

Sulphonamides and trimethoprim

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SÜLFONAMİDLER

KONU 40

Sülfonamidler	<ol style="list-style-type: none">1. Sülfadiazin (<i>Jenerik</i>)2. Sülfadoksin (preparatı yok)3. Sülfametizol (<i>Thiosülfid</i>)4. Sülfametoksazol (<i>Urobak</i>)5. Sülfametokspirdazin (<i>Metamid</i>)6. Sülfasidin (<i>Renoquid</i>)7. Sülfisoksazol (<i>Ganzol</i>)
Özel kullanımlı sülfonamidler	<ol style="list-style-type: none">1. Gümüş sülfadiazin (<i>Silverdin</i>)2. Malenid (<i>Sulfanylon</i>)3. Sülfanilamid (<i>AVC</i>)4. Sülfasalazin (Salazopyrine-EN)5. Sülfasetamid (<i>Optamid</i>)
İki ardışık basamağı inhibe eden kombinasyonlar	<ol style="list-style-type: none">1. Primetamin + sülfadoksin (<i>Fansidar</i>)2. Trimetoprim + sülfadiazin (<i>Sulfatrim</i>)3. Trimetoprim + sülfametoksazol (<i>Bactrim</i>)

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Sulphonamides

History

- In the 1930's Domagk first demonstrated that a chemotherapeutic agent could influence the course of a bacterial infection.
- The historical drug was **prontosil** which was effective in *Streptococcal* infections of mice as well as men.
- Prontosil was then proved to be a prodrug, inactive in vitro and needing to be metabolized in vivo to give the active product **sulphanilamide**.

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Development of of sulphanilamides

- A large number of sulphanilamides have been developed, and although their therapeutic importance has declined somewhat, they are still useful drugs.
- Furthermore chemical modification of the sulphonamide structure has given rise to several important groups of drugs.
Examples are:
 - Diuretics (acetazolamide and thiazides)
 - Tuberculostatic and antileprotic agents (sulphones)
 - Oral hypoglycemic drugs (sulphonylureas)

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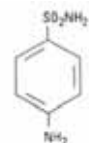
Sulphonamides in clinical use

Examples are:

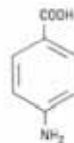
- Sulphadiazine, sulphadimidine, sulphamethoxazole; short acting well absorbed from GIS.
- Sulphametopyrazine; long acting well absorbed from GIS.
- Sulphasalazine; poorly absorbed from GIS.

Sulphamethoxazole + trimethoprim = co-trimoxazole.

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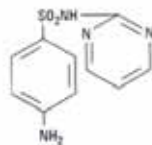


Sulfanilamide

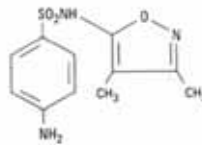


p-Aminobenzoic acid (PABA)

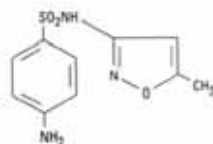
Sulphonamides and PABA



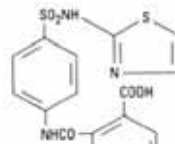
Sulfadiazine



Sulfisoxazole



Sulfamethoxazole



Sulfathalidine
(phthalylsulfathiazole)

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Mechanism of action

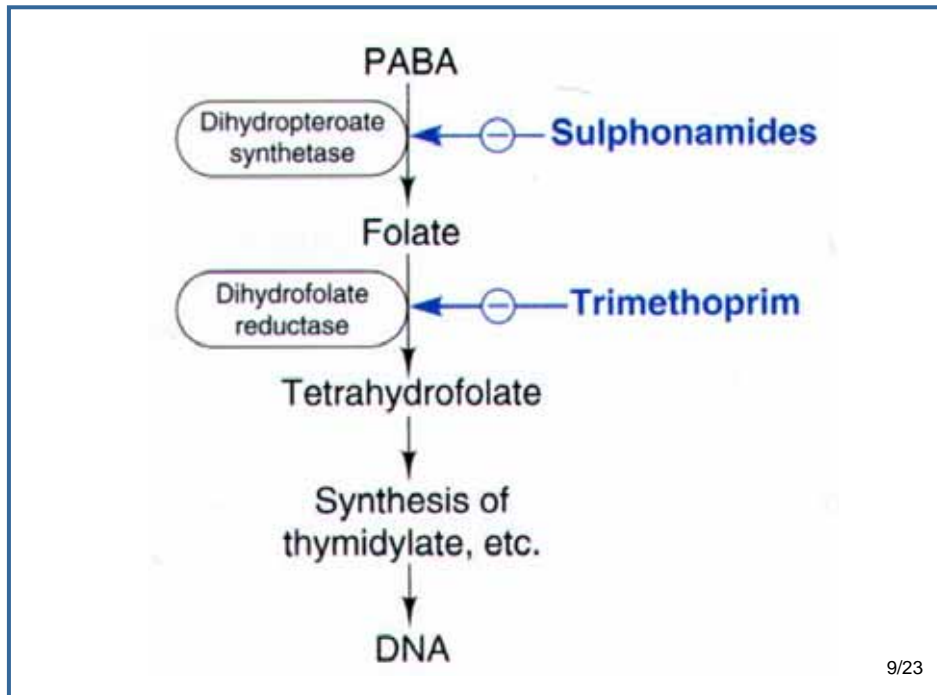
- Sulfanilamide is a structural analogue of *p*-amino benzoic acid (PABA) which is essential for the synthesis of folic acid in bacteria.
- Folate is required for the synthesis of the precursors of DNA and RNA in both bacteria and mammals.
- The difference is mammals obtain their folic acid in their diet whereas bacteria synthesize it.

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Sulphonamides: dihydropteroate synthetase inhibitors

- Sulphonamides compete with PABA for the enzyme *dihydropteroate synthetase*.
- The action of a sulphonamide is to inhibit growth of the bacteria.
- The bacteriostatic action is negated by the presence of pus and the products of tissue breakdown.
- Resistance is common and is plasmid mediated, and due to the synthesis of an enzyme insensitive to the drug.

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Pharmacokinetics of sulphonamides I

- Because the action of sulphonamides is bacteriostatic and reversible, successful treatment necessitates maintaining an adequate concentration for long enough to allow cellular defense mechanisms to destroy the pathogenic bacteria.
- Most sulphonamides are readily absorbed in the GIS and reach maximum concentrations in the plasma in 4-6 hours.

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Pharmacokinetics of sulphonamides II

- Except for silver sulphadiazine which is used topically in the treatment of infected burns, sulphonamides are not usually given topically mainly because of the risk of sensitization and allergic reactions.
- They are partly protein bound and pass into inflammatory exudes, cross placental barrier; most reach an effective concentration in the cerebrospinal fluid.
- They are acetylated in the liver and then excreted in the urine.

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Pharmacokinetics of sulphonamides III

Drug	Half-Life	Oral Absorption
Sulfonamides		
Sulfacytine	Short	Prompt (peak levels in 1–4 hours)
Sulfisoxazole	Short (6 hours)	Prompt
Sulfamethizole	Short (9 hours)	Prompt
Sulfadiazine	Intermediate (10–17 hours)	Slow (peak levels in 4–8 hours)
Sulfamethoxazole	Intermediate (10–12 hours)	Slow
Sulfapyridine	No data	Slow
Sulfadoxine	Long (7–9 days)	Intermediate
Pyrimidines		
Trimethoprim	Intermediate (11 hours)	Prompt

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Unwanted effects

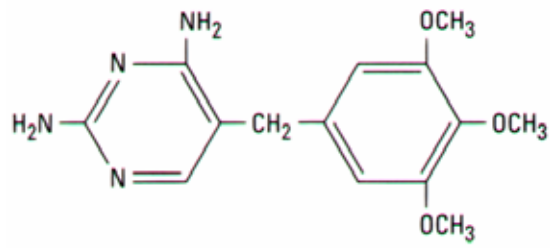
- Side effects mild to moderate, which do not necessarily warrant withdrawal of the drug: nausea, vomiting, headache, mental depression, methemoglobinemia.
- Serious toxic effects (not very common): hepatitis, hypersensitivity reactions (rashes, fever, anaphylactoid reactions), bone marrow depression and crystalluria.

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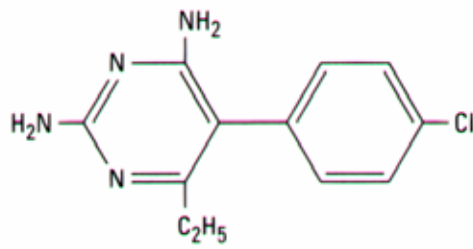
Trimethoprim

- The structure of trimethoprim has some resemblance to the pteridine moiety of folate.
- It inhibits the bacterial form of the enzyme *dihydrofolate reductase* which converts folate to tetrahydrofolate.

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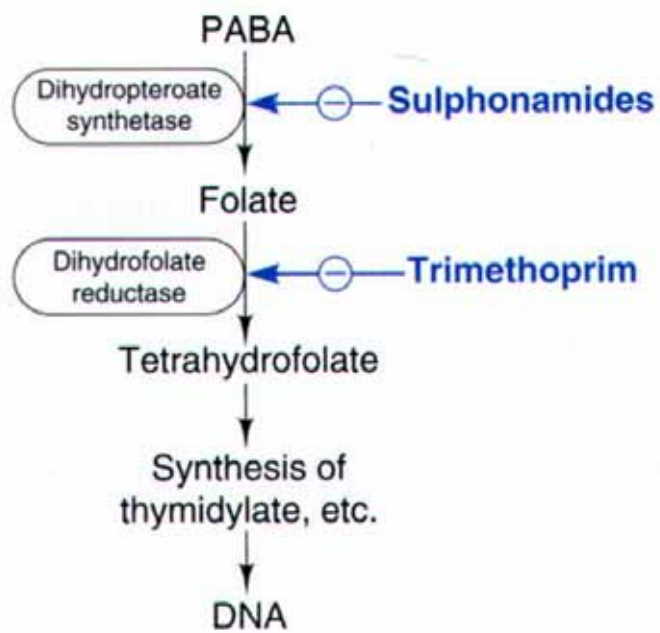


Trimethoprim



Pyrimethamine

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Trimethoprim (II)

- Trimethoprim itself is a bacteriostatic agent against most common bacterial pathogens, it is more often given as a mixture with sulphamethoxazole in a combination called co-trimoxazole which is bactericidal or at least the dosage given is reduced to one tenth.
- Thus, unwanted effects other than hypersensitivity reactions are greatly reduced.
- The use of the combination slows the development of resistance.

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Pharmacokinetics of trimethoprim

- In co-trimoxazole 1 part of trimethoprim is given with 5 parts of sulphamethoxazole. These drugs are selected because of similar pharmacokinetic properties (esp. half life). This combination reaches the ratio 1/20 in plasma which is optimum.
- Dosage should be reduced by half for patients with plasma creatinine clearances of 15 to 30 ml/min.
- As a weak base, trimethoprim concentrates in prostatic and vaginal fluids.

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Unwanted effects of trimethoprim

- Besides nausea, vomiting and skin rashes, trimethoprim may result in folate deficiency with resultant megaloblastic anemia.
- This toxic effect can be prevented by giving **folinic acid**.

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Clinical uses of sulphonamides I

Absolute indications are very few, but sulphonamides may be used as follows:

- Combined with trimethoprim (co-trimoxazole) for *Pneumocystis carinii*
- Combined with pyrimethamine for drug-resistant *Malaria*, and for *Toxoplasmosis*
- In inflammatory bowel disease and as an anti-inflammatory drug **sulphasalazine** (sulpha-pyridine-salicylate combination) is so used

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Clinical uses of sulphonamides II

- For infected burns (**silver sulphadiazine** given topically)
- For some sexually transmitted infections (e.g. *Trachoma, Chlamydia, Chancroid*)
- For respiratory infections; use now confined to a few special problems (e.g. infection with *Nocardia*)
- For acute urinary tract infection (now seldom used).

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Clinical uses of co-trimoxazole

The main uses are as follows:

- For urinary tract and respiratory infections
- For infection with *Pneumocystis carinii*, which causes pneumonia in patients with AIDS (in high dose).

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Thank you...

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