Sulfonamides

Anti-metabolites

- Drug interferes with endogenous metabolites
- **Includes**:-
- Sulfonamides
- Trimethoprim & iclaprim
- Pyrimethamine

- These are first **synthetic antibacterial agents**,
- Not Antibiotics (because antibiotics are obtained from some fungi or bacteria)
- Used for coccal infection in 1935
- They are bacteriostatic because it inhibits bacterial synthesis of folic acid
- They continue to occupy a small space in therapy
- **Current utility- limited (Narrow spectrum)**
  - ❖Rapid emergence of bacterial resistance
  - ❖superseded by more effective antibiotics

  (Excpt-combination with trimethoprim & pyrimethamine**)**

➢ Physically – **available as white powder, mildly acidic, form water soluble salts with bases.**

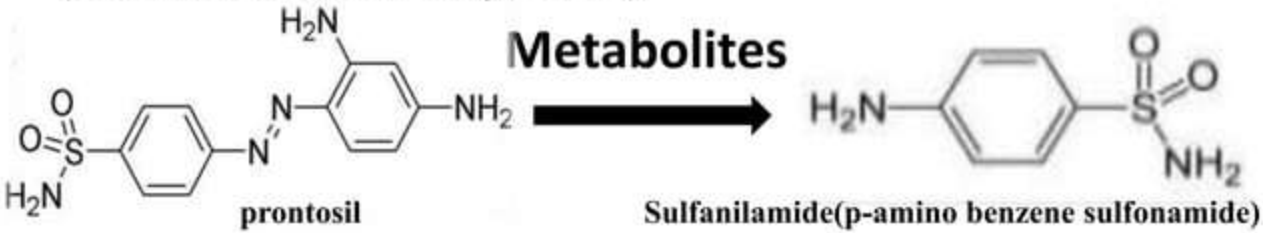
-:History:-

- **"Prontosil red" dyes**

(Sulfonamido chrysoidine) protected mice from streptococcal infection

(**Gerhard Domagk**1935)

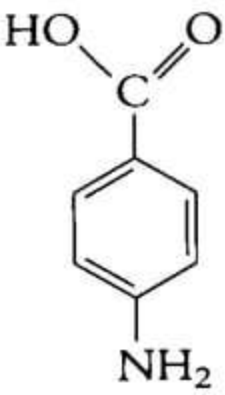
- Nobel Prize in medicine 1938
- Cure of staphylococcal septicaemia in an infant (Foerster, 1933) by prontosil
- Sulfanilamide, active metabolite of **prontosil** (Colebrook and Kenny, 1936)



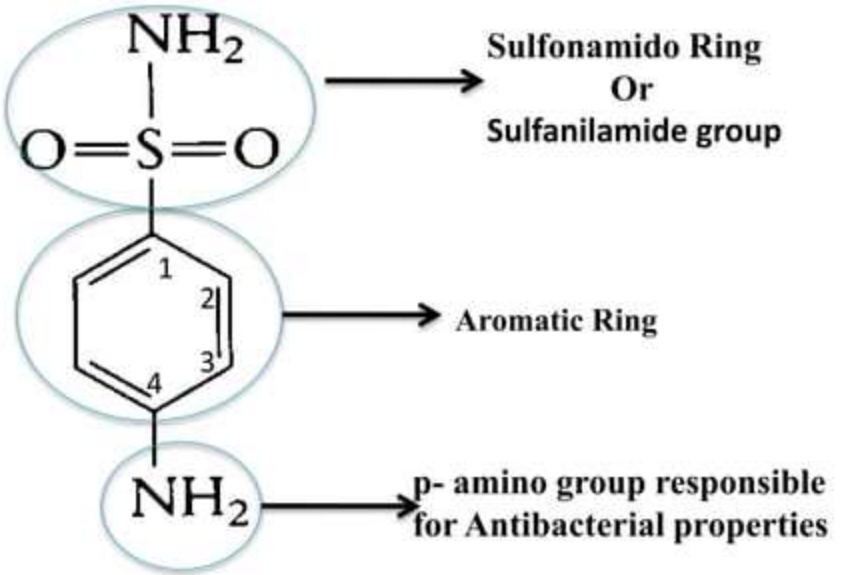
prontosil **Sulfanilamide(p-amino benzene sulfonamide)**

Chemistry

- Derivatives of Sulfanilamide (p-aminobenzene sulfonamide)
- Contain- "Sulfonamido" Ring ($S0_2NH_2$) attached to aniline
- Structurally related to PABA



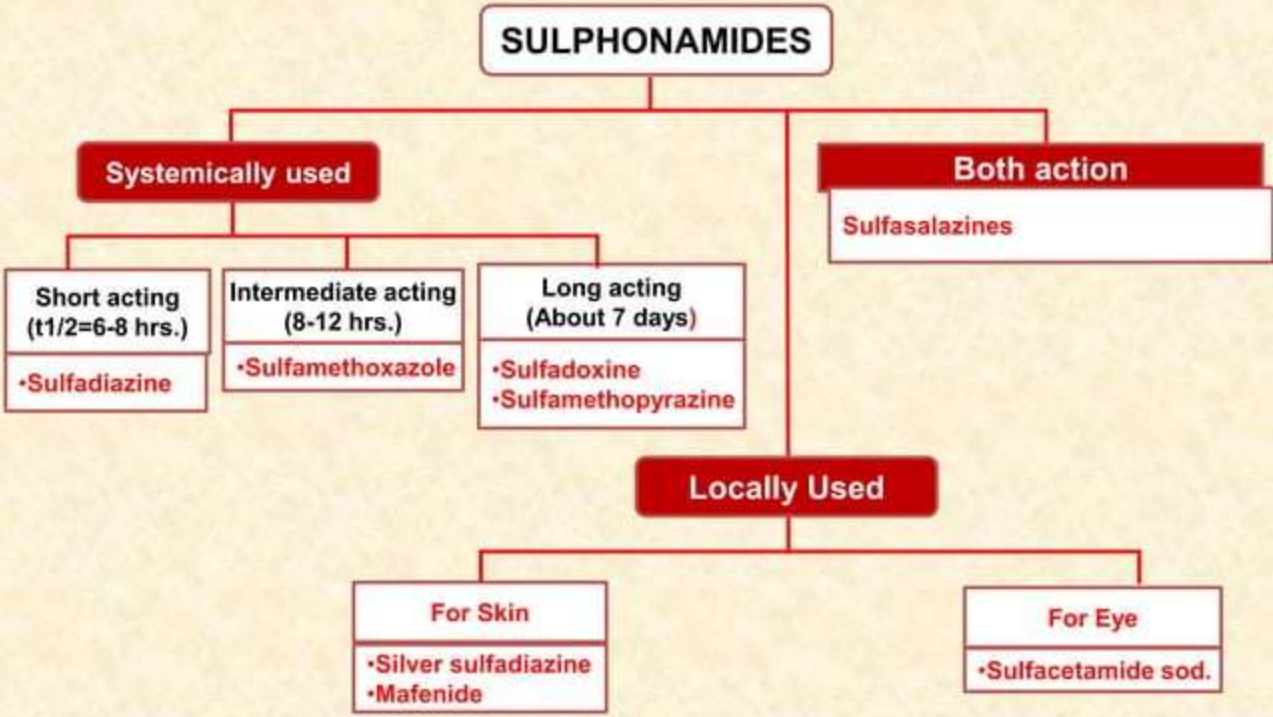
PABA



- The amino group & sulphonyl groups on the benzene ring are essential & should be in 1,4 position

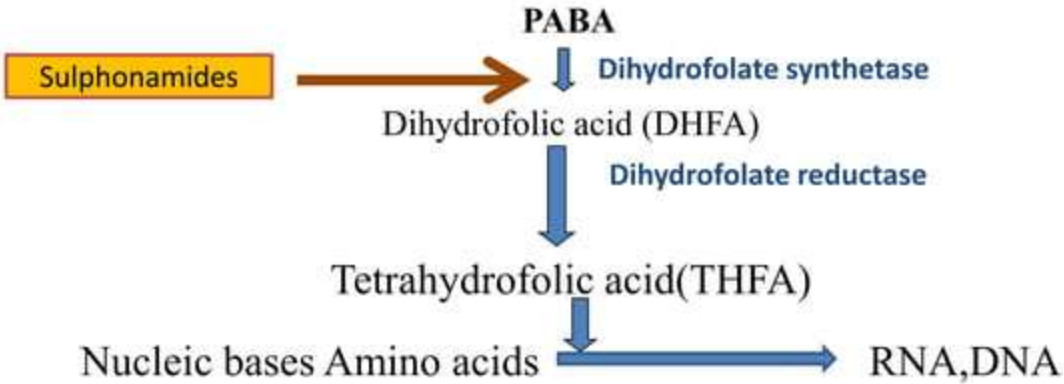
- Additional of substitutions on it decreases or abolish activity

- This group is also present in other non- bacterial compounds like
  - **Sulphonureas**
  - **Benzothiazids**
  - **Furosemide**
  - **Acetazolamide**


SULPHONAMIDES
Systemically used
Short acting (t1/2=6-8 hrs.)
•Sulfadiazine
Intermediate acting (8-12 hrs.)
•Sulfamethoxazole
Long acting (About 7 days)
•Sulfadoxine
•Sulfamethopyrazine
Both action
Sulfasalazines
Locally Used
For Skin
•Silver sulfadiazine
•Mafenide
For Eye
•Sulfacetamide sod.

Mechanism of action

- (PABA) is a precursor of folic acid, which is essential for the growth and multiplication of many bacteria
- Sulfonamides are structurally similar to PABA, so they compete with PABA for the enzyme dihydrofolate synthetase
- Inhibit bacterial growth without affecting normal cells



➢ Sulfonamides therefore are reversible inhibitors of folic acid synthesis and **bacteriostatic** not **bacteriocidal.**

Antibacterial Spectrum

- **Narrow spectrum Antibiotics**-due to development of resistance (Most Bacteria)
- Susceptible organisms include
  - *Strep. Pyogenes* (septic infections)
  - *Strep. pneumoniae* (pneumonia)
  - *Haemophilus influenzae* (meningitis)
  - *H. ducreyi* (chancroid)
  - *Toxoplasma*
  - *Plasmodium sp.*

  Resistance to-staphylococci, Enterococci, Pseudomonas
- **MIC**-0.1 μg/ml for *C. trachomatis*
- 4 to 64 μg/ml for *E. coli*

Pharmacokinetics

- Mainly given orally
- **Absorption**-Rapidly absorbed from stomach and small intestine.(70-100% absorption orally)
- **Distribution**-Widely distributed to tissues and body fluids (including CNS, CSF), placenta and fetus.
- Absorbed sulfonamides bind to serum protein (approx. 70%)
- Displacement reaction- with bilirubin (↑conc.)
- **Metabolism** →liver (acetylation).
- Major metabolite –acetylated product (no antibacterial action, but **toxicity retained**)
- **Excretion**- in the urine

Therapeutic Uses

A.TOPICAL

1. **Opthalmology:-** ocular infections(conjunctivitis)
   Sulfacetamide 10- 30% (eye drop or ointment)
2. **Ulcerative colitis:-** Sulfasalazine (sulfapyridine+ 5-amino salicylate)-(orally, not absorbed)
3. **Infected burns:-**

- **Drugs**-Mafenide acetate (sulfamylon cream),Silver sulfadiazine
- Effective against p.aeruginosa
- Less effective against staphyllococci

B. ORAL

1. Pneumocystis carinii pneumonia **
2. Nocardiosis-sulfadiazine

(apart from amphicillin,Erythromycine,)

3. Toxoplasmosis-**DOC**
   (Sulfadiazine+pyrimethamine)
4. RTIs (H. influenza; S. pneumonia)
6. Acute otitis media in children
7. Prostatitis
8. Shigellosis
9. Falciparum malaria (chloroquine resistant)

   Fansidar (sulfadoxine+ pyrimethamine)

Adverse effects

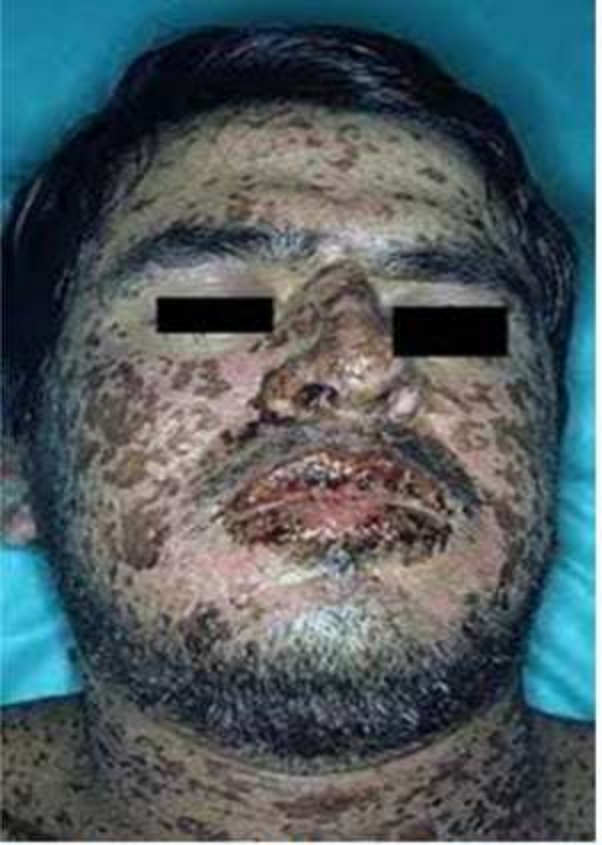
- **Urinary tract disturbances**-acetylated product less soluble in acidic urine leading to **Crystalluria**, **haematuria**, obstruction

R_x- 1.more water intake

2. Alkalizing urine

- Haemolytic anaemia- pt with G6PD deficiency - Granulocytopenia etc
- Fever, skin rashes, dermatitis, photosensitivity, urticaria, nausea, vomiting, diarrhoea
- **Hypersensitivity (allergic) reactions** like skin rashes, **Stevens-Johnson syndrome**

- Cyanosis due to methaemoglobenemia



- **Stevens-Johnson syndrome-ADR of sulfonamides**

Kernicterus:- neonate BBB not fully developed

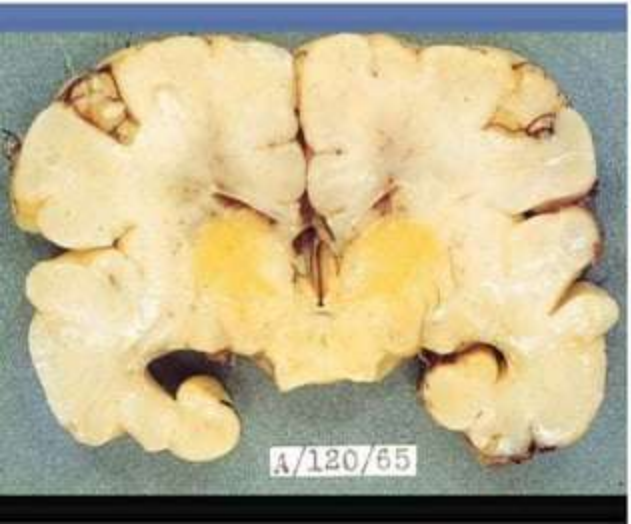
Sulfonamides —displace→ bilirubin from protein binding site

↓ Free bilirubin passed to BBB

Deposited in basal ganglia(subthalmic nucleus)

↓

Cause toxic Encephalopathy



Drug interactions

Sulfonamides ✖ Sulphonylureas
Oral anticoagulants
Hydantoins

Sulfonamides
Potentiate the action
of those drugs

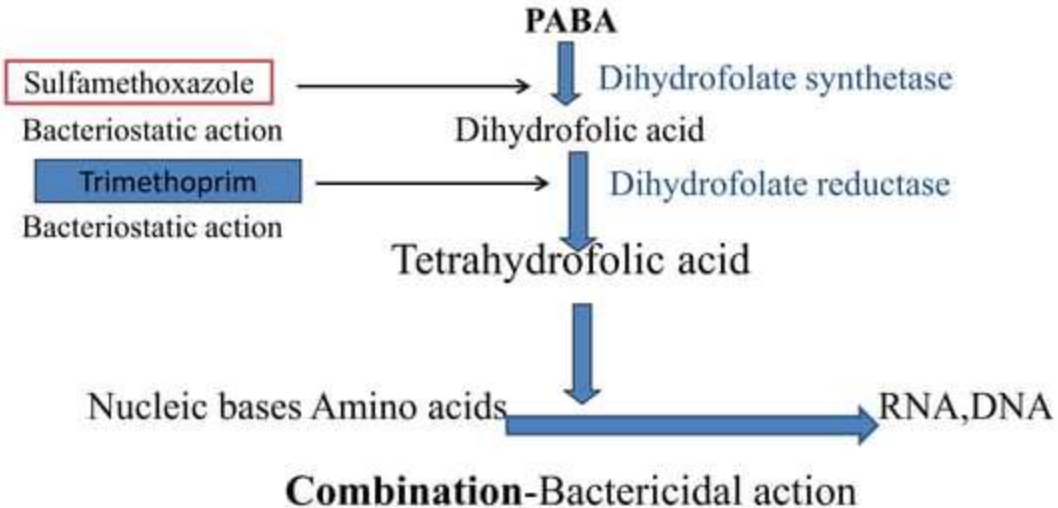
Sulfonamides ✖ Aspirin, NSAID's

Sulfonamides displaced
by this drugs

Co-trimoxazole

- WHO approve Fixed dose Combination of Sulfamethoxazole with trimethoprim (5:1 gives 20:1 C_p)
- Sequential inhibition of enzymatic pathway Synergistic combination (**Supra-additive effect**)

MOA:-



Combination-Bactericidal action

Rational of combination of sulfamethoxazole & trimethoprim

1.Individually both are bacteriostatic but the combination becomes bactericidal

2.Combination therapy ↓MIC of both the agents resulted in widens the spectrum

3.↓chances of development of bacterial resistance

4.Individual agents have similar t1/2(10hrs)

- **Antibacterial spectrum:-**
- **Wide antibacterial spectrum**
- *Chlamydia diphtheriae, N. meningitidis, S. pneumoniae*
- *Staph, E coli, Proteus, Salmonella, Shigella, Klebsiella, Brucella*
- Maximum synergism when microbes are sensitive to both drugs
- **Resistance:-**
- Reduced cell permeability
- Overproduction of DHFR or altered reductases
- By mutation or plasmid encoded

Therapeutic uses:-

- **Urinary tract infections**:- cause by gram negative organisms such as E. Coli, Proteus, Enterobacter spp. specially in women
- Dose-(800mg+160mg) BD for 3 days
- Prophylaxis in recurrent UTI-small dose
- **Prostatitis**-bacterial prostatitis as it is concentrated in prostatic tissue
- **Pneumonia** (*P. jiroveci*) Bacterial diarrhoea-Shigellosis, E.coli
- **Preferred drug**-fluoroqinolones
- Systemic salmonella infections

- **Bacterial Respiratory tract infections-** Acute & chronic bronchitis due to s. pneumoniae, H influenzae.
- **Also effective against-**maxillary sinusitis & otitis media
- **Typhoid fever- effective** but fluoroquinolones DOC
- **Nocardiosis**:-infection due to Nocardia spp.
- **Chancroid**:-cause by H.ducreyi.DOC is Azithromycin as cotrimoxazole is equally effective

Adverse effects

- Megaloblastic anaemia
- Leukopenia, Granulocytopenia
- Drug fever, nausea, vomiting
- Renal damage, vasculitis
- Occasional CNS disturbances

Question paper discussion

Q1.Explain why:- (2M)

- Combination of sulfamethoxazole with trimethoprime exhibits supradditive synergism

Q2.Classify sulfonamides and describe their mechanism of action,side effects and therapeutic uses.discuss the rational of combination of sulfamethoxazole & trimethoprim (15M)

Q3.Discuss the rational of using:- (4M)

Sulfamethoxazole with Trimethoprim

4.Write short notes on:- **Cotrimoxazole**

Quinolones

- **Nalidixic acid**-The first quinolone is a urinary antiseptic but doesn't contain fluorine
- It is useful in the treatment of uncomplicated UTI due to gram-negative bacteria and diarrhea due to Shigella or Salmonella.
- **Fluoroquinolones** -synthetic fluorinated analogues of nalidixic acid
- **Classification**:- According to Antibacterial spectrum

1st Generation	2nd Generation	3rd Generation	4th Generation
Norfloxacin, ciprofloxacin, pefloxacin, ofloxacin	levofloxacin, moxifloxacin	Gemifloxacin Sparfloxacin Gatifloxacin	Moxifloxacin Trovafloxacin
Mainly effective-Gm-ve but ineffective against MRSA & Anaerobes	Better spectrum towards Gm+Ve as compare to 1st generation	More effective aginsnt Gm+ve also MAC in AIDS and anaerobes	**Broad spectrum** Significantly greater activity against anaerobes

MOA:- **Quinolones**

↓↓

Inhibition of DNA gyrase (Topoisomerase II) in gram-negative bacteria & topoisomerase IV in gram positive bacteria

↓↓

Inhibition of bacterial DNA replication

↓↓

Inhibition of bacterial growth and reproduction

(**Bactericidal Action**)

- **Antibacterial spectrum:-**
- Ciprofloxacin is the prototype drug.
- Ciprofloxacin is highly effective against aerobic **gram-negative organisms**—*E. coli, Enterobacter, Proteus, Klebsiella, Salmonella, Shigella, H. ducreyi, H. infl uenzae, N.gonorrhoeae, N. meningitidis, Vibrio cholerae and Campylobacter jejuni*.
- It has activity against—*S. aureus, Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*.
- Most of the anaerobes—*Bacteroides fragilis, C. difficile,* etc. are resistant to ciprofloxacin.
- Newer fluoroquinolones like levofloxacin, gemifloxacin, moxifloxacin, etc. have greater activity against streptococci and some activity against anaerobes.

- **Pharmacokinetics**
- Ciprofloxacin is administered by oral, i.v. or topical routes.
- It is well absorbed from the gut
- Food delays its absorption
- **BA**:-Maximum -levofloxacin, Minimum -Norfloxacin
- **Distribution**-widely distributed in the body, reaches high concentration in kidney, lungs, prostatic tissue, bile, macrophages, etc.
- Longest acting- sparfloxacin
- Most Potent-Moxifloxacin
- **Excretion**-Urine
- (so dose reduction is needed in renal insufficiency

Fluoroquinolone	Routes of Administration	Oral Bioavailability	Antibacterial Spectrum and Uses	Drug Interactions
Norfloxacin	Oral, topical (eye)	30–40%	Mainly against gram-negative organisms, but not *Pseudomonas* **Uses:** It is used mainly in the treatment of urinary tract infections and bacterial diarrhoeas	Inhibits metabolism of theophylline and warfarin
Ciprofloxacin	Oral, i.v. infusion, topical (eye)	70%		Inhibits metabolism of theophylline and warfarin
Pefloxacin	Oral, i.v. infusion	Almost 100%	Similar to ciprofloxacin, also effective against *Mycobacterium leprae* **Uses:** Typhoid, gonococcal infection, UTI, bacterial diarrhoeas and leprosy	Inhibits metabolism of theophylline and warfarin
Ofloxacin	Oral, i.v. infusion, topical (eye)	Almost 100%	Effective against gram-negative organisms, gram-positive organisms and some anaerobes; has activity against *Chlamydia, Mycoplasma* and mycobacteria **Uses:** Tuberculosis (TB), leprosy	Inhibits the metabolism of theophylline, but to a lesser extent
Moxifloxacin	Oral, i.v. infusion, topical (eye)	90%	More active against gram-positive bacteria including *S. pneumoniae, M. tuberculosis* and some anaerobes (*Bacteroides fragilis*) **Uses:** Community-acquired pneumonia, chronic bronchitis and sinusitis. It is useful in odontogenic infection as it has activity against gram-positive and some of the anaerobes.	
Levofloxacin	Oral, i.v., topical (eye drops)	100%	Increased activity against *S. pneumoniae*; effective against gram-negative bacteria and anaerobes. **Uses:** Community-acquired pneumonia, sinusitis, chronic bronchitis, etc.	

Side effects

- The common adverse effects are related to GI tract, e.g. nausea, vomiting and abdominal discomfort.
- **CNS effects:-** include headache, dizziness, insomnia, confusion, hallucinations and convulsions.
- Hypersensitivity reactions include skin rashes, urticaria, itching, eosinophilia and photosensitivity
- Tenosynovitis and **tendon rupture** can occur, especially in athletes.
- Moxifloxacin can cause prolongation of QT interval.
- Fluoroquinolones are contraindicated in pregnancy.
- Fluoroquinolones -caused **cartilage damage** in animals, hence should be avoided in young children.

Drug interactions

- Ciprofloxacin × **Theophylline, warfarin**

  Ciprofloxacin-inhibit theophylline & warfarin metabolism leading to ↑Cp (toxicity)

- Fluoroquinolones × **NSAIDs** (potentiate the CNS side effects of fluoroquinolones) confusion, irritability and rarely convulsions may occur

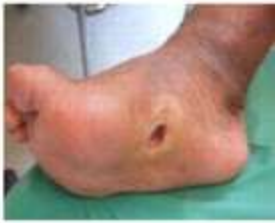
- Fluoroquinolones × **Tetracyclines, antacids, ferrous salts and sucralfate**
- ↓absorption of fluoroquinolones

Therapeutic uses

- **UTI**:- preferred over(superior) co-trimoxazole as they are effective against gram-negative bacilli such as E.coli, proteus & Enterobacter.
- **Bacterial prostatitis**-effective as they concentrated in prostatic tissue (not responding to co-trimoxazole)
- ciprofloxacin-750mg b.d. for 3 weeks
- **Bacterial diarrhoeas**:-caused E.coli,shigella,salmonella
- **Drugs**-Norfloxacin, ciprofloxacin (3-5days)
- **Travellers diarrhoea-**(due to enterotoxins produced by E.coli)-as effective as co-trimoxazole

- **Typhoid fever(Enteric fever)**- caused by salmonella typhi
- **DOC**-Ciprofloxacin (750mg orally BD-for 10days)
- Other drugs-ofloxacin, levofloxacin
- **Advantage**:- prevents bacterial relapse
- **STD(sextually transmitted disease)**:-
- **Gonococcal infection**- cause by N.gonorrhoea
- **DOC**-ceftriaxone (due to resistance)
- **Chancroid**-ciprofloxacin
- **Chlamydial cervicitis & urethritis**- levofloxacin/ofloxacin
- **Anthrax**-ciprofloxacin (prophylaxis of anthrax)

- **Skin,soft tissue and bone infections**- due to S. aureus & gram-Negative bacilli
- **Diabetic foot infections**-most effective



- **Respiratory infections**:- Newer fluoroquinolones (levofloxacin and moxifloxacin) are highly effective for community-acquired pneumonias and chronic bronchitis
- **MAC** (Mycobacterium avium complex)- Levofloxacin + clarithromycin,rifabutin
- **Others**- ophthalmic (conjunctivitis) infection- topically use

Question paper discussion

Q1.Fluoroquinolones (4M)

Q2.Classify quinolones. Discuss the Pharmacological effects, side effects and clinical uses of ciprofloxacin (8M/15M)

Q3.Discuss the therapeutic uses and Adverse effects of: (4M)

A. Ciprofloxacin

B. Fluoroquinolones