Chemotherapy

Sulfonamides, Nitrofurans and Quinolones

CHEMOTHERAPY

Chemotherapy is the use of chemical compounds for the treatment of infectious diseases by killing or inhibiting the growth of causative organisms without damaging the host tissues or cells.

Paul Ehrlich demonstrated the effective use of methylene blue in the treatment of malaria. He also synthesized arsenical compounds (**neoarsphenamine**) effective in the treatment of syphilis. The synthesis of newer and powerful antibacterial substances gave the recognition to Paul Ehrlich as 'the father of modern chemotherapy' and awarded the Nobel prize of medicine in 1909.

In 1928, Sir **Alexander Fleming** found that a diffusible substance was elaborated by Penicillium notatum (a fungus) which prevented the growth of surrounding bacterial colonies in culture plate. He named this as 'penicillin' but this discovery remained a scientific curiosity for more than a decade.

This work was followed up by **Chain, Falk and Florey** who established the efficacy of penicillin in 1941 and in 1945, Fleming, Chain and Florey were awarded the Nobel Prize.

The general mechanism of action of antimicrobial agents is listed in table 9.1.1.

Table 9.1.1: *Mechanism of action of antimicrobial agents.*

1. **Inhibit cell wall synthesis**	Penicillins, cephalosporins, bacitracin, vancomycin and cycloserine.
2. **Damage to the cytoplasmic membrane**	
Polypeptides	Polymyxin, bacitracin, colistin.
Polycines	Nystatin, amphotericin B, hamycin.
3. **Inhibit protein synthesis & impairment of functions of ribosomes**	Tetracyclines, chloramphenicol, aminoglycosides, erythromycin, clindamycin and other macrolide antibiotics.
4. **Inhibit DNA gyrase**	Fluoroquinolones i.e. ciprofloxacin, ofloxacin.
5. **Interfere with DNA function**	Rifampicin, metronidazole.
6. **Interfere with DNA synthesis**	Acyclovir, idoxuridine, zidovudine.
7. **Antimetabolite action**	Sulfonamides, sulfones, INH, ethambutol, trimethoprim, PAS, pyrimethamine.

Antimicrobials can be classified according to type of action into:

a. **Primarily bactericidal:** Penicillin, cephalosporins, aminoglycosides, vancomycin, polypeptides, INH, cotrimoxazole, rifampicin, fluoro quinolones, nalidixic acid.

b. **Primarily bacteriostatic**: Ethambutol, erythromycin, chloramphenicol, tetra cyclines, sulfonamides. Beta lactam antibiotics having a β-lactam ring, which includes penicillin, in which a thiazolidine ring is attached to a betalactam ring that carries a secondary amino group.

Other similar compounds are **cephalosporins**, **monobactams** and **carbapenems**.

ANTIMICROBIALS USED IN DENTISTRY:

as simple extraction and other minor peridental procedures are associated with very low risk of any wound infection. Prophylaxis is recommended when the procedure in which a prosthesis is inserted into bone or soft tissue (e.g., dental implants), or in other extensive reconstructive surgery. In dentistry, the antimicrobials agents which should be active against gram positive cocci and oral anaerobes and which yields peak blood levels higher than minimum inhibitry concentration for the common oral pathogens is recommended. **Amoxycillin**, safe & bactericidal in nature is generally the drug of choice. Antiseptic rinse (chlorhexidine 0.2%) is also used as an adjuvant to reduce the bacteraemia following dental extraction.

1- SULFONAMIDES

Chemically, all sulfonamides may be considered to be derivatives of sulfanilamide(p-aminobenzene sulfonamide). Sulfonamides were the first antimicrobial agents effective against pyogenic bacterial infections. The antimicrobial compounds con taining a sulfonamido (SO_2 NH_2) group are called sulfonamides and a free amino group at the para position is required for its antibacterial activity. The same sulfonamido group is also present in other non-bacterial compounds such as tolbutamide (oral anti diabetic drug), chlorothiazide, furosemide and acetazolamide (diuretics) etc. The sulfonamides can be classified according to their therapeutic utility and pharmacokinetic parameters (table 9.1.2). However, because of bacterial resistance and discovery of many safer and more effective antibiotics, the utility of sulfonamides is limited to few infections which are of clinical interest.

Pharmacological Actions

The most important pharmacological action of sulfonamides is its antibacterial activity against variety of gram positive and gram negative organisms (mainly bacterio static) and certain species of chlamydia in fections such as:

- Streptococci, staphylococci, pneumococci, gonococci, meningococci, Haemophilus influenzae, H. ducreyi, Calymmatobacterium granulomatis, Vibrio comma, Vibrio cholerae, E. coli, Pasteurella pestis, Shigella.
- Actinomyces, Nocardia and Toxoplasma.
- Chlamydia causing lymphogranuloma venereum, psittacosis, trachoma and inclusion conjunctivitis.

Table 9.1.2: *Classification of sulfonamides.*

I. **Highly absorbed sulfonamides**	
a. Short acting	
Sulfadiazine	2 g initially then 1 g 4-6 hourly
Sulfadimidine	2 g initially then 0.5 g 6-8 hourly
Sulfafurazole (GANTRISIN)	2 g initially then 1 g 4-6 hourly
Sulfamethizole (UROLUCOSIL)	1.0-2 g 4-6 hourly
b. Intermediate acting	
Sulfamethoxazole (used in combination with trimethoprim; SEPTRAN: Sulfamethoxazole 400 mg + Trimethoprim 80 mg)	160 mg of trimethoprim & 800 mg of sulfamethoxazole every 12 hourly
c. Long acting	
Sulfadimethoxine (MADRIBON)	1 g initially then 0.5 g OD
Sulfamethoxine (SULFADOXINE)	1 g initially then 0.5 g OD
Sulfamethoxypyridazine (LEDERKYN)	1 g initially then 0.5 g OD
Sulfamethopyrazine (used in malaria; METAKELFIN)	
II. **Poorly absorbed sulfonamides (for GIT local action)**	
Phthalyl sulfathiazole (THALAZOLE)	3-6 g/day
Succinyl sulfathiazole (SULFASUXIDINE)	3-6 g/day
Sulfaguanidine	3-6 g/day
III. **Special purpose sulfonamides**	
Sulfacetamide (ALBUCID)	10-30% eye drops
Sulfacetamide (NEBASULF)	6% powder used externally
Sulfasalazine (for autoimmune bowel disease; SALAZOPYRIN)	1-2 g QID initially then 0.5 g TDS-QID
Silver sulfadiazine (burn etc. local application; SILVIRIN)	1% local cream
Mafenide propionate (MARFANIL)	1% local cream

Pharmacokinetics

After oral administration, sulfonamides are rapidly and completely absorbed from gastrointestinal tract and approximately 70 to 90 percent of oral dose reaches to the blood stream, but the binding with plasma proteins differ considerably among different groups. The highly plasma protein bound sulfonamides have longer action. The main site of absorption is small intestine.

Adverse Reactions

The common side effects are nausea and vomiting. The others are allergic symptoms including drug fever, skin rash, urticaria, eosinophilia, photosensitization reactions, serum sickness like syndrome. Stevens Johnson syndrome and exfoliative dermatitis are also common with longer acting agents.

The uncommon allergic reactions include acute toxic hepatitis, toxic nephrosis and acute haemolytic anaemia.

Sulfonamides also cause renal irritation and may precipitate renal colic. Crystalluria, haematuria and albuminuria can also occur which may lead to the development of oliguria and anuria.

The hematopoietic toxicity includes agranulocytosis, thrombocytopenia and rarely aplastic anaemia and in patients with glucose-6-phosphate dehydrogenase (G-6 PD) deficiency, sulfonamides may cause intravascular haemolysis. The other CNS effects include depression, confusion, tinnitus, fatigue etc.

Therapeutic Uses

Because of development of resistance and availability of more advanced antimicrobial agents, the use of sulfonamides is limited. However they are used in combination with trimethoprim. **The important therapeutic uses are:**

i. **Urinary tract infection**: Used in chronic suppressive therapy in various UTI conditions e.g. acute cystitis.
ii. **Acute bacillary dysentery**.
iii. **Ulcerative colitis,** mainly sulfasalazine (a chemical combination of sulfapyri dine and 5-amino salicylic acid) is used in the treatment of ulcerative colitis.
iv. **Streptococcal pharyngitis**, prophylaxis of rheumatic fever and tonsillitis.
v. **Trachoma and inclusion conjunctivitis:** Sulphacetamide (10-30%) local eye drops are used.
vi. **Chancroid:** Sulfadimidine may be used. vii. In the treatment of meningococcal meningitis.
vii. **Sulfonamides** in combination with py rimethamine are used in the treatment of chloroquine resistant malaria.
viii. **Toxoplasmosis:** Sulfadiazine and pyrimethamine combination is used.
ix. **Burns:** Topical silver sulfadiazine or mafenide is used.

TRIMETHOPRIM

Trimethoprim is a pyrimidine derivative (diaminopyrimidine) related to antimalarial drug pyrimethamine, which selectively inhib its bacterial dihydrofolate reductase, neces sary for the conversion of dihydrofolate to tetrahydrofolic acid. Sulfonamides act by in hibiting the incorporation of PABA into dihydrofolate by bacteria. A combination of trimethoprim and sulfamethoxazole (cotrimoxazole) act sequentially in the same metabolic pathway in the synthesis of nucleotides.

Adverse Effects

All those side effects seen with sulfonamides.

The common indications are:

i. **Urinary tract infection:** Acute cystitis.
ii. **Bacterial diarrhoea and dysentery**.
iii. **Respiratory tract infection** such as chronic bronchitis and otitis media etc.
iv. **In the treatment of typhoid**.

v. **Chancroid**.

vi. Sexually transmitted diseases.

vii. **Prophylaxis** and treatment of certain HIV associated infections.

viii. **For the prophylaxis** of certain concurrent bacterial infections e.g. organ transplantation patients receiving immunosuppressant's.

ix. Nosocomial infections.

2- NITROFURANS

It possesses antimicrobial action against gram positive and negative organisms including *staphylococci*, *streptococci*, *E. coli*, *Salmonella* and *Shigella* species.

1- NITROFURANTOIN

Bacteriostatic drug. It is effective against a variety of gram positive and negative organisms including E. coli and Aerobacter.

It is most commonly used as urinary antiseptic for prophylaxis and treatment of urinary tract infections.

Adverse effects are nausea, diarrhoea, haemolytic anaemia in persons with G-6-PD deficiency and peripheral neuritis (on long term use).

Dose: FURADANTIN; 50-100 mg TDS-QID.

2- NITROFURAZONE

Bactericidal drug for both gram positive and negative bacteria. Acts by inhibiting enzymes necessary for carbohydrate metabolism in bacteria. It is available as ointment.

Used for the topical treatment of superficial wounds and skin infections.

Dose: FURACIN; 0.2% ointment/cream.

3- FURAZOLIDONE

This is mainly employed for the treatment of gastrointestinal infections e.g. bacillary dysentery, giardiasis, bacterial enteritis etc.

Dose: FUROXONE; 100-200 mg TDS QID.

3- QUINOLONES

Quinolones, are synthetic antimicrobial agents effective against gram negative bacteria. Although newer compounds (second generation quinolones – the fluoroquinolones) are also effective against gram positive bacteria. The important quinolones are synthetic fluorinated analogs of nalidixic acid (which was introduced in mid 1960s and had limited use in UTI and GIT infections). They are active against a variety of gram positive and gram negative bacteria. Quinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. Inhibition of DNA gyrase prevents

the relaxation of positively supercoiled DNA that is required for normal transcription and replication. The important quinolones are listed in table 9.1.3.

Table 9.1.3: *Classification of quinolones.*

Nalidixic acid (GRAMONEG)	0.5-1.0 g QID
Ciprofloxacin (CIPLOX)	250-750 mg BD
Norfloxacin (NORFLOX)	400 mg BD
Pefloxacin (QUCIN)	400 mg BD
Sparfloxacin (SPARFLOX)	200-400 mg OD
Ofloxacin (OFLIN)	200-400 mg BD
Levofloxacin (LOXOF)	500 mg OD
Gatifloxacin (GATILOX)	400 mg OD, eye drop (0.3%)

FLUOROQUINOLONES

These are quinolone antimicrobial agents having one or more fluorine substitutions, relatively broad spectrum of action and effective against gram positive and gram negative organisms. They are highly effective against *E. coli*, *Klebsiella*, *Proteus mirabilis*, *Shigella*, *Salmonella species*, *H. ducreyi* etc. The fluoroquinolones inhibit bacterial enzyme DNA gyrase. The presence of a 6-fluoro and 7 piperazine substitution greatly enhances their antimicrobial efficacy as compared to nalidixic acid. The fluorine atom is responsible for increased potency against gram negative organisms and broadens the spectrum of their activity including gram positive organism. The piperazine moiety imparts antipseudomonal activity. After oral administration, the fluoroquinolones are well absorbed with the bioavailability of 80 to 95 % and distributed widely in body fluids and tissues. Depending upon the newer compound, the different dose regimen have been adopted. The fluoroquinolones are excreted mainly by tubular secretion and by glomerular filtration. Fluoroquinolones are well tolerated.

The most common adverse effects are nausea, vomiting, diarrhoea, headache, insomnia, skin rash and occasionally abnormal liver function tests (with trovafloxacin). Phototoxicity has been particularly reported with pefloxacin, lomefloxacin, sparfloxacin and ofloxacin. Tendinitis is a serious side effect rarely reported in adults. Because of cartilage damage in children it must be used under close supervision.

Therapeutic Uses

The most common conditions in which fluoroquinolones may be useful is:

- Urinary tract infections.
- Bacterial gastroenteritis.
- Typhoid fever.
- In septicemia.

- In otitis media.
- Respiratory infections e.g. acute pneumonia etc.
- Ocular infections and
- Other infections caused by *E. coli, K. pneumoniae, Enterobacter, Salmonella typhi, N. gonorrhoeae, N. meningitidis, H. influenzae, H. ducreyi, Shilgella, Vibrio cholerae, Pseudomonas aeruginosa, Staph. aureus* etc.

1- Nalidixic acid (GRAMONEG)

It is 4-quinolone derivative effective against gram negative bacteria mainly E. coli and Shigella. It is less effective against *Klebsiella* and Aerobacter species and very rarely against Pseudomonas. Acts by inhibiting bacterial DNA gyrase.

It is mainly used as urinary antiseptic and in diarrhoea caused by E. coli, Shigella, Salmonella.

The main side effects are GIT upset, headache, drowsiness, vertigo, visual disturbances and on prolonged use can produce parkinsonism like symptoms. In individuals with G-6-PD deficiency can cause haemolysis.

2- Ciprofloxacin (CIPLOX)

It is the most potent first generation fluoroquinolone, effective against a broad range of microorganisms. The most susceptible one are the aerobic gram negative bacilli. It attains several times higher concentration in the urine than plasma. Ciprofloxacin produces rapid and complete clinical relief in nosocomial bronchopneumonia patients. It has been successfully used prior to cardiac surgery and has attained levels higher than MICs for the commonly susceptible pathogens for at least 8 hours. The bone, soft tissue and skin infections, bacterial gastroenteritis, severe/ complicated UTI will respond to ciprofloxacin. It has been used widely as a drug of first choice for typhoid fever, however, resistance has also been reported. It is also useful in respiratory infections due to Mycoplasma, Legionella, multidrug resistant tuberculosis and as topical agent in conjunctivitis. The drug has been used alone as well as in combination.

3- NORFLOXACIN

It is less potent than ciprofloxacin and is primarily used in genitourinary tract infections. It is relatively more potent than ciprofloxacin in above condition. It is not useful in respiratory and systemic infections due to gram positive cocci.

4- Pefloxacin (QUCIN)

It is a methyl derivative of norfloxacin which penetrates tissues better and attains higher plasma concentration. Concentration in CSF is higher than other fluoroquinolones, therefore is preferred drug for meningeal infections. It is used in the treatment of gonorrhoea and typhoid. Genotoxicity has been reported at higher concentration of pefloxacin.

5- Sparfloxacin (SPARFLOX)

It is difluorinated quinolone effective against gram positive bacteria, anaerobes and mycobacteria. **It is used** in the treatment of pneumonia, chronic bronchitis, sinusitis etc.

6- Ofloxacin (OFLIN)

It is more potent than ciprofloxacin for gram positive organisms. It also inhibits Mycobacterium tuberculosis and Mycobacterium leprae and used as alternative in multidrug resistant therapeutic regimens. **It is also used** in the treatment of chronic bronchitis and other ENT infections. **Also used** in gonorrhoea, gonococcal urethritis and urinary tract infections due to *E. coli, K. pneumoniae, P. mirabilis, Citrobacter diversus or paeruginosa. Mycoplasma pneumoniae, U. urealyticum* are also susceptible. The anaerobes like Bacteroides *fragilis, Clostridium perfringens, B. intermedium, C. welchii, Peptococcus niger, Peptostreptococcus sp* respond well to ofloxacin in vitro. It does not inhibit the cytochrome P450.

7- Levofloxacin (LOXOF)

It is the levoisomer of ofloxacin and having better activity than ciprofloxacin and ofloxacin against *S. pneumoniae*. It is also used in chronic bronchitis, sinusitis, pyelonephritis, and other related infections of soft tissues. Due to high oral bioavailability, patient can be shifted from IV to oral therapy. It can be administered just once a day regimen as an alternate to other fluoroquinolones in the treatment of respiratory infections.

8- Gatifloxacin (GATILOX)

The antibacterial action of gatifloxacin result from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. **Topoisomerase** IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division.

Gatifloxacin ophthalmic solution is the first FDA approved fourth generation fluoroquinolone and is available in Indian market.

Reference:

Singh, Surender. ***Pharmacology for dentistry***. New Age International, 2007.