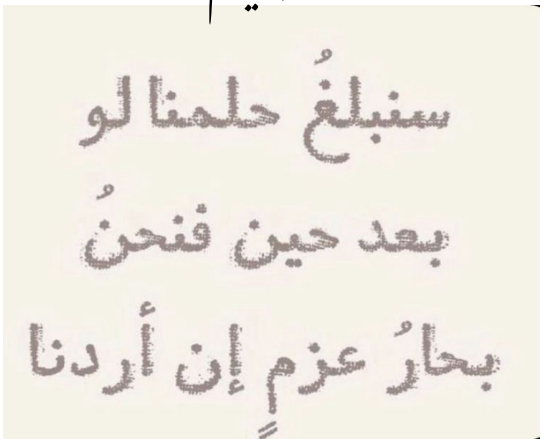
Pharmacology of Quinolones & sulphonamides

رسالة اليوم



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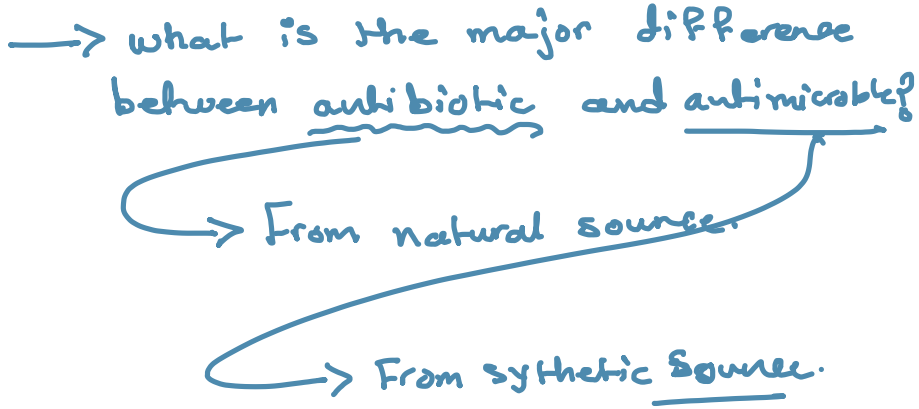
Objectives

- What are quinolones?
- Nalidixic acid
- Floroquinolones: generations, spectrum, advantages, mechanism of action, resistance, uses, adverse effects and contraindications
- Inhibitors of synthesis of essential metabolites: sulphonamides
- Sulphadiazine: PKs and PDs
- Co-trimixazole
- Other sulphonamides combinations
- Adverse effects of sulphonamides



Quinolones

- ✓ Synthetic antimicrobials = Synthetic
- ✓ Bactericidal ⇒ The Target ⇒ DNA
- ✓ Primarily gram-negative bacteria

Nalidixic acid (& pipemidic acid)

- First member: prototype (الأب الروحي) = First generation of Quinolones.
- **Advantages**:
- 1- Cover G-ve bacteria → (exs) ① E-coli , ② pseudomonas.
- 2- Rapidly excreted in urine in concentrations enough for treatment of UTIs ... Rapidly excreted in urine in large amount, so it used to treat infection in Urinary tract.

Disadvantages of nalidixic acid

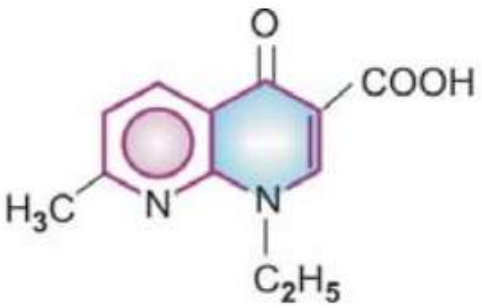
- Concentration of free drug in plasma & most tissues is **non-therapeutic** for **systemic infections** / due to Highly excreated, it can't treat other infections in different tissue.
- Narrow spectrum
- Rapid development of bacterial resistance. ⇒ Limited therapeutic use.
- So:
- Limited therapeutic use

Fluoroquinolones

- Quinolones are molecules **structurally derived from the heterobicyclic aromatic compound quinoline.**

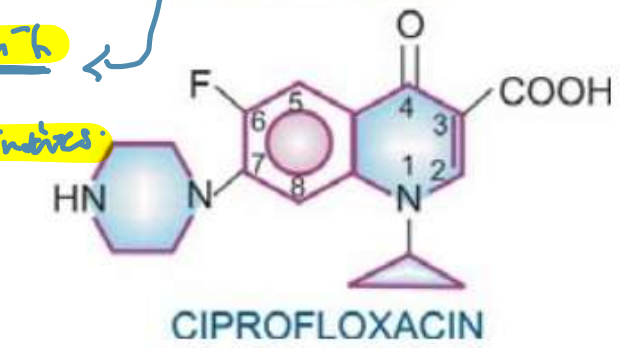
- **Fluorination** of quinolone structure at position 6 resulted in derivatives called **fluoroquinolones**

2- aromatic ring.



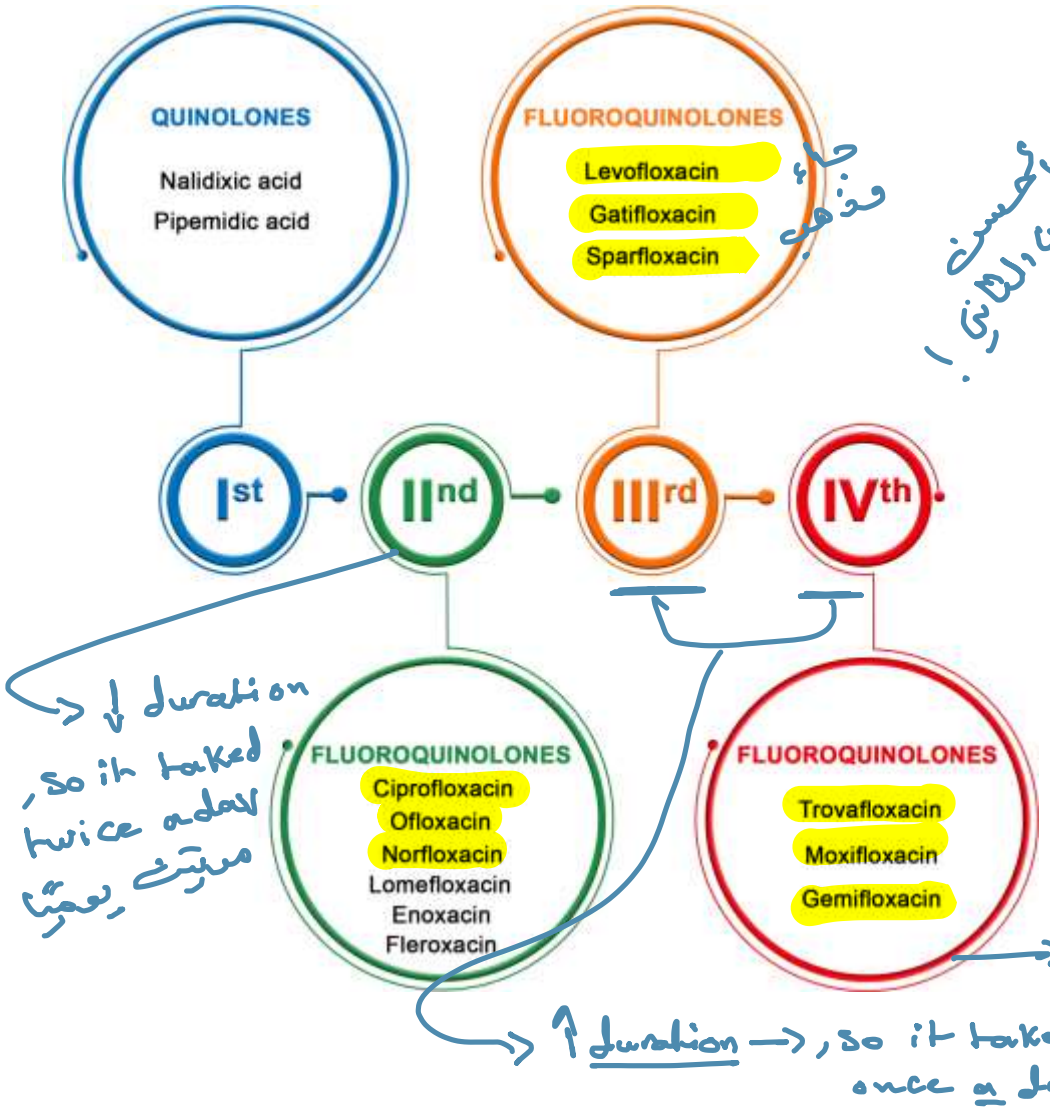
Quinolones = NALIDIXIC ACID

we can't call it fluroquinolones.



⇒ To go over the disadvantage of first generation they add F atom to ring ⇒, so it become and have good advantages.

Generations & Spectrum



During the releasing of new generation these standers are get better:
① ↑ spectrum ② ↑ potency ③ ↑ duration.

2nd generation | 3rd generation | 4th generation

mutalikpharmacology	Gram negative aerobes		
Anerobes +	++	+++	++++
Gram +ve +	++	+++	++++
Atypical +	++	+++	++++
Long (bd)	Longer + (qd)	Longer ++ (qd)	Longer ++ (qd)
UTI, Gonorrhea, Typhoid fever, Respiratory, CAP, Mycoplasma, Chlamydia, Tuberculosis, Post-op/Hospital infections, Gynecological infections			

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Advantages of floroquinolones

1- High potency
2- Broad antimicrobial spectrum
3- Slow development of resistance
4- Better tissue penetration
5- Prolonged duration of action

❖**Used for wide variety of infectious diseases**

Pharmacokinetics of quinolones

- Key: MW less than 500, chemical structure has no –OH groups
- **Absorption**:
- Rapid and complete **oral** absorption, avoid with food (or drugs) containing Al, Ca, Iron
- **Distribution:**
- High tissue penetration: Concentration in lung, sputum, muscle, bone, cartilage (minerals), prostate, and phagocytes & neutrophils (IC) exceeds that in plasma
- Can pass BBB: reaching concentrations to treat CNS infections
- Pass placentral barrier: teratogenic
- **Excreted** in breast milk
- **Metabolism**: liver
- **Excretion**: in urine unchanged : Urinary are 10-50-fold higher than in plasma: UTIs
- **Moxifloxacin** excreted by non-renal routes: not used in UTIs

High absorbation.

The presence of it (–) ⇒ repealing the drug.

decreased absorbation.

↑ pentration → ↑ treatment of infection.

minerals loving [Affinity to minerals]

[adverse effect]

can't be given to pregnant woman.

Flora quionlones :- يستخدم لعلاج المسالك البولية.

Mechanism of action

Quinolones target bacterial **DNA gyrase** = **Topoisomerase IV**

Same enzyms but with different names due to main types of bacteria (-, +)

- Gram negative bacteria - **DNA Gyrase** → related to surface of DNA
- Gram positive bacteria - **Topoisomerase IV**

→ They're the same ≠ related to morphological of DNA.
DNA ↓ ↓ ↓

- **In mammalian cells(human cells) Topoisomerase II**

1- Low affinity for flouroquinolones ↑ doses

2- Inhibited by quinolones only at much higher concentrations.

Low toxicity to host cells

Mechanism of action

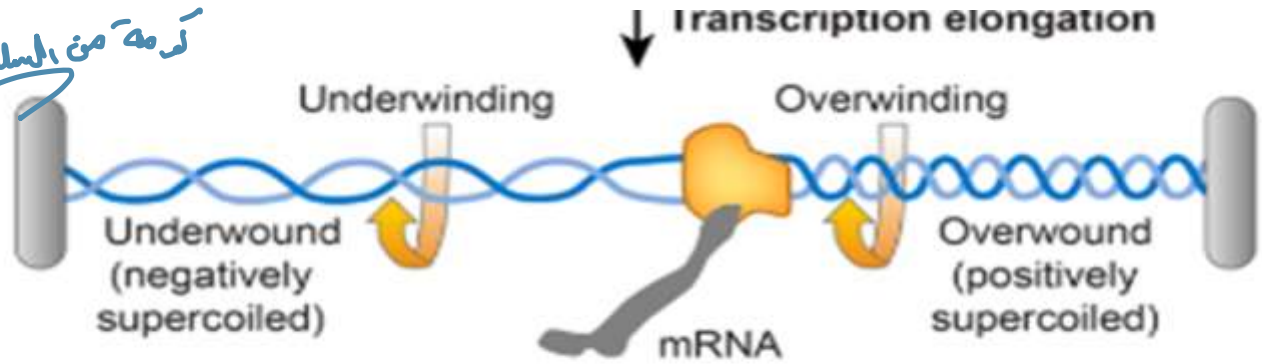
→ Result in bacteria death and misfolded protein.

- Two strands of double helical DNA must separate to permit DNA replication / transcription
- "over winding" / excessive positive supercoiling of DNA leads to faulty protein synthesis and bacterial death.

No DNA Transcription

→ To go under DNA replication and transcription, the 2 strand have to denaturated → DNA gyrase and Topo (+) Responsable about this

C.



→ Any inhabition in these 2 enzymes lead to inhabition of (Replication and Transcription) or release of misfolded protein.

Mechanism of resistance

- **1- Chromosomal mutation:**

  bacteria produce DNA Gyrase/ Topoisomerase IV with **reduced affinity** for quinolones.

- **2- Drug efflux:** across bacterial membranes

- Resistance is **slow** to develop

Therapeutic indications

1- Urinary tract infections:

- **Most commonly used antimicrobials for UTI**
- **Very effective against Gram negative bacilli like**

  E.coli

  Proteus

  Enterobacter

  Psuedomonas

  Ciprofloxacin 500 mg bd / 2ed generation → Twice a day.

2- Salmonella typhi infection (typhoid fever):

- **Ciprofloxacin** 500 mg bd x 10 days / Twice a day.
- Prevents carrier state also

بنفس حامل المرض ← عدوى

→ patient still carry the disease →, So this is will lead to pass disease to others

→ if the Typhoid doesn't treat well → The diagon's will decreased, buh the

why they are respiratory quinolones. ؟؟

① They have ability to enter intra Cellular, also

② They have a ↑ spectrum, also

③ They can treat infections caused by Gram(+)

3- Respiratory infections:

- Pneumonia
- Acute sinusitis الجيوب الأنفية
- Chr. Bronchitis
- **Respiratory quinolones**: **levofloxacin, moxifloxacin, Gemifloxacin**. why?
- They are distributed IC in macropgages and polymorphs
- Cover G+ve and atypical bacteria

My Great Lung

4-Bone and joint infections: Osteomyelitis & joint infections

5- Meningitis

6- - Atypical infections

↳ Mycoplasma

Adverse effects

1- Musculoskeletal:

- **Tendonitis & tendon rupture**: ciprofloxacin: tendinopathy of Tendo Achillis
- **Arthropathy (Joint disease)** in immature animals

Contraindication: children less than 6-12 years, pregnancy and during breast feeding contraindicated

- **2- CNS:** excitation due to blocking of GABA receptors: seizures have occurred predominantly in patients receiving theophylline or a NSAIDs and epilepsy patients (contraindications)

Adverse effects

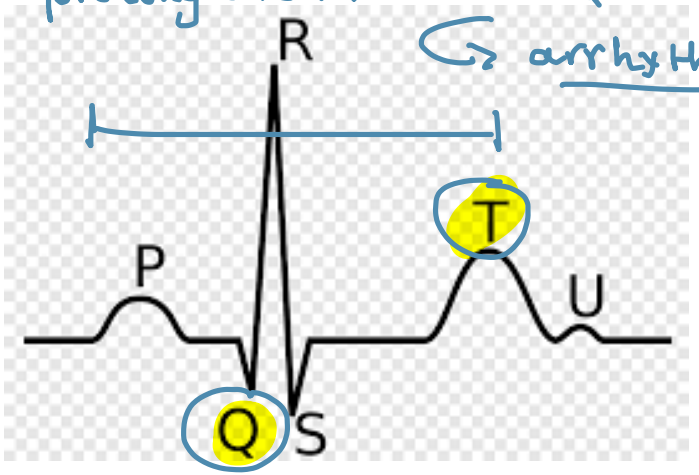
- **3- QT interval prolongation**: trovafloxacin withdrawn in 2016.
- Cautious use in patients who are taking drugs that are known to prolong the QT interval: tricyclic antidepressants, Phenothiazine and class I anti-arrhythmics
- **4- Drug interactions:**

➢ NSAIDs & theophylline may enhance CNS toxicity of floroquinolones

– Seizures reported

➢ Antacids, Sucralfate, Iron salts reduce absorption of quinolones

➢ Quinolones are cytochrome p450 inhibitors

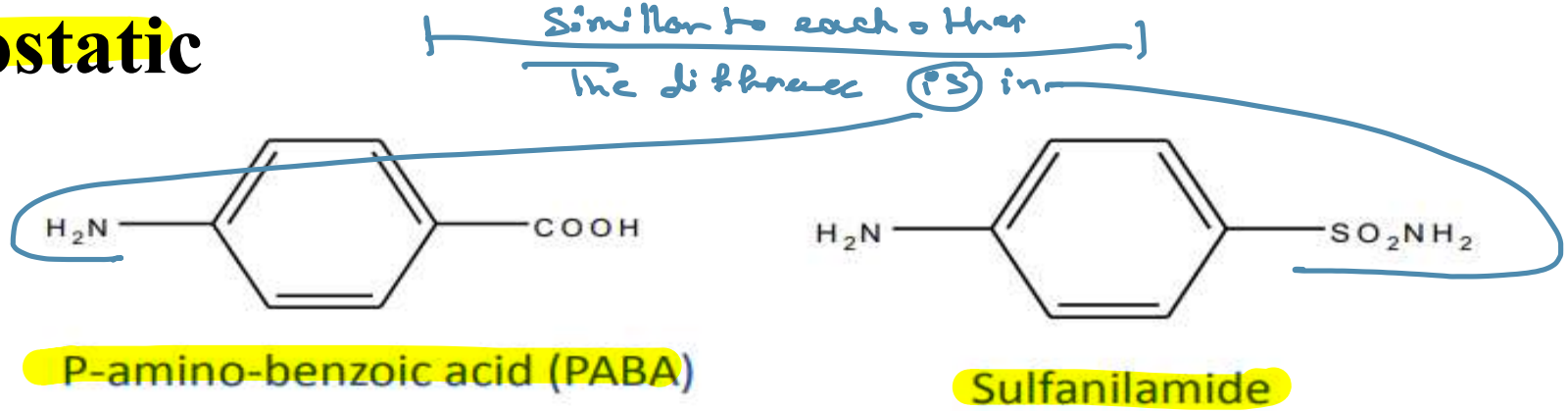


Inhibitors of synthesis of essential metabolites

= Bacteriostatics

Sulphonamides (sulpha drugs) & trimethoprim

- **<u>Antimicrobials in this class:</u>**
- Sulfonamides
- Trimethoprim
- **Bacteriostatic**



PKs

- **Example: sulphadiazine**
- **Absorption**: good oral absorption, **not affected by food**
- **Distribution**:
- BBB: pass: used with penicillin for treatment of bacterial meningitis in 1930s-1940s
- Good tissue penetration: prostate ⇒ effective in treat prostate infection and UTI
- Placenta: pass and excreted in breast milk / contraindicated ممنوع
- **Metabolism**: liver
- **Excretion**: renal: acylated but active metabolite (UTIs, alkalinization of urine) → because it deposited in acid urine بحل حصوات
- **Uses**: treatment of CNS toxoplasmosis and plasmodium falciparum

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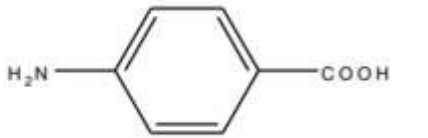
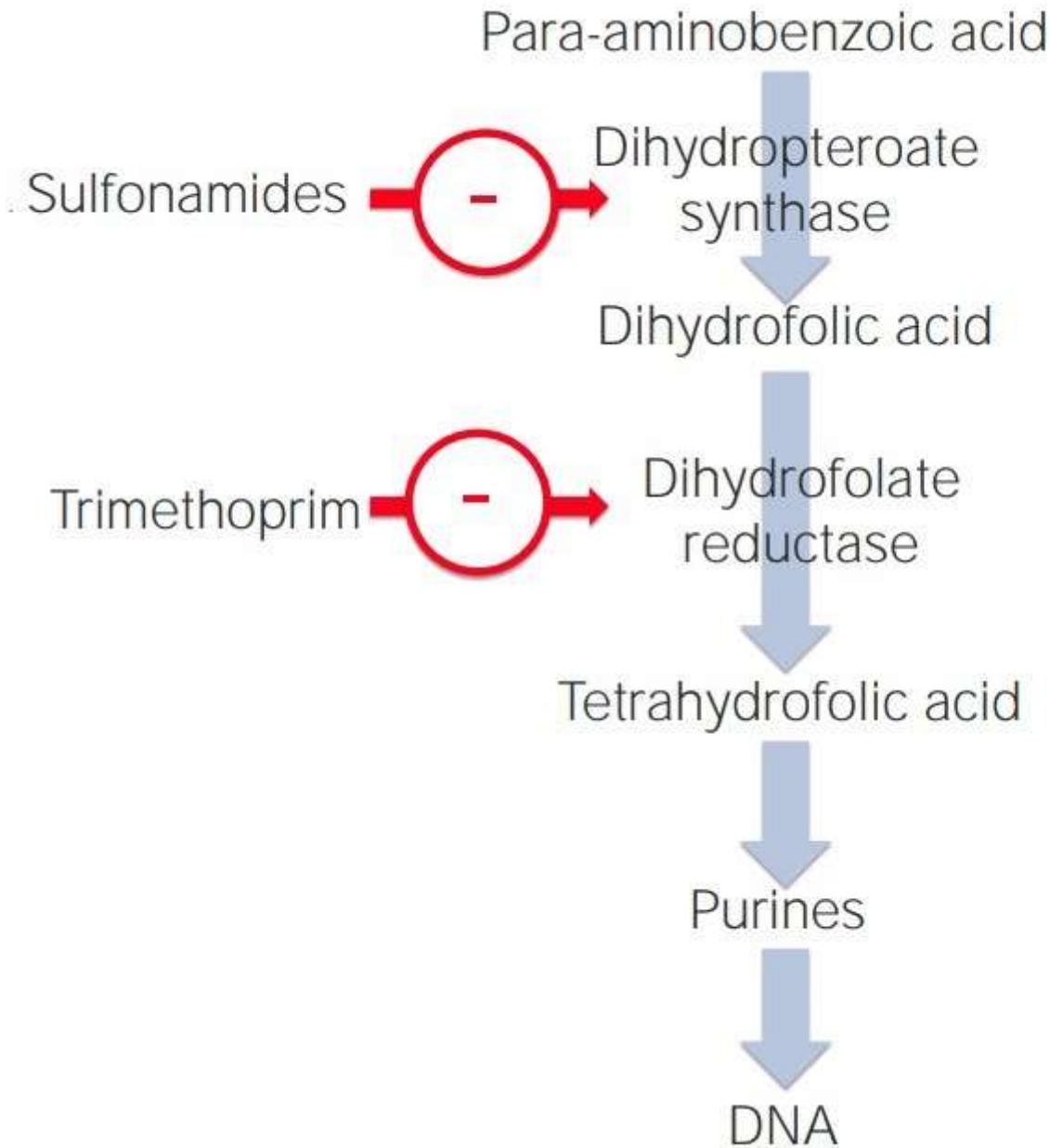
PDs

- Competitive inhibitors of **dihydrofolate synthase** bacterial enzyme responsible for the incorporation of **PABA** into **dihydrofolic acid** (immediate precursor of folic acid).
- Folic acid required for synthesis of purines and nucleic acid
- Sulfonamides are structural analogue of P-aminobenzoic acid (PABA)



P-amino-benzoic acid (PABA)

Sulfanilamide


Para-aminobenzoic acid
Sulfonamides
Dihydropteroate synthase
Dihydrofolic acid
Trimethoprim
Dihydrofolate reductase
Tetrahydrofolic acid
Purines
DNA

CO-TRİMOXAZOLE

•Sulfamethoxazole with **trimethoprim** in 5: 1

•**Tablets contain** 400 mg of sulfamethoxazole plus 80 mg of trimethoprim.

• **Mechanism of action**: Trimetoprim inhibits the enzyme dihydrofolic acid reductase (sequential block)

• **Bacteriostatic activity**.

•**Spectrum:**

•**Some G+ve**: streptococcal tonsillitis, pharyngitis

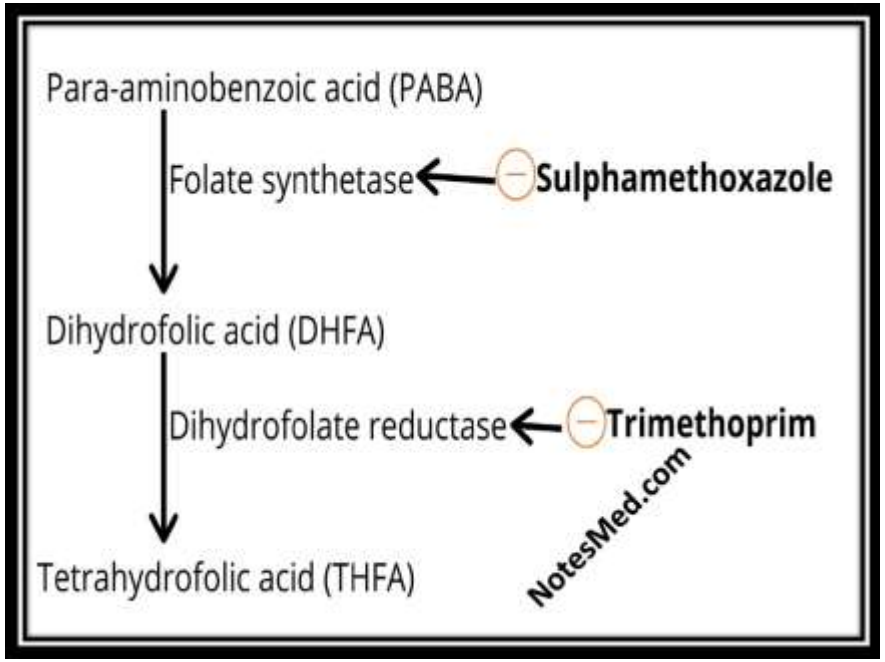
•**Some G-ve**: E.coli: UTIs

•**Atypical bacteria**: chlamydia: eye, genital

•**Toxoplasma**

•**Plasmodium falciparum**

•**Pneumocystis carinii**



Indications of co-trimoxazole

- **1- UTIs**: excreted in high concentration in urine (alkalinization of urine)
- **2- Streptococcal infections:** pharyngitis, tonsillitis
- **3- AIDS**: PCP: **Pneumocystis carinii (drug of choice): oral or IV for 3 weeks**
- **4- Toxoplasmosis of CNS**

Other sulphonamides combinations

- **Silver Sulfadiazine (cream)**

•Inhibits growth of nearly all pathogenic **bacteria (psudomonus)** & **fungi**

•Used topically to reduce incidence of infections of wounds from burns

–Slowly releases silver ions -antimicrobial action

–**Sulphadoxine & pyrimethamine**: malignant malaria (plasmodium falciparum): sequential block

–**Sulphasalazine**: sulphapyridine & **5-aminosalicylic acid: ulcerative colitis: will not cure the disease but reduce number of attacks**

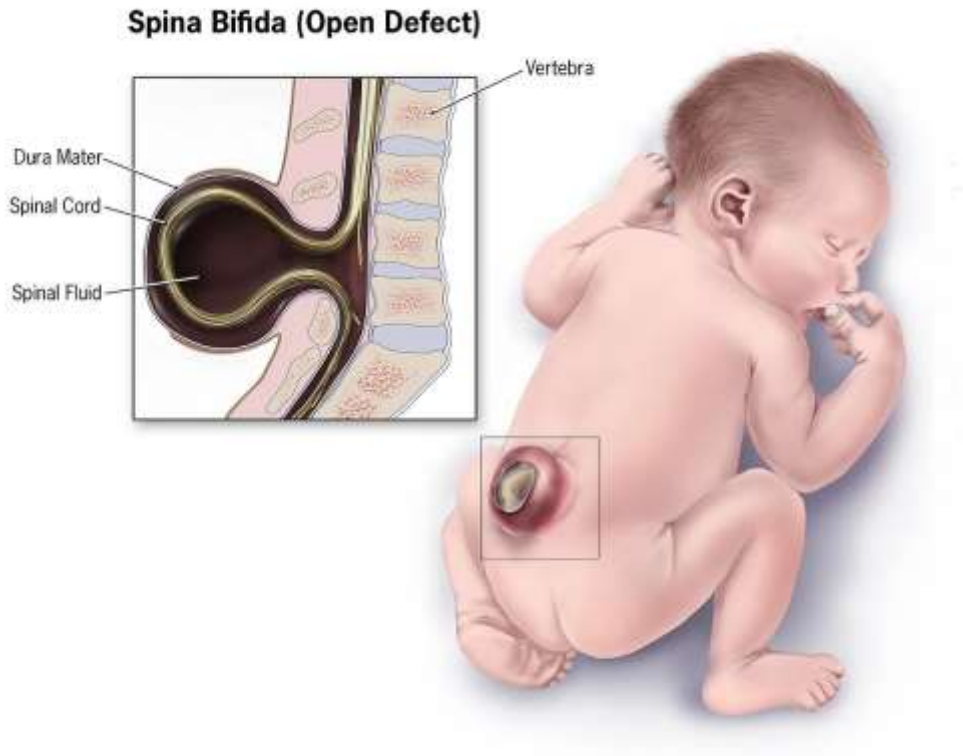
Adverse effects

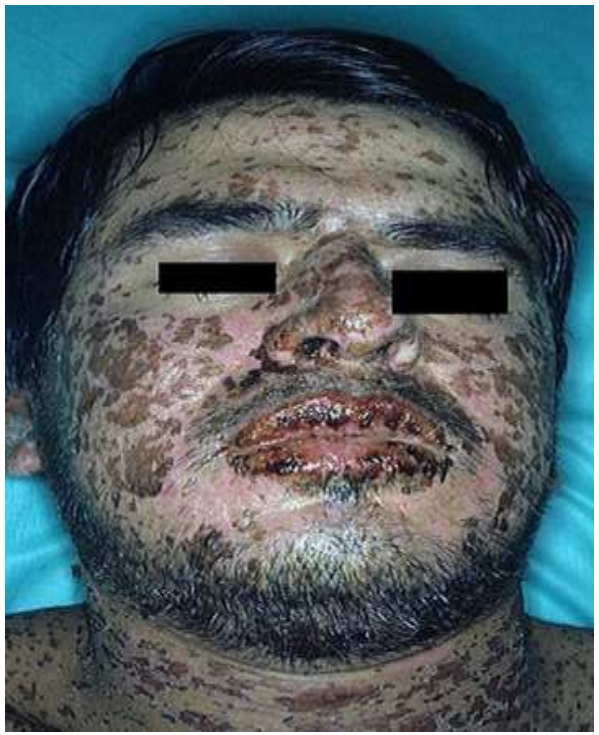
- 1- **Allergy**: skin rash: common
- Stevens-Johnson syndrome (SJS) (TEN: toxic epidermal necrolysis): rare
- **2- Crystalluria**
- Insoluble in acidic urine
- Precipitate, forming crystalline deposits that can cause urinary obstruction
- Fluid intake sufficient to ensure a daily urine volume of at least 1200ml
- Alkalinization of the urine

3- kernicterus

- Administration to **newborn infants esp. premature**
  - Sulfonamides displace **bilirubin (jaundice)** from plasma albumin.
  - Free bilirubin is deposited in **basal ganglia & sub-thalamic nuclei** of the brain causing an encephalopathy & permanent brain damage called **kernicterus**.

- **4- anemia**:
- Hemolytic anemia: G6PD deficiency
- Megaloblastic anemia: treated by folic acid tab. 5 mg once daily
- **5- during pregnancy**:
- 1st trimester: neural tube defect (spina bifida): teratogenic
- 3rd trimester: kernicterus
- **Contraindications**: pregnancy, children less than 2 y, allergy to sulpha, fauvism, renal stones


Spina Bifida (Open Defect)
Vertebra
Dura Mater
Spinal Cord
Spinal Fluid



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