

**Passion
Academic
team**

YU-Medicine

Sheet #20

Lec. Date: 14.Novmeber

**Lec.Title: Inhibitors of Nucleic acid
Function or Synthesis**

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2. Folic Acid Antagonists

- Coenzymes containing folic acid
 - required for the synthesis of purines and pyrimidines
 - and other compounds necessary for cellular growth and replication.
- In the absence of folic acid, bacteria cannot grow or divide.
 - Humans cannot synthesize folic acid and must obtain preformed folate as a vitamin from the diet.
 - Many bacteria are impermeable to folic acid, and must synthesize folate de novo.

Sheet#1

* DNA synthesis is important for **PRODUCTION** Of nucleotides which are precursor for synthesis of DNA which is important in synthesis of enzymes and proteins and in bacterial growth and multiplication.

* So this type of antibiotics is «**Bactericidal**».

** Again : any drug to treat **UTI** must be eliminated **actively** in the urine 90% and highly **concentrated** (**not PRODRUG**).

* Why do we need **Folic acid**?

– **for nucleotide synthesis.**

* we can synthesize it inside our bodies and take it from outside and enter the cell compared with bacterial cell that is impermeable to folic acid. (so it depends only on synthesis of it)

** so when I prevent it from folic acid, just it affected not our cells.

--Which are cells need Folic acid Most?

Stem cells and bone marrow (more affected) because they produce RBCs and WBCs daily because they are **HIGHLY REPLICATED.**

Inhibitors of Folate Synthesis and Metabolism

1. Sulfonamides Work on the first enzyme

- Sulfasalazine enzyme
- Silver sulfadiazine*
- Sulfamethoxazole
- Sulfadiazine
- Sulfadoxine

2. Pyrimethamine Works on the second enzyme

(used with SA in parasitic infections)

2. Trimethoprim Works on the second enzyme

- Cotrimoxazole (Trimethoprim + Sulfamethoxazole)

4. methotrexate (in cancer chemotherapy).

When it first emerged, it was used as an antibacterial, affecting bone marrow enormously (causing leukopenia).

It was found to be very effective in treating tumours, specially breast cancer.

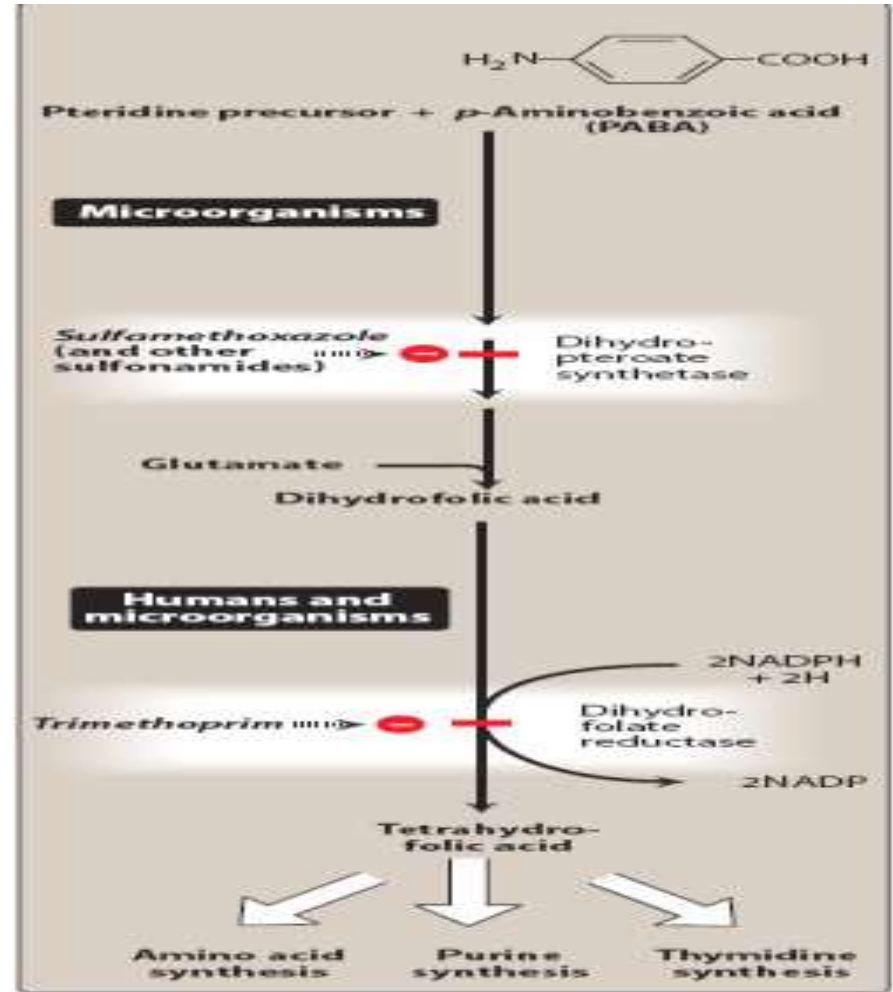


Figure 40.7
Inhibition of tetrahydrofolate synthesis by sulfonamides and trimethoprim.

Sheet #2

Methotrexate **excluded from antibacterial as it has many many side effects such as Nephrotoxicity in high concentration and bone marrow depression.

**Sulfonamides not drug ; they are group of drugs.

Each drug **differs** from the others in its dosage form, applications and combination.

They are highly protein binding<< when they given with **warfarrin**, they dicplace it from its binding sites then **bleeding**.

~~Is it true to give 2 drugs from different groups? (one works on the first enzyme and the another on the second one).

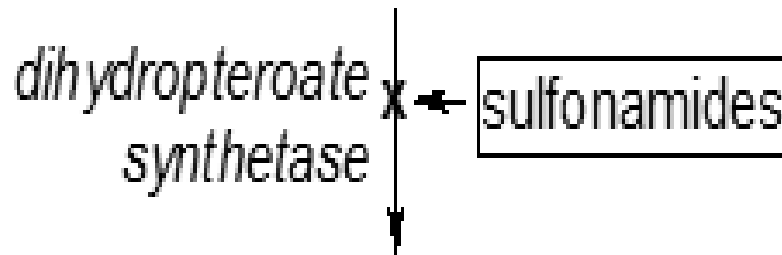
Ans: **YES**

As in Cotrimoxazol which is a combination of Trimethoprine and Sulfamethaxazol

1+1>2 (additive). Effect **more** than expected.

dihydropteroate diphosphate + p-aminobenzoic acid (PABA)

The first enzyme



Drug works on first enzyme

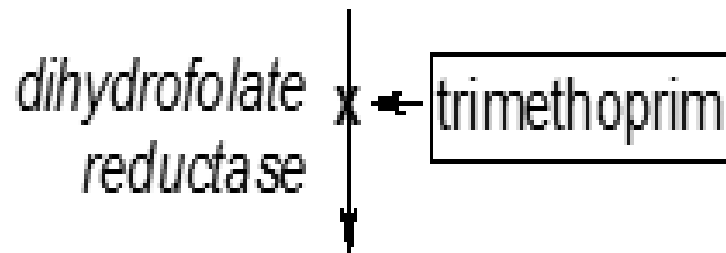
dihydropteroic acid

**Two enzymes involved for the synthesis of Tetrahydrofolic Acid which in the folinic acid << another name.



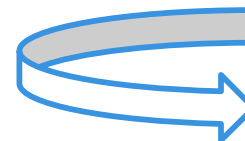
dihydrofolic acid

The second enzyme



Drug works on second enzyme

tetrahydrofolic acid



Folic Acid

Sulfonamides

MOA:

- Inhibit dihydropteroate reductase.
- Inhibit the synthesis of folic acid

• **Spectrum**

- enterobacteriaceae,
- chlamydia
- Toxoplasmosis
- Malaria

Sulfonamides - PK

- well absorbed after oral administration Except Sulfasalazine not absorbed orally
- Bound (in a different extent) to serum albumin
- Distribution in the body, good penetration into CSF
 - They can pass the placental barrier – C/I in pregnancy .
- Metabolism: acetylated in the liver.
- Excretion by glomerular filtration : Formed crystalluria ("stone formation") and potential damage to the kidney.
- may also be eliminated in breast milk. c/i

Sheet #3

- **Sulfonamides are very **acidic**, and go to the urine (also acidic, PH= 4-5).
- SO when acidic in acidic **<<Crystallization>>** non ionized, so crystalluria or stone formation.
- crystalluria is the precursor of stones <<accumulation in the kidney.
- × How can I prevent that?
- Don't take with it any acidic food juices like orange juice or with aspirin **« anything cause acidification »**

to prevent crystalluria formation.&Drinking enough amount of water(Hydration) & Alkalization **NAHCO3**<not necessary.

Sulfonamides Uses

1. *Sulfasalazine* is not absorbed orally
 - reserved for treatment of chronic inflammatory bowel disease (e.g., Crohn disease or ulcerative colitis).
 - Intestinal flora split sulfasalazine into *sulfapyridine* and *5-aminosalicylate* (anti-inflammatory effect)
2. *silver sulfadiazine* -**Topically**: creams of effective in reducing burn-associated sepsis.



Sheet #4

*Sulfasalazine: is **not** absorbed orally **BUT** some is in oral tablets, **How?**

Ans: to treat locally in the GIT, does **not** go to the plasma.

LIKE: Chron disease disease(autoimmune disease).

** Sulfasalazine is **anti-inflammatory** as antibiotic, when entering GIT this will be hydrolyzed by normal flora into 2 and active drugs :

- 1.Sulfapyridine (**antibacterial**)
2. 5-aminosalicylate(**anti-inflammatory** as aspirin)

Sulfonamides Uses

3. sulfadiazine + pyrimethamine is the preferred form of treatment for toxoplasmosis (T. gondii)
4. Fansidar is Sulfadoxine in combination with pyrimethamine
 - used as an antimalarial drug

#NOTE:

The combination in point 3 does not have a specific name.

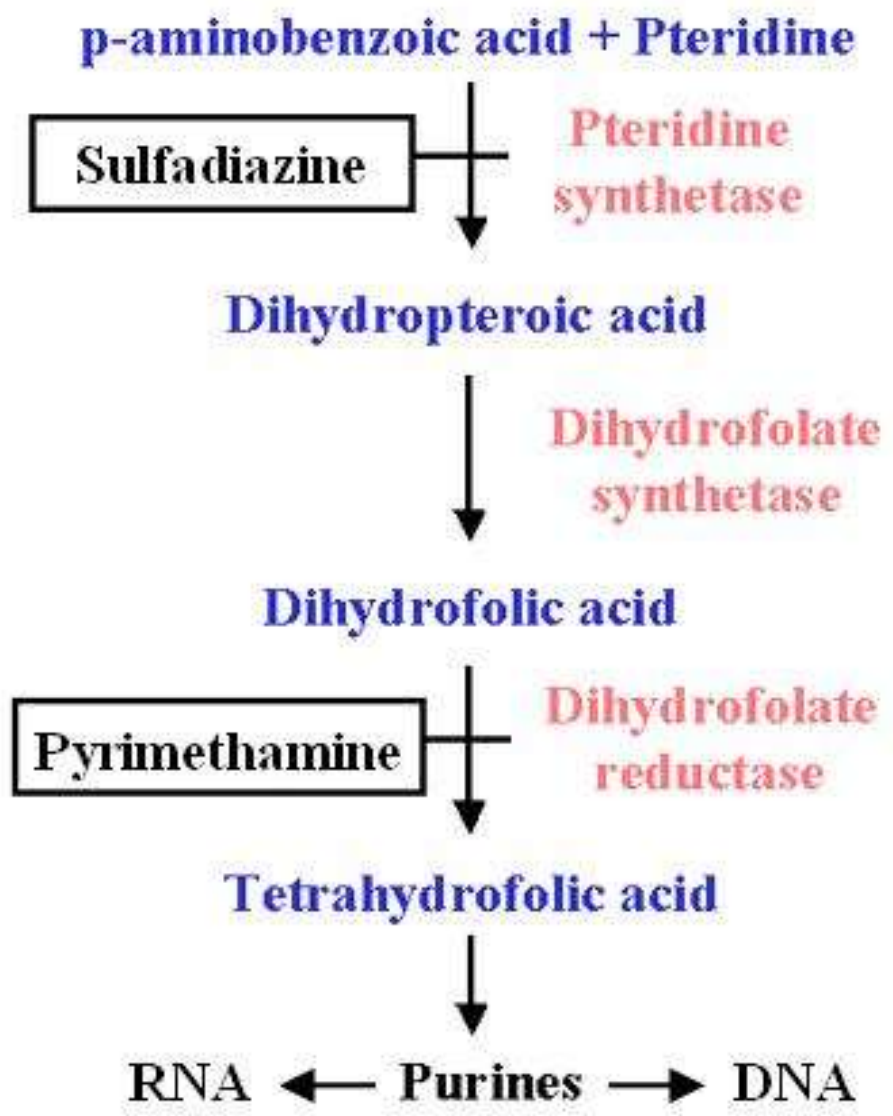
Sheet #5

** to treat toxoplasmosis you give the patient 3 drugs :

1. **Sulfasalazine**

2. **Pyrimethamine**

3. **Leucovorine** (folinic acid) to protect my body from the affected bone marrow.



Sulfonamides - AE



- **Crystalluria and Nephrotoxicity** : Adequate hydration and alkalization of urine is necessary
 - Note: It is contraindicated to use acidic drugs (salicylates) or food (oranges etc.)!!!
- **Hypersensitivity** - common
 - rashes, fever, angioedema, anaphylactoid reactions,
- **Hematopoietic disturbances**: Hemolytic anemia is encountered in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency
- **Drug potentiation**: Transient potentiation of the anticoagulant effect of *warfarin* results from the displacement from binding sites on serum albumin.



Crystalluria



Hypersensitivity



Hemolytic anemia

Sheet #6

**Angioedema is allergic reaction happened in the Orall area.

What is your action then?

Immediately withdrawn the drug because it may convert to an anaphylactic shock to and then Death.

**Hematopoietic disturbance (تفول) is a G6PD Deficiency which (the enzyme) protects the RBCs from any oxidant effect by Reduction (this happens Normally), but when the patient takes Sulfonamides it is contra indicated because they cause hemolytic anemia (hemolysis in the blood).

**Drug potentiation :the patient uses Warfarin, and with UTI so also use AB (Bactrim +Trimethoprim) << Bleeding >>.

**If the patient is with Toxoplasmosis, here we have to take INR reading for Warfarin and decrease its dose to prevent Bleeding.

Trimethoprim

MOA:

- Inhibit Dihydrofolate reductase enzymes (DFR)
- Inhibit prevents the conversion of folic acid to its active, coenzyme form (tetrahydrofolic acid).

Spectrum: antibacterial spectrum similar to sulfonamide

Uses: May be used alone in the treatment of acute UTIs, and in the treatment of bacterial prostatitis and vaginitis.

- **Trimethoprim is 20- 50 fold more potent than SA.**
- Mostly compounded with sulfamethoxazole = **co-trimoxazole.**

Sheet #7

**** Available alone (rarely used) and in combination with Sulfamethaxazol. (every 12 hours).**

**** Note: to combine 2 drugs, they must have the same characteristics ; both have the same $t_{1/2}$ (here every 12 hours).**

**** Trimethoprim is (20-50)fold more than Sulfonamides!**

It means that it's concentration is less than Sulfonamides by 20 times.

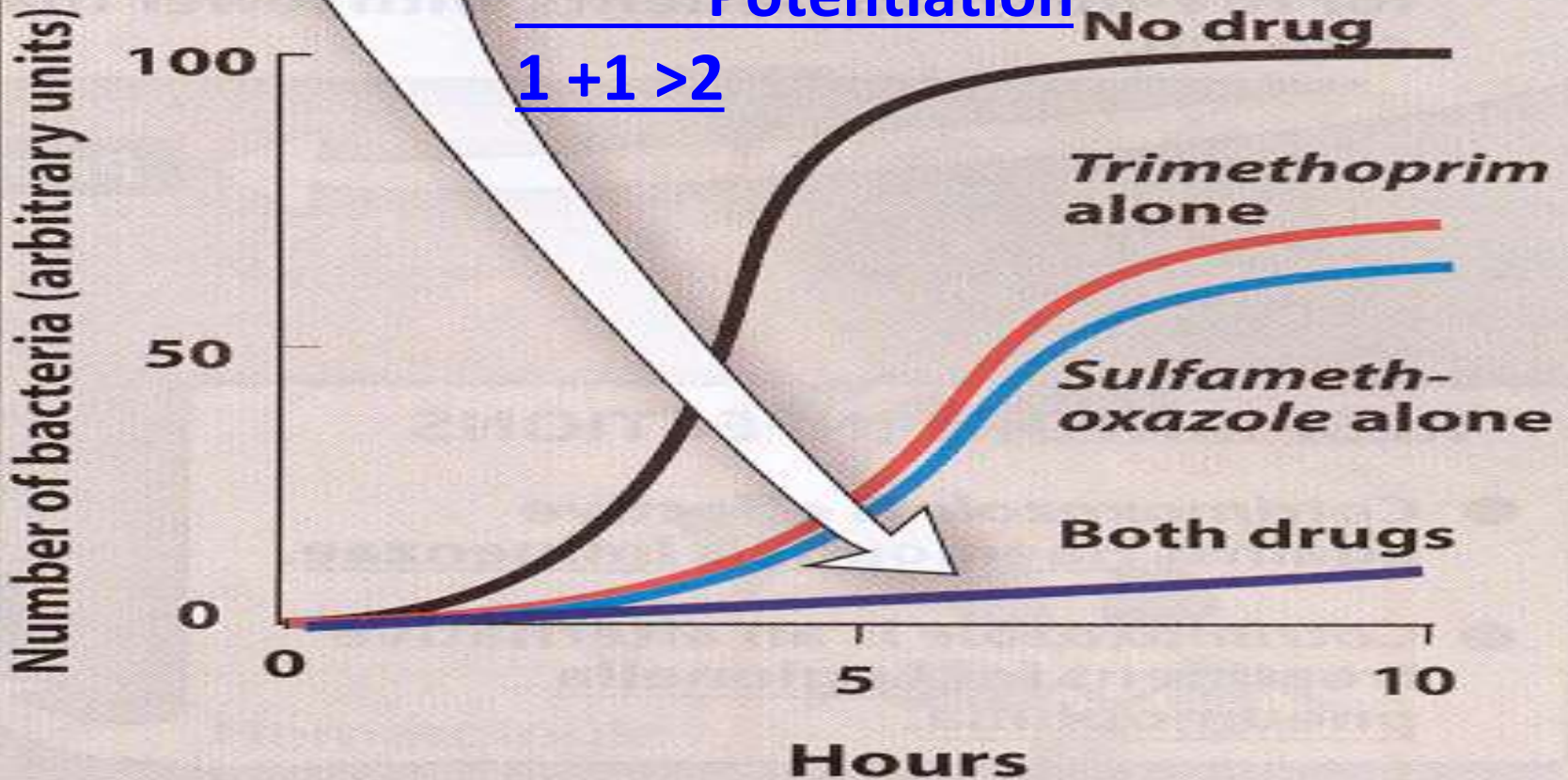
Conc of TMT is 25..... Conc of SA is 500.

**** Co-trimoxazole is the Generic name, Bactrime is the Brand name.**

Trimethoprim and sulfamethoxazole together (cotrimoxazole) show greater inhibition of bacterial growth.

*******Potentiation**

1 + 1 > 2



Trimethoprim

- Pharmacokinetics similar to sulfamethoxazole.
- Adverse effects
 - **folic acid deficiency**
 - megaloblastic anemia, leukopenia, granulocytopenia – especially in pregnant women and patients with a poor diets
 - The blood disorders can be reversed by the simultaneous **administration of folinic acid**, which does not enter bacteria.
 - **nausea, vomiting, skin rashes**

Sheet #8

**** if we use it for long time it causes anemia, and but not for example in 7 days!**

Then, there is no need to give the patient Folic acid.

**** But in case of **Malaria** or **Toxoplasmosis** , the duration of treatment is very long so we have to take care about that.**

**** The pregnancy must take folic acid (Leucovorine) - **until birth** - because she is more likely to have folic acid deficiency.**

Cotrimoxazole

- Trimethoprim & sulfamethoxazole (1:5)→(1:20).
- Combination is synergistic; **bactericidal**.
- Greater antimicrobial activity than either alone.
- Available orally and I.V
- Effective in:
 - Chronic UTI.
 - RTI (Community acquired pneumonia)
 - Prostatic & vaginal infections.
 - Alternative to Ampicillin-or chloramphenicol- for resistant typhoid fever.

Sheet #9

**** Co-trimoxazole treats the conditions that are allergic to penicillin.**

**** Three alternatives for Typhoid fever :**

1. Ampicillin

2 Chloramphenicol

3. Co-trimoxazole

Cotrimoxazole

Adverse effects

- Gastrointestinal; N/V, glossitis, stomatitis
- Dermatologic; Skin rash common & severe
- Hematologic; Megaloblastic anemia, leukopenia, thrombocytopenia, hemolytic anemia in pts. deficient in G6PD so its C/I.
- Drug interactions; Warfarin,??, cause bleeding

****Note : The side effects of Co-trimoxazole are the same as SA**

Leucovorin or folinic acid (antidote)

- Leucovorin is folinic acid analogues
- This medication is used to treat or prevent serious blood cell disorders (such as thrombocytopenia, neutropenia, anemia) caused by folic acid antagonists such as methotrexate, trimethoprim, pyrimethamine.
- Available orally and I.V

****Note :**

Leucovorine used to ANTAGONISE the effect of antibacterials on Human body not on Bacteria.

Thrombocytopenia is a decrease in platelets count.

3. Urinary Tract Antiseptics

- **Nitrofurantoin**
- MOA: damages bacterial DNA
- Spectrum : E.Coli and Gram-positive cocci (for example, *S. saprophyticus*)
- Uses: Uncomplicated UTI
- S/e: Hemolytic anemia may occur with *nitrofurantoin* use in patients with G6PD deficiency
- Safe for pregnancy FDA (B) up to 38 weeks
- C/I:
 - The drug should not be used in patients with significant renal impairment
 - or women who are 38 weeks or more pregnant WHY?

Sheet #10

-Q: What is the difference between Antiseptics and Disinfectants?

-Ans: Antiseptics are on living tissues (human).

Disinfectants are on non-living tissues.

****Antiseptic is a drug that treats and clean UTI without systemic effect (locally).**

****used for uncomplicated UTI; Cannot affect patients with nephritis or kidney infections**

****Very safe (safer than Co-trimoxazole).**