Principles of Drug Therapy:

SULPHONAMIDES, METRANIDAZOLE and CHLORAMPHENICOL

OUTLINE

- Mechanism of action
- Basis of selectivity
- Mechanisms of resistance
- Pharmacokinetics
- Clinical uses
- Adverse effects

SULPHONAMIDES

- Synthetic anti microbial agents containing the sulphonamide group
- Some sulphonamides are devoid of anti bacterial activity
- Sulphonylureas and thiazide diuretics are newer drug groups

SULPHONAMIDES

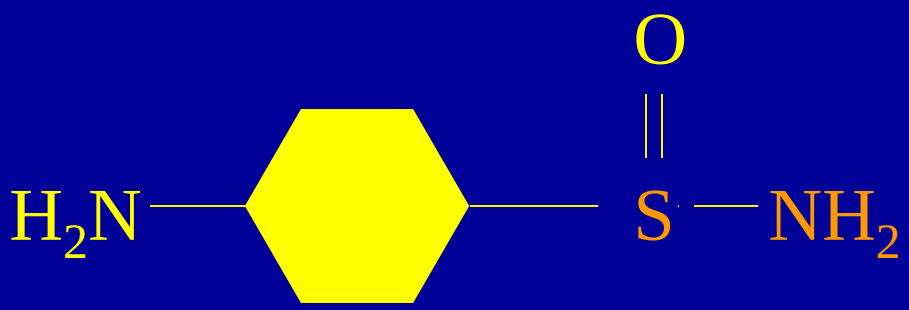
- Sulphamethoxazole
- Sulphadiazene

- CO-TRIMOXAZOLE
- SULPHASALAZINE
- FANSIDAR

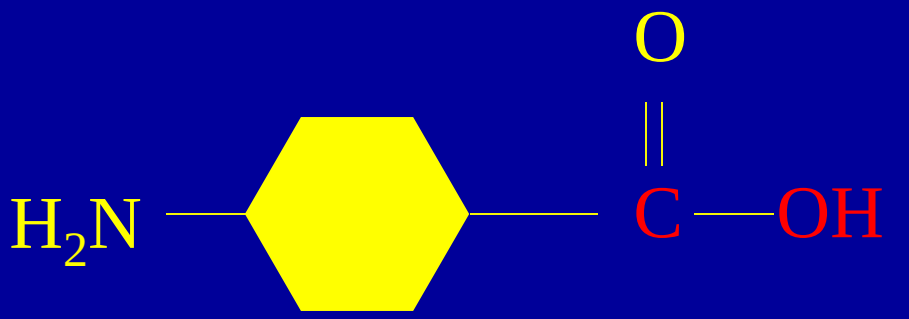
SULPHONAMIDES

- Allergy
- Important to make the distinction between sulpha drugs and sulpha containing drugs

SULPHONAMIDES:
STRUCTURAL ANALOGUE

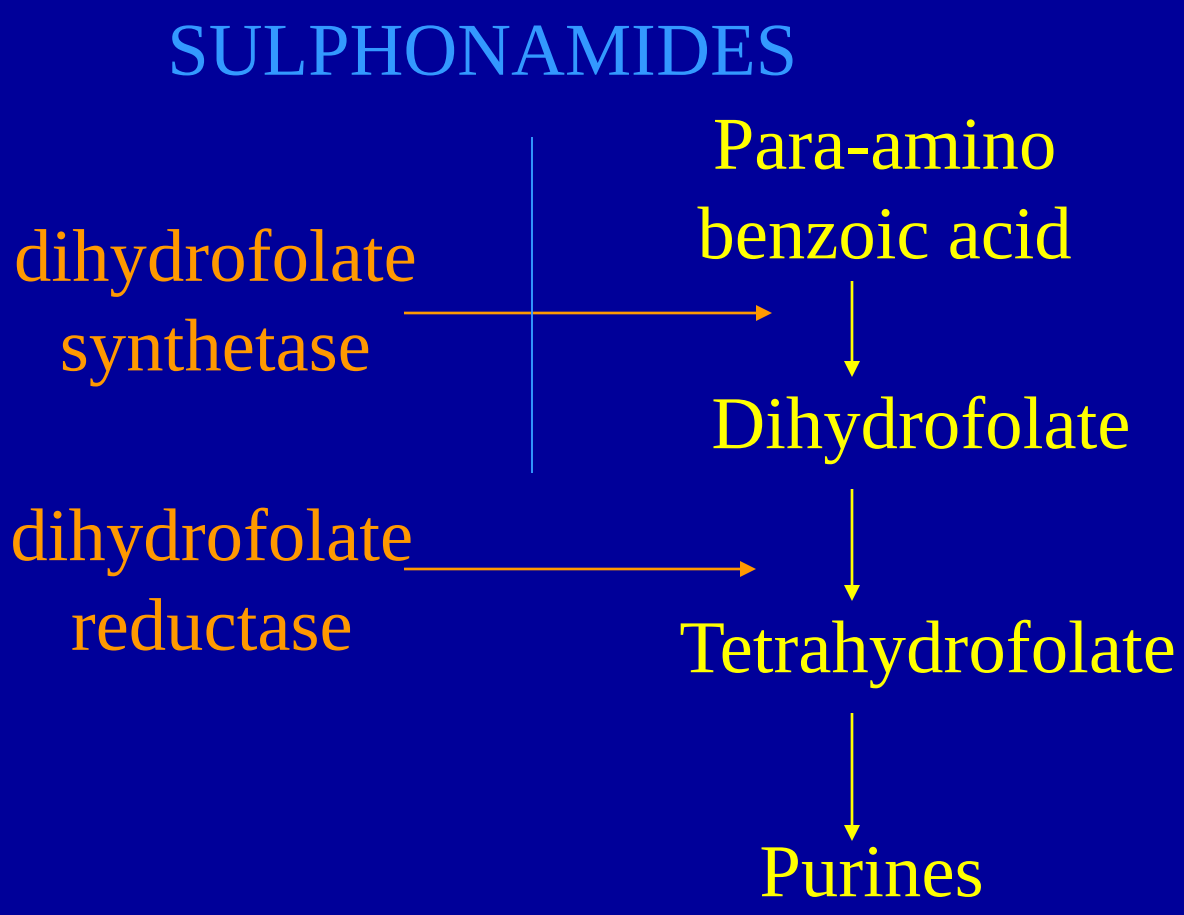


Sulfanilamide



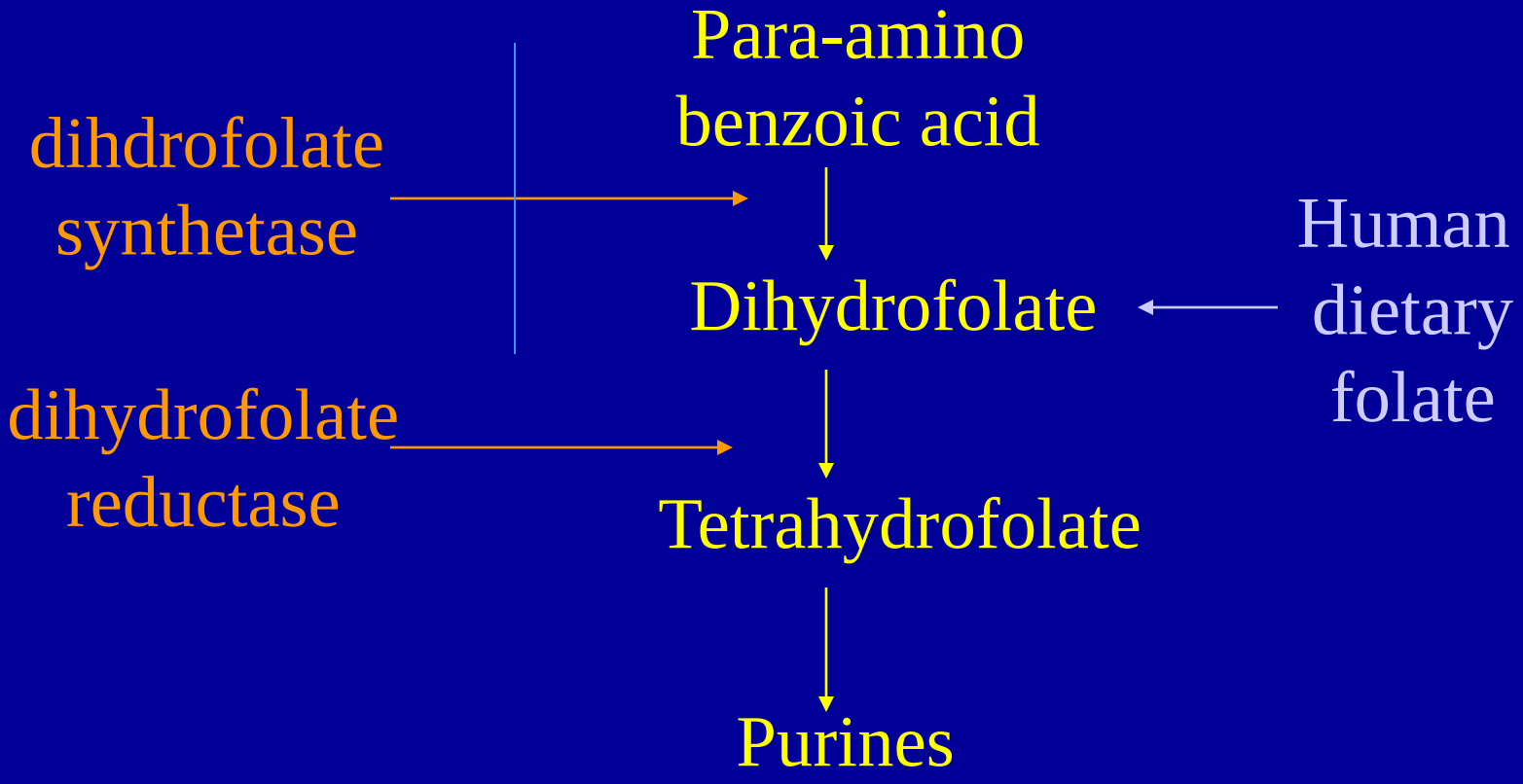
Para-amino benzoic acid (PABA)

SULPHONAMIDES:
MECHANISM OF ACTION



SULPHONAMIDES:
BASIS OF SELECTIVITY

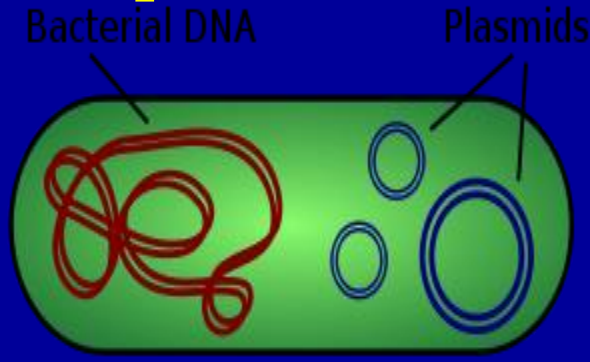
SULPHONAMIDES



SULPHONAMIDES:
ACQUIRED RESISTANCE

- Three mechanisms:
  - Enzyme modification to reduce susceptibility
  - Alternate metabolic pathway to source folate
  - Production of metabolite to destroy drug

- Occurs by random mutation or plasmid transfer



SULPHONAMIDES:
PHARMACOKINETICS

- Well absorbed & bound to albumin
- Widely distributed: CSF, pleura, peritoneum
- Metabolised in the liver by *genetically determined* acetylation
  - with loss of anti-bacterial effect
  - unaltered side effect profile
- Excreted in the urine
  - reduce dose in renal failure
  - may precipitate in acid urine

SULPHONAMIDES:
SPECTRUM OF USE

Wide range of activity against gram +ve & – ve organisms

- Predominantly used for lower respiratory and urinary tract infection
- Specific use: prophylaxis against rheumatic fever in penicillin-sensitive individuals

Less widely used

- Resistance
- Adverse effects

SULPHONAMIDES:
ADVERSE EFFECTS (1/2)

Numerous, varied and common (5%)

- Bone marrow:
  - haemolytic anaemia, aplastic anaemia & agranulocytosis
- Hypersensitivity reactions:
  - Skin rashes -erythema multiforme and Stevens-Johnsons reaction
  - Hepatitis

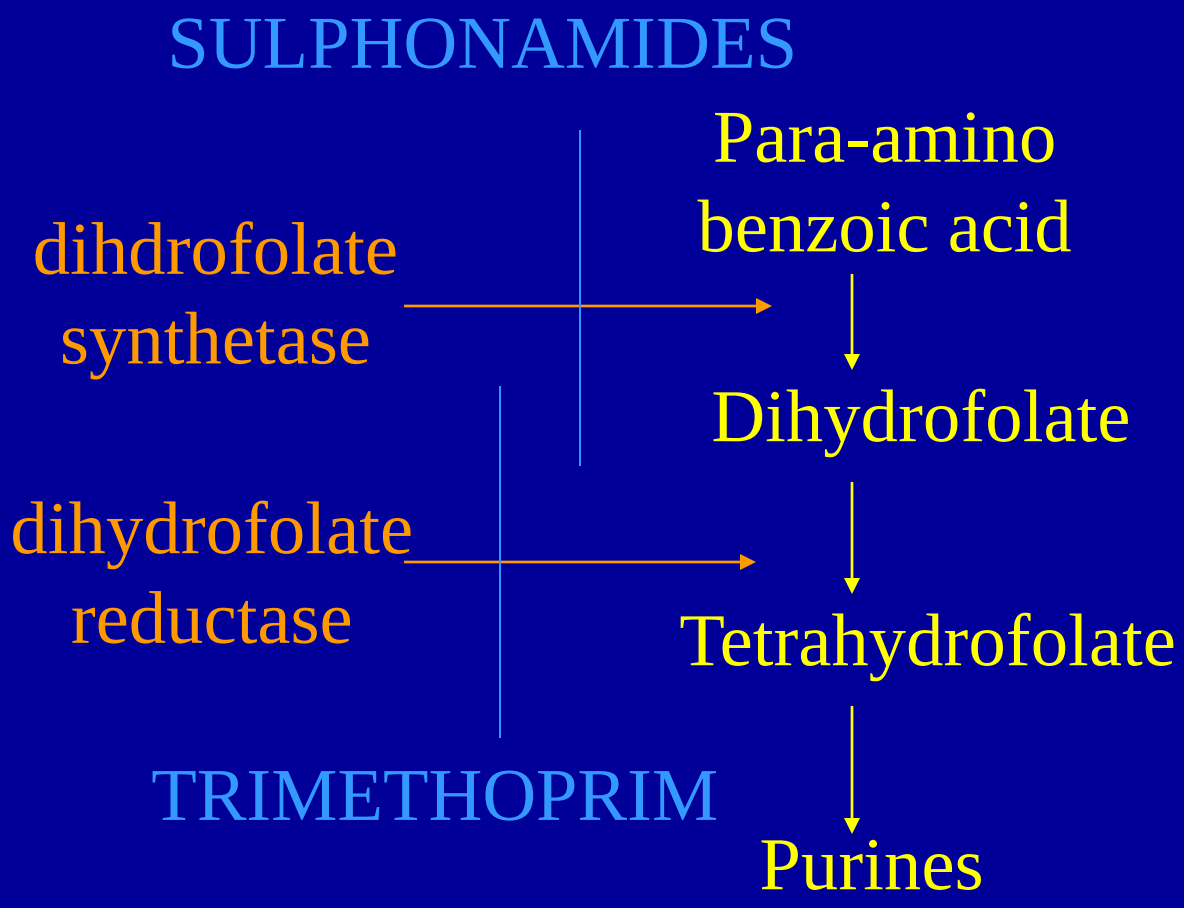
SULPHONAMIDES:
ADVERSE EFFECTS (2/2)

- Urinary tract system:
  - Crystalluria (older drugs) in acidic urine
- Kernicterus: a form of brain damage
  - New born infants have immature glucuronyl transferase
  - Sulphonamides displace bilirubin from albumin
  - Free bilirubin is deposited in the basal ganglia
  - Avoid in pregnancy

CO-TRIMOXAZOLE: (TRIMETHOPRIM & SULPHAMETHOXAZOLE)

- Synergistic combination (ratio 5S:1T)
- Reduce dose (less adverse effects)
- Similar spectrum
- Largely replaced single agent sulphonamide
- Particularly used in 2 opportunistic infections (esp HIV disease) as Rx & prophylaxis
  - *Pneumocystis carinii*
  - *Toxoplasma gondi*

CO-TRIMOXAZOLE:
MECHANISM OF ACTION



OTHER SULPHONAMIDES

- Silver sulphadiazene for topical use in cuts and burns
- Sulphasalazine (sulphapyridine + 5-amino salicylic acid) in IBD esp. ulcerative colitis
  - Sulphonamide: vehicle + adverse effects
  - Salicylic acid: anti-inflammatory action
- Fansidar (pyrimethamine + sulfadoxine)
  - Both anti-folates
  - Second line Rx against *P. falciparum*

METRONIDAZOLE

Tinidazole

OUTLINE

- Mechanism of action
- Basis of selectivity
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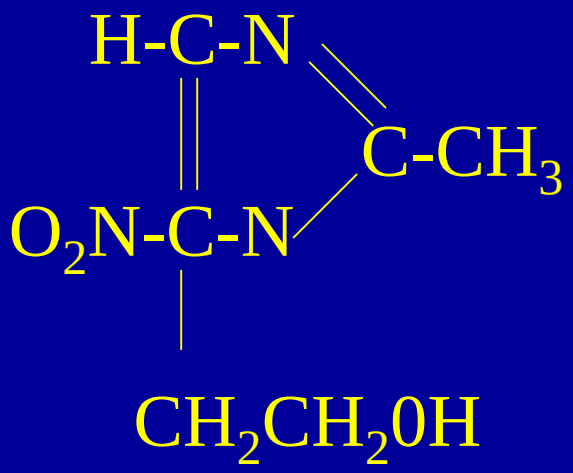
METRONIDAZOLE

STRUCTURE



5-nitroimidazole antibiotic

METRONIDAZOLE:
MECHANISM OF ACTION

- Nitro group accepts electrons (reduction)
- Disrupts DNA helical structure and strand integrity
- Particularly effective in hypoxia conditions

<u>Mechanism of resistance</u>

Organisms transfer electrons to the drug less readily

METRONIDAZOLE:
PHARMACOKINETICS

- Well absorbed
- Widely distributed: saliva, seminal and vaginal fluid, breast milk, CSF
- T1/2 8hrs
- Metabolised in the liver by p450 enzyme system
- Wide therapeutic ratio

METRONIDAZOLE:
CLINICAL USES

- Anaerobic bacteria: bacteroides, clostridia
  - Oral cavity, liver abscess, GI/GU surgery
- Trichomonas vaginalis in males and females
- Entamoeba histolytica
- Giardia lamblia
- Helicobacter pylori (as part of triple therapy)

METRONIDAZOLE:
ADVERSE EFFECTS

- Well tolerated
- Occasional metallic taste & GI upset
- Rare neurotoxicity: peripheral neuropathy to ataxia
- High doses for prolonged time are carcinogenic in rats and mutagenic in bacteria; no evidence of these in man

CHLORAMPHENICOL

OUTLINE

- Mechanism of action
- Basis of selectivity
- Mechanisms of resistance
- Pharmacokinetics
- Clinical uses
- Adverse effects

CHLORAMPHENICOL:
MECHANISM OF ACTION 1/3

Inhibits bacterial protein synthesis by interrupting transcription

- Binds reversibly to the 50 S ribosomal unit
- Prevents elongation of the polypeptide chain

Bacteriostatic antibiotic

CHLORAMPHENICOL:
MECHANISM OF ACTION 2/3

Basis of selectivity

Eukaryotic cells have 80 S ribosomes which are relatively unaffected by chloramphenicol

- Bacterial and mammalian mitochondrial ribosomes are both 70 S, which are more effected.
- Main cause of mammalian toxicity is mitochondrial effect

CHLORAMPHENICOL:
MECHANISM OF ACTION 3/3

Mechanism of Resistance

Largely due to modification of the drug by the bacteria

- Plasmid derived acetyltrasferases lead to drug acetylation
- Usually codes for tetracycline resistance too

CHLORAMPHENICOL: PHARMACOKINETICS

- Well absorbed, administered orally, iv & im
- Metabolised in the liver by glucuronidation and excreted in the kidney
  - Neonates have immature glucuronyl transferase and toxic concentration can build up leading to vascular collapse: grey baby syndrome
- Widely distributed including CSF, bile, breast milk, placenta and aqueous humour after conjunctival application

CHLORAMPHENICOL:
ADVERSE EFFECTS

Bone marrow toxicity is most important

2 mechanisms:

- Dose dependent reversible depression of of all 3 cell lines, usually early in treatment.
- Rare, idiosyncratic, non-dose related, usually fatal aplastic anaemia (1 in 30,000)

- Also causes hypersensitivity reactions: rashes

CHLORAMPHENICOL:
CLINICAL USES

Broad spectrum, widely distributed & cheap. Adverse effects (though rare) limit its use.

- Typhoid fever (25% cases resistant in SL, ciprofloxacin is a better choice)
- Blind treatment of bacterial meningitis to cover *H. influenzae*; 3rd generation cephalosporins are preferred
- *Rickettsia* and *brucella* infections; tetracyclines preferred