Inhibitors of Metabolism & Inhibitors of Nucleic Acid Function or Synthesis

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- **Inhibitors of metabolism:**

  - Sulfonamides, trimethoprim

- **Inhibitors of nucleic acid function or synthesis:**

  - Fluoroquinolones

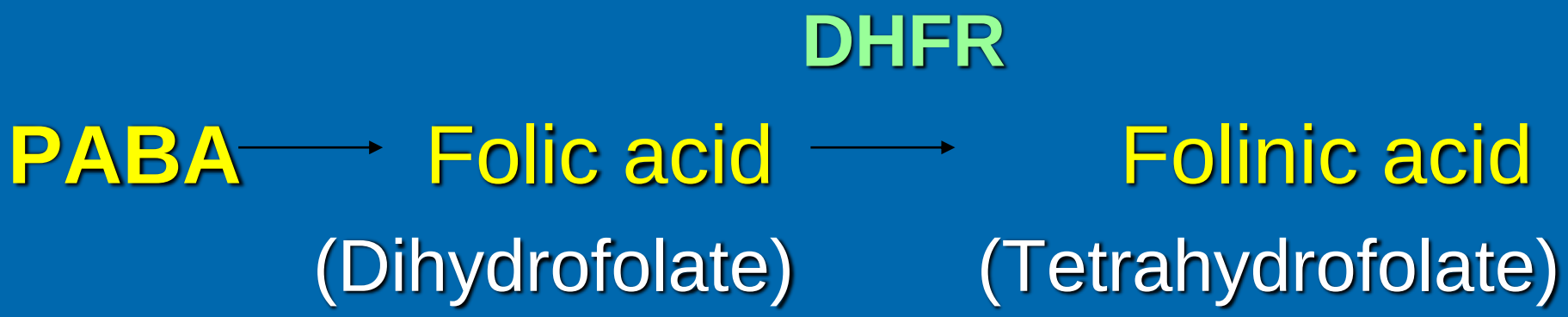
Folic Acid Antagonists

- **Sulpha drugs (sulphonamides), Trimethoprim**
- These are synthetic agents that **inhibit folic acid synthesis in bacteria**, therefore, leading to **interference with nucleic acid synthesis**
- **Interfere with ability of bacteria to divide**

- **Bacteria** require **folic acid**, which is synthesized in bacteria from **para-amino-benzoic acid (PABA)**
- **Sulpha drugs** **compete** with **PABA** **preventing synthesis of folic acid** in bacteria

- **Trimethoprim inhibits DHFR (dihydrofolate reductase)** enzyme which **converts folic acid into folinic acid** resulting in **impaired synthesis of folinic acid** (an essential **coenzyme in nucleic acid synthesis**) leading **to antibacterial effects**

Mechanism of action



- **Sulpha drugs** & **trimethoprim** are **bacteriostatic** when given **alone**
- However, **their combination (co-trimoxazole)** inhibits above 2 steps resulting in **bactericidal effect**

Sulpha Drugs

- These agents were active against many **Gram +ve** & **Gram -ve bacteria** & others
- At the present time, they are **infrequently used** with limited indications because of **increased bacterial resistance**
- **Safer more effective agents** have replaced sulpha drugs
- The following **sulpha** are important:

Sulpha Drugs

- Sulphadiazine
- Sulphadoxine
- Sulphacetamide
- Sulphamethoxazole
- Sulphasalazine

Sulphadiazine

- It is an **oral** well absorbed **short acting sulpha** that **crosses well BBB into CSF**
- Useful in treatment of **meningitis** (with penicillin)
- Useful in treatment of **toxoplasmosis** (with pyrimethamine)
- **Flamazine (silver sulphadiazine):** useful topically in prevention & treatment of infections in burns, leg ulcers & pressure sores

Sulphadoxine

- **A long acting sulpha** useful in treatment of **malaria** (with pyrimethamine)
- **Fansidar: sulphadoxine + pyrimethamine**

Sulphacetamide

- It is useful **topically for eye infections**

Sulphamethoxazole

- It is combined with trimethoprim producing co-trimoxazole

Sulphasalazine (salazopyrine)

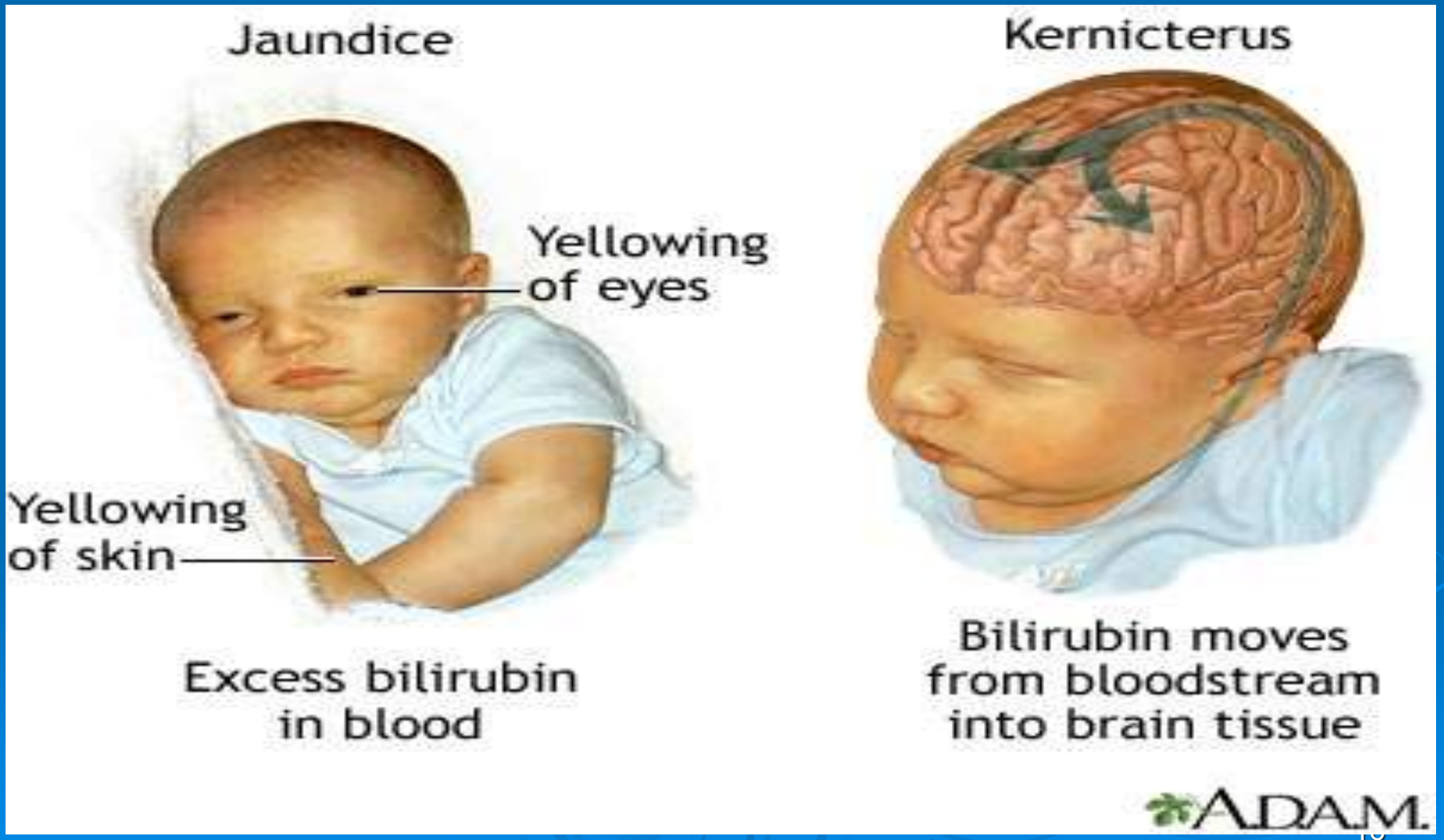
- It is useful in **chronic inflammatory bowel disease (IBD)** like **ulcerative colitis & Crohn's disease**
- It is used **orally**
- **In colon**, it is splitted by bacterial flora into **sulphapyridine** & **5-aminosalicylic acid** which is the **active part** that produces **anti-inflammatory effect of the drug**

- **Sulpha drugs** are **metabolised in liver** by process of **acetylation**
- People are either **rapid** or **slow acetylators**
- **Slow acetylators** accumulate drug & are **more prone to adverse effects**
- The drug & its metabolites are **excreted in urine** (excretion increases in alkaine urine)

Contraindications

- **Newborn babies** because of **risk of kernicterus** due to displacement of **billirubin** from binding sites on plasma proteins & **increased entry into brain tissues** through **immature BBB** leading to **mental retardation**
- **Late pregnancy** due to possible passage to fetus & risk of **kernicterus**
- **Allergy**
- **G6-PD deficiency** leading to **hemolytic anemia**

Kernicterus



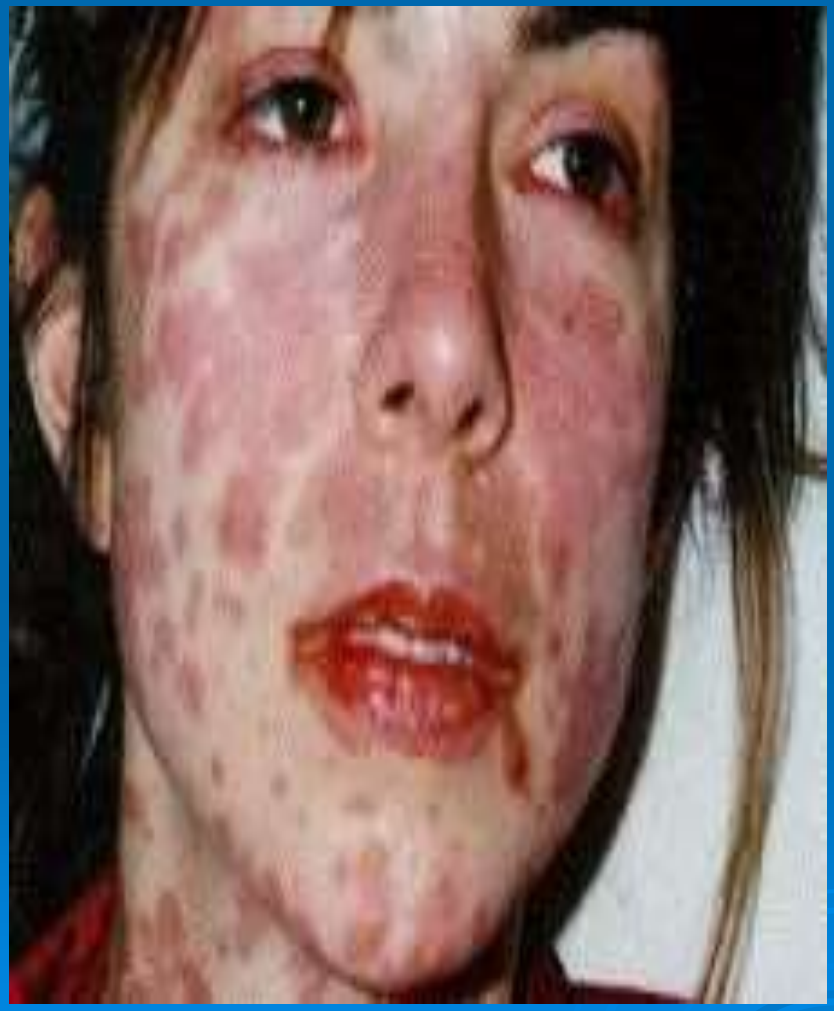
Adverse effects

- **Crystalluria:** **Sulpha** may **precipitate in urine** leading to **hematuria** & even **obstruction**; can be prevented by **increasing water intake** & **urine alkalinization**
- **Haemolytic anaemia** in patient deficient of G6-PD enzyme
- **Kernicterus**

Adverse effects

- **Hypersensitivity reactions (HSR):** **fever, skin rashes,** including severe **Stevens-Johnson syndrome (SJD) & TEN (Toxic epidermal necrolysis)** (Erythema multiform; target lesions in skin & mucous membrane)

Stevens- Johnson syndrome (SJS)



Trimethoprim

- This is a **DHFR inhibitor** that **inhibits conversion of folic acid into folinic acid**
- It can be used **alone** or **with sulphamethoxazole (co-trimoxazole)**
- It may be used in **UTI**, **prostatitis** & in **respiratory infections**

- **Prolonged therapy** may produce **blood disorders** (**macrocytic anemia, leucopenia & thrombocytopenia**) due to **effect on folic acid pathway in cells**

Co-trimoxazole (Septrin)

- It consists of **Sulphamethoxazole** 400 mg **& trimethoprim** 80 mg (ratio is 5:1)

Pharmacokinetics:

- It is usually used **orally** & sometimes **IV** in serious infections
- It is well absorbed from GIT & its **t½ is** about **10 hours** (given **twice daily)**

Therapeutic uses

- **Respiratory TI:** (pneumococci, haemophilus, klebsiella infections, Pneumocystis carini pneumonia in patients with AIDS)
- **UTI** (caused by E.coli, Proteus)
- **Enteric fever (salmonellosis)**
- **Brucellosis**
- **Gonorrhoea**

Fluroquinolones

- **First generation:**

  Nalidixic acid, used less today, Gram – ve

  (narrow spectrum mainly in UTI)

- **Second generation:**

  Gram –ve, Gram +ve, Atypical bacteria (chlamydia, mycoplasma)

  Ciprofloxacin, norfloxacin & ofloxacin

- **Third generation:**

  Gram –ve, Gram +ve (streptococcus pneumonia), Atypical bacteria (chlamydia, mycoplasma)

  Levofloxacin (Tavanic) (UTIs & respiratory infections: acute sinusitis, chronic bronchitis, community acquired & nonsocial pneumonia)

- **Fourth generation:**

  Gram –ve, Gram +ve, Anaerobic

  Moxifloxacin

- **Mechanism of action:**
- Acts by inhibiting DNA gyrase enzymes (inhibit topoisomerases) in bacteria leading to interference with DNA synthesis & anti-bacterial effect

Fluroquinolones

Nalidixic acid (Negram)

- Active against **Gram –ve organisms** including E.coli, salmonella, shigella & H. influenza
- This is **useful in** UTI (concentrated in urine) but has limited systemic anti-bacterial actions
- Its derivatives called **fluroquinolones (ciprofloxacin, norfloxacin & ofloxacin)** are 60 times more potent with systemic anti-bacterial actions

Ciprofloxacin

- Most frequently used
- This is a synthetic fluroquinolone which is bactericidal agent with **broad spectrum anti-bacterial actions** (mainly against Gram –ve & moderate activity against Gram +ve bacteria) & atypical pathogens

Pharmacokinetics

- It is usually given **orally twice daily**
- **It can be given IV**
- It is well absorbed & widely distributed in tissues with a half-life of about 3 hours
- The drug is partly metabolized and is eliminated through kidneys (**smaller doses** are used in **renal impairment**)

Therapeutic uses

- **UTI** (prostatitis) even those caused by resistant Gram –ve b. as Pseudomonas
- **Traveler's diarrhea (E.coli)**
- **Enteric fever (salmonellosis)** & shigellosis
- **Gonorrhoea**
- **Septicemia**
- **bone infections**
- **Chlamydia** & **Helicobacter infections**
- **Serious respiratory TI** like that caused by H. influenza & atypical pneumonia (mycoplasma, chlamydia)
- **Topically** in some **eye infections** like that caused by Pseudomonas

Contraindications

- Pregnancy & lactation
- Children
- Epilepsy
- G6-PD deficiency

Adverse effects

Usually well tolerated with few adverse reactions which may include:

- **GI:** nausea, vomiting , diarrhea
- **Arthralgia**
- **Allergy:** rash, photosensitivity, anaphylaxis, Stevens-Johnson syndrome
- **CNS manifestations:** (headache, hallucination & convulsions).
- **Tendon damage** like rupture of Achilles tendon