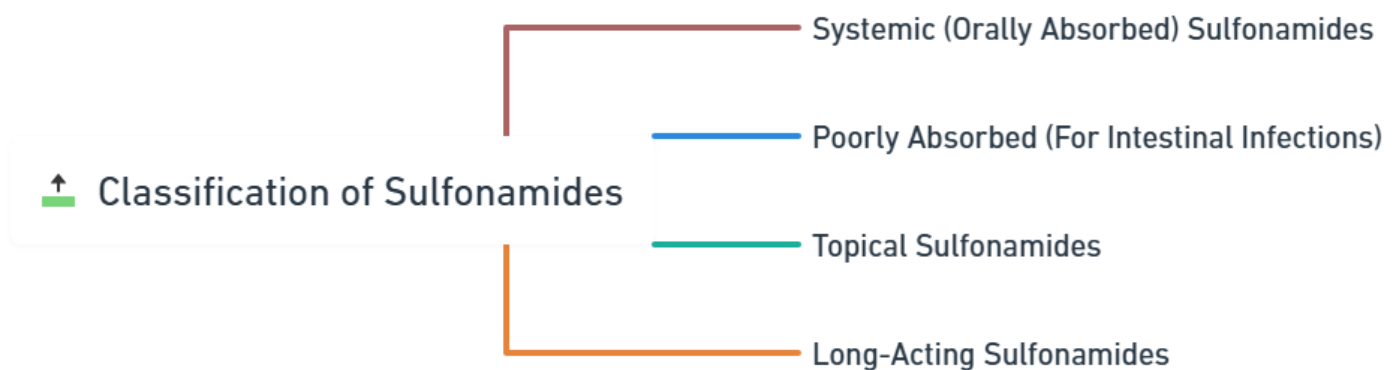


Sulfonamides

Introduction

- Sulfonamides are synthetic antimicrobial agents that were among the earliest drugs used to treat bacterial infections.
- They act as bacteriostatic agents, meaning they inhibit the growth and multiplication of bacteria rather than directly killing them.
- They work by inhibiting folic acid synthesis in bacteria, which is essential for DNA, RNA, and protein synthesis. Since humans obtain folic acid from diet and do not synthesize it, selective toxicity is achieved.

Classification of Sulfonamides



1. Systemic (Orally Absorbed) Sulfonamides

➤ **Used for systemic infections:**

- Sulfisoxazole
- Sulfadiazine
- Sulfamethoxazole

2. Poorly Absorbed (For Intestinal Infections)

➤ **Used in intestinal infections:**

- Sulfasalazine

3. Topical Sulfonamides

➤ **Used locally on skin, eyes:**

- Sulfacetamide sodium (ophthalmic use)
- Silver sulfadiazine (burn wounds)
- Mafenide acetate (burns)

4. Long-Acting Sulfonamides

- Sulfadoxine (often combined with pyrimethamine for malaria treatment)

Mechanism of Action

- Sulfonamides inhibit bacterial folic acid synthesis.
- Bacteria synthesize folic acid from p-aminobenzoic acid (PABA).
- Sulfonamides are structural analogs of PABA and competitively inhibit the enzyme:
 - Dihydropteroate synthase → inhibits dihydrofolic acid synthesis → inhibits DNA synthesis
- Thus, sulfonamides are bacteriostatic.

Pharmacokinetics (ADME)

- **Absorption:** Well absorbed orally except sulfasalazine (poorly absorbed).
- **Distribution:** Widely distributed, including CSF and placenta.
- **Metabolism:** Acetylated in the liver to inactive metabolites.
- **Excretion:** Mostly excreted through the kidneys; dose adjustment required in renal impairment.

Pharmacodynamics

- Bacteriostatic action, requiring an intact immune system for full effect.
- More effective against gram-positive and some gram-negative bacteria.
- Often used in combination with trimethoprim (Co-trimoxazole) for a bactericidal effect.

Adverse Effects

1. Hypersensitivity Reactions

- Rashes, fever, Stevens-Johnson syndrome.

2. Hematologic Disorders

- Hemolytic anemia (especially in G6PD-deficient patients)
- Aplastic anemia
- Agranulocytosis

3. Crystalluria

- Precipitation of sulfonamide crystals in urine; prevented by drinking plenty of water.

4. Kernicterus (in newborns)

- Sulfonamides displace bilirubin from albumin and may cause brain damage.

Contraindications

- Pregnancy (especially late trimester)
- Newborns and infants under 2 months (risk of kernicterus)
- Patients with G6PD deficiency

- Patients with sulfonamide hypersensitivity

Therapeutic Uses

- Urinary tract infections (UTIs)
- Nocardiosis
- Toxoplasmosis (with pyrimethamine)
- Malaria prophylaxis (sulfadoxine + pyrimethamine)
- Burn wound infections (silver sulfadiazine topical)

Drug Interactions

- Potentiates effects of warfarin, sulfonylureas, and phenytoin (due to protein binding displacement).
- May increase risk of hypoglycemia when used with oral antidiabetic drugs.

Dose and Route of Administration

- **Oral:** Sulfamethoxazole (commonly given as co-trimoxazole)
- **Topical:** Silver sulfadiazine for burns
- **Parenteral:** Rare, mostly replaced by safer agents
- Typical example dose (for understanding only, clinical doses vary by condition):
 - **Sulfamethoxazole:** 500–1000 mg orally every 8–12 hours (usually combined with Trimethoprim).

Co-trimoxazole

Introduction

- Co-trimoxazole is a fixed-dose combination of two antimicrobial agents:
 - **Trimethoprim (TMP)**
 - **Sulfamethoxazole (SMX)**
- This combination is used to achieve synergistic bactericidal action, although each component alone is bacteriostatic.
- It is widely used for the treatment of various bacterial infections, especially urinary and respiratory tract infections.
- The optimal ratio of TMP to SMX is 1:5 (by weight), which yields a serum concentration ratio of approximately 1:20, the ratio that provides maximum synergistic effect.

Classification

- Sulfonamide + Dihydrofolate Reductase Inhibitor

- Bactericidal when combined, though both components alone are bacteriostatic.

Mechanism of Action

Co-trimoxazole inhibits two sequential steps in the bacterial folate synthesis pathway, leading to synergistic inhibition of DNA synthesis.

1. Sulfamethoxazole

- Inhibits dihydropteroate synthase
 - Prevents conversion of PABA to dihydropteroic acid
 - Blocks formation of dihydrofolic acid.
- Trimethoprim

2. Inhibits dihydrofolate reductase

- Prevents conversion of dihydrofolic acid to tetrahydrofolic acid
- Inhibits DNA, RNA, and protein synthesis.

Net Effect: Bactericidal inhibition of folate-dependent nucleic acid synthesis in bacteria.

Pharmacokinetics (ADME)

- **Absorption:** Both components are well absorbed orally.
- **Distribution:** Widely distributed to body fluids and tissues including lungs, CSF, middle ear fluid, and prostate.
- **Metabolism:**
 - SMX: Metabolized in the liver (N-acetylation and glucuronidation)
 - TMP: Partially metabolized in liver
- **Excretion:** Primarily via the kidneys. Dose adjustment is required in renal impairment.
- **Half-life:**
 - SMX: ~10 hours
 - TMP: ~11 hours

This similarity allows for effective combination therapy.

Pharmacodynamics

- Time-dependent killing
- Bactericidal synergy due to sequential blockade in folate pathway
- Effective against a broad range of gram-positive and gram-negative organisms

Antimicrobial Spectrum

Sensitive organisms include:

- Escherichia coli



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