Folate Antagonists

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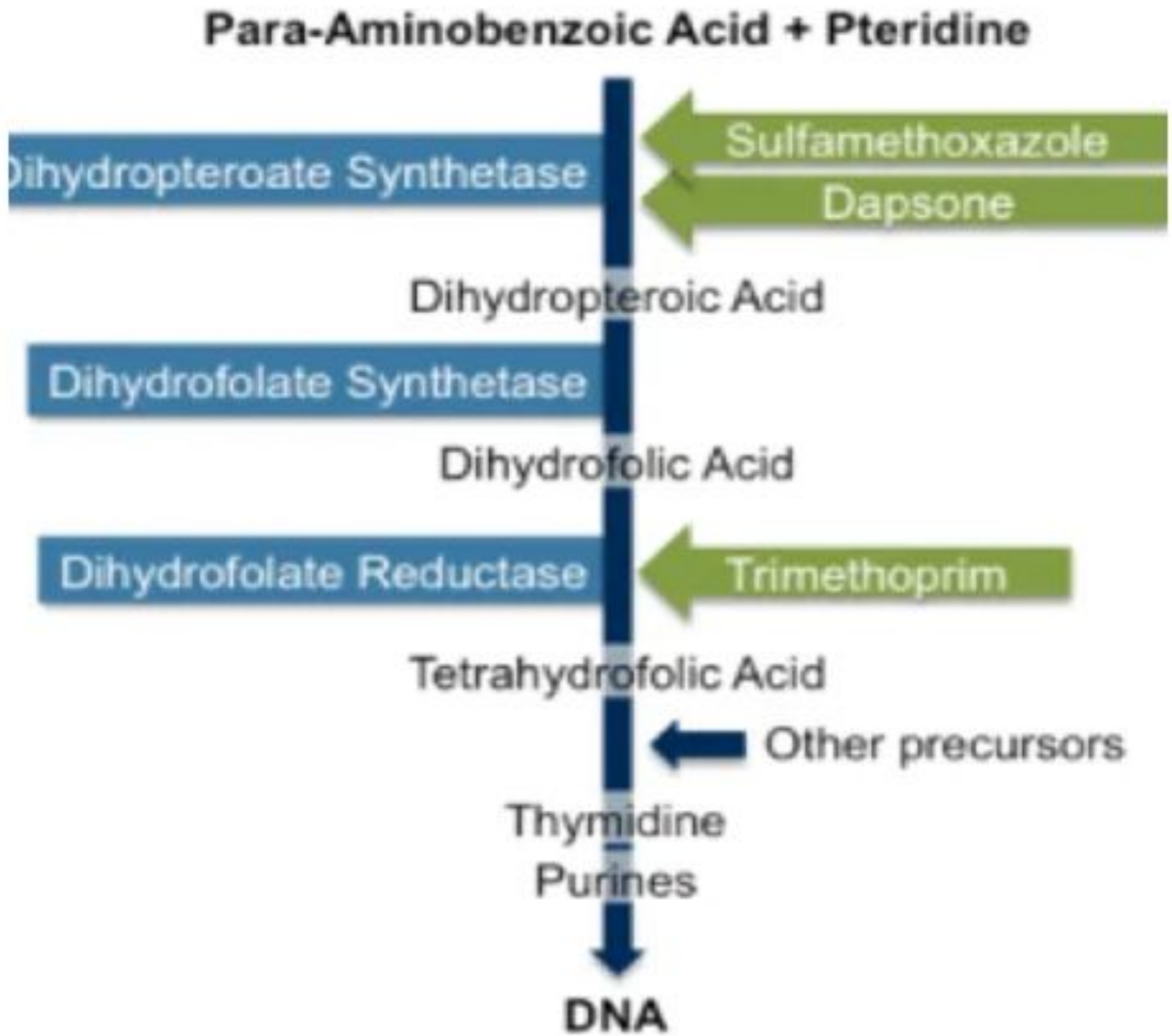
Folate Antagonists

- **Products of folate biosynthesis** are essential for the synthesis of **purines (Adenine and guanine) and pyrimidine (Cytosine, thymine, uracil)**. **Humans** obtain **preformed folate from the diet**. In contrast, **bacteria synthesize folate de novo**.

Sulfonamides

- **All sulfonamides** currently in clinical use are **synthetic analogs of *p*-aminobenzoic acid (PABA).**


Para-Aminobenzoic Acid + Pteridine
ihydropteroate Synthetase
Sulfamethoxazole
Dapsone
Dihydropteroic Acid
Dihydrofolate Synthetase
Dihydrofolic Acid
Dihydrofolate Reductase
Trimethoprim
Tetrahydrofolic Acid
Other precursors
Thymidine
Purines
DNA

•Mechanism of action

•Because of their structural similarity to PABA, the sulfonamides **compete with this substrate** for the **bacterial enzyme, dihydropteroate synthetase**. They thus **inhibit the synthesis** of bacterial **dihydrofolic acid**. The sulfa drugs, including cotrimoxazole, are **bacteriostatic antibiotics**.

•Antibacterial spectrum:

- Sulfa drugs are active against **selected enterobacteria in the urinary tract** and **nocardia**.
- **Sulfa drugs** combined with the **dihydrofolate reductase inhibitor pyrimethamine**, are the preferred form of treatment for **toxoplasmosis** and **chloroquine-resistant malaria.**
- Many strains of formerly susceptible species **(meningococci, pneumococci, streptococci, staphylococci and gonococci)** are **now resistant.**

- **Resistance:**

- Organisms resistant to **one member** of this drug family are **resistant to all** and may be due to:
- 1) an **altered dihydropteroate synthetase**
- 2) **decreased cellular permeability** to sulfa drugs
- 3) **enhanced production of** the **natural substrate, PABA.**

- **Pharmacokinetics:**

- **Sulfonamides can be divided into three major groups:**

1. **Oral absorbable agents:**
   a. ***Short acting agents:*** e.g. **sulfisoxazole**
   b. ***Medium acting agents:*** e.g. **sulfadiazine**, **sulfamethoxazole**

- **Sulfamethoxazole** + **trimethoprim** = **cotrimoxazole**
- **Sulfadiazine** + **pyrimethamine** □ **toxoplasmosis**

   b. ***Long acting agents:*** e.g. **sulfadoxine**.

- **Sulfadoxine** + **pyrimethamine** = **Fansidar** □ **malaria**

•After oral administration, these drugs are **well absorbed** via the small intestine.

•They are **bound to serum albumin** in the circulation. Sulfa drugs distribute throughout the body's water and **penetrate well into CSF** even in the **absence of inflammation**.

•They can also **pass the placental barrier and enter fetal tissues**. The sulfa drugs are **acetylated, primarily in the liver**.

•**The product** is devoid of antimicrobial activity but **retains the toxic potential** to **precipitate at neutral or acidic pH**. This causes **crystalluria (stone formation)** and, therefore, potential damage to the kidney. Sulfa drugs are **eliminated by glomerular filtration.** Therefore, **depressed kidney function** causes **accumulation** of both the parent compounds and their metabolites. The sulfonamides may also be eliminated in **breast milk**.

2- Oral non-absorbable agents:

- **Sulfasalazine** is not absorbed when administered orally and, therefore, is reserved for treatment of **inflammatory bowel disease** (***Crohn's disease or ulcerative colitis***).
- Local **intestinal flora split sulfasalazine into (sulfapyridine and 5-aminosalicylate)**, with the **latter** exerting the **anti-inflammatory effect**. **Absorption of the sulfapyridine** can lead to **toxicity** in patients who are slow acetylators.

3- Topical agents:

- **Sodium sulfacetamide bacterial conjunctivitis**
- **Silver sulfadiazine prevention of infection of burn wounds**

•Adverse effects:

•**Crystalluria:** Nephrotoxicity develops as a result of crystalluria. **Adequate hydration and alkalinization of urine prevent the problem. Sulfisoxazole and sulfamethoxazole** are more soluble at urinary pH and are **less liable to cause crystalluria.**

•**Hypersensitivity:** Hypersensitivity reactions, such as **rashes**, **angioedema,** and **Stevens-Johnson syndrome**, are common.

•**Hemopoietic disturbances:** Hemolytic anemia is encountered in patients with G6PD deficiency. Granulocytopenia and thrombocytopenia can also occur.

•**Kernicterus:** This disorder may occur **in newborns**, because **sulfa drugs displace bilirubin from binding sites on serum albumin**. The bilirubin is then free to **pass into the CNS**, because the baby's **BBB is not fully developed**.

•Drug interactions:

•**Transient potentiation** of the **hypoglycemic effect of tolbutamide** or the **anticoagulant effect of warfarin** results from their **displacement from binding sites on serum albumin**.

•Contraindications:

•Due to the danger of kernicterus, sulfa drugs should be avoided in **newborns** and **infants less than 2 months of age** as well as in **pregnant women at term**.

•**Trimethoprim** is a **potent inhibitor of bacterial dihydrofolate reductase**, exhibits an **antibacterial spectrum similar to that of the sulfonamides**. Trimethoprim is **most often compounded with sulfamethoxazole**, producing the combination that called "**Cotrimoxazole**".

•Mechanism of action:

•The active form of folate is the tetrahydrofolate that is formed through reduction of dihydrofolate by **dihydrofolate reductase**. This **enzymatic reaction is inhibited by trimethoprim**. The **bacterial reductase** has a **much stronger affinity for trimethoprim** than does the mammalian enzyme.

•[Examples of other drugs that function as **dihydrofolate reductase inhibitors** include **pyrimethamine**, which is **used with sulfonamides in treating parasitic infections,** and **methotrexate**, which is used in the treatment of **cancer, RA & psoriasis**].

•Antibacterial spectrum:

•The antibacterial spectrum of trimethoprim is **similar to that of sulfamethoxazole**. However, **trimethoprim is 20- to 50-fold more potent than the sulfonamide**. Trimethoprim may be **used alone** in the treatment of **acute UTI** and in the treatment of **bacterial prostatitis** and **vaginitis**.

•Resistance:

•Resistance in G-ve bacteria is due to the presence of an **altered dihydrofolate reductase** that has a lower affinity for trimethoprim.

•Pharmacokinetics:

•The **$t_{1/2}$** of trimethoprim is **similar to that of sulfamethoxazole**. However, because the drug is a **weak base**, **higher concentrations** of trimethoprim are achieved in the **relatively acidic prostatic and vaginal fluids (ion trapping).** Most of the drug is **excreted unchanged in urine**.

•Adverse effects:

•Trimethoprim can produce the effects of **folic acid deficiency**. These effects include **megaloblastic anemia**, **leukopenia**, and **granulocytopenia**, especially in **pregnant patients** and those having **very poor diets**. These blood disorders **can be reversed** by the simultaneous administration of ***folinic acid***, which **does not enter bacteria.**

•Cotrimoxazole

•The combination of trimethoprim with sulfamethoxazole **(in ratio of 1:5)**, shows greater antimicrobial activity than equivalent quantities of either drug used alone. **This synergistic effect results from inhibition of two sequential steps in the folate biosynthesis.**

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•Clinical uses:

1. Opportunistic infection with **pneumocystis carinii** complicating AIDS (causes pneumonia)
2. **Listeriosis**: septicemia and meningitis caused by listeria monocytogenes (ampicillin or cotrimoxazole is used)
3. **UTI, prostatitis and vaginitis**
4. **Respiratory infections**: **H influenzae and legionella**
5. **GIT infections**: shigellosis and non-typhoid salmonella

•Miscellaneous Antibacterial Agents

•Nitrofurantoin

- Synthetic drug active against a range of G +ve and G –ve bact.
- **Resistance is rare**
- Mechanism of action is not known.
  - ❖ Given orally, **rapidly absorbed, and rapidly excreted** in urine
  - ❖ **Used only in the treatment of UTI**
  - ❖ **Toxicity** (hepatic & renal) may occur in **pt. with renal failure**

•Metronidazole

•**Antiprotozoal agent**, but also active against **anaerobic bacteria** like: **Bacteroides, clostridia sp., some streptococci**.

•In addition to treatment of many protozoal diseases it is used in:

- Effective in the treatment of **pseudomembranous colitis**
- Treatment of **serious anaerobic infections** like sepsis secondary to bowel disease.
- **Eradication of H pylori**