Pharmacology of sulfonamides and synthetic antibacterial agents from various groups. Pharmacology of drugs used to treatment tuberculosis, syphilis and leprosy.

Sulfonamides

The sulfonamide story began in 1935 when it was discovered that a red dye called prontosil had antibacterial properties in vivo (when given to laboratory animals)

The first use of sulfonamides for streptococcal infection was in 1936 Sulfonamide was firstly noted as anti-bacterial in 1900's by Gerhard Domagk; a Nobel Prize winner in 1939. In his attempt to save his daughter from streptococci killing infection, he observed that prontosil; a sulfonamide dye, is able to selectively restrain the infectious bacteria cells. In 1936, Ernest Fourneau found out prontosil pathway in human body. He discovered that this dye was a pro-drug. It, actually changes in human body to sulfanilamide which is the anti-bacterial active agent.

This invention triggered the discoveries of other anti-bacterial members derived from this chemical group such as sulfapyridine in 1938 against pneumonia, and sulfacetamide in 1941 against urinary tract infections, and succinoylsulfathiazole in 1942 against gastrointestinal tract infections. Sulfathiazole was commonly used during World War II to cure soldier wounds' infections. On the contrary, sulfanilamide was not very used due to its greater human toxicity. Later on, sulfisoxaide, sulfamethoxazole, sulfacetamide, mafenide and sulfadiazine silver were discovered, and those four agents are the sulfonamide anti-bacterial agents have been in the clinical use so far.
Sulfonamide anti-bacterial medications; also called sulfa drugs, are competitive inhibitors of p- amino benzoic acid in the folic acid metabolism cycle in the organisms . They have a common core structure shown in Figure 1.

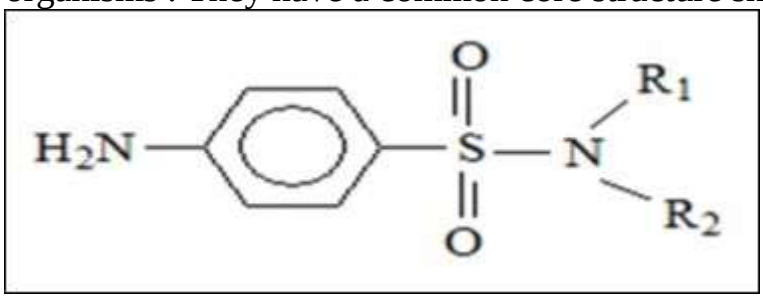


Figure 1
They can be classified as Oral absorbable, oral non-absorbable, and topical agents. [4]Oral absorbable agents are also divided into short acting agents such as sulfisoxaide, medium acting agents such as sulfamethoxazole and long acting agents such as sulfasalazine.
Oral non absorbable agent group includes only sulfasalazine, while topical agents have sulfacetamide, mafenide, and silver sulfadiazine.

Classification:

I. Sulfanilamides for topical use: Sulfacetamide (Sulfacyl-sodium), Mafenide, Algimaf, Silver sulfadiazine

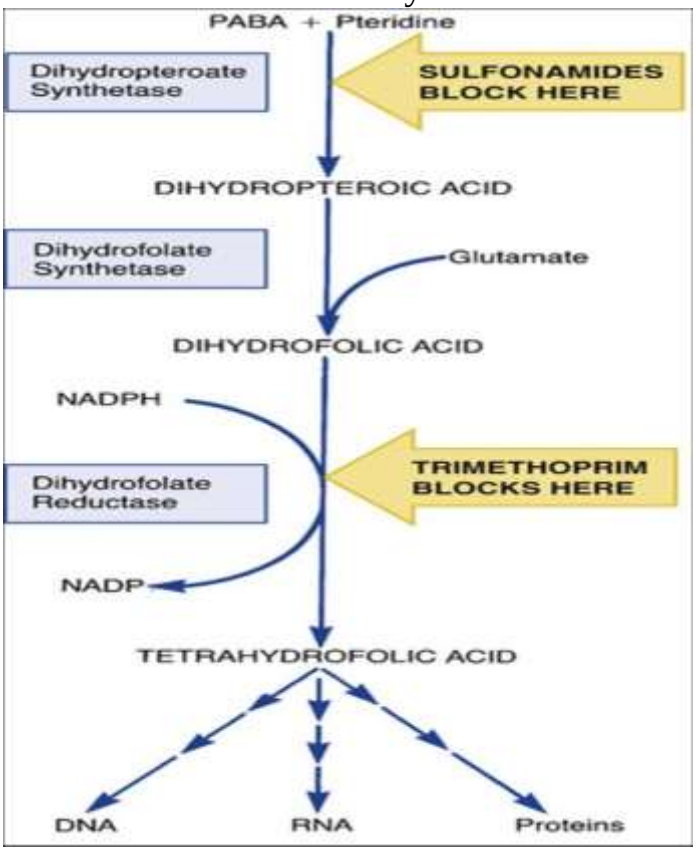
II. Sulfanilamides for systemic use:
а) Short duration action (t1/2 = 8 hours) Sulfanilamide (Streptoside), Sulfathiazole (Norsulfazole), Sulfadimidine (Sulfadimezine) , Sulfadiazine (Sulfazine), Sulfaetidole (Etazole) , Sulfacarbamide (Urosulfane)
б) Long duration action (t1/2 = 24-48 hours) Sulfamethoxypyridazine (Sulfapiridazine) , Sulfamonomethoxine, Sulfadimethoxine,
в) Very long duration action (t1/2 = 65 hours)Sulfalene

III. Sulfanilamides poorly absorbed from the gut
Phtalazole (Phthalylsulfathiazole) , Sulgine, Phtazine, Sulfasalazine
IY. Combined sulfanilamides
а) Combined with trimethoprim: *Bactrim (Sulfamethoxzole/trimetoprim) Sulfaton Lidaprim Poteseptil*
б) Combined with aminosalicylic acid: *Salazosulfapiridazine Salazodimetoxine*

Pharmacokinetics:
- ✓ Most sulfa-drugs are well absorbed via stomach and the small intestine Sulfasalazine not absorbed (used in treatment of chronic inflammatory bowel disease).
- ✓ Highly bound to plasma proteins. Displace bilirubin and increase serum bilirubin. Protein binding varies from 20% to over 90%
- ✓ Distributed widely to tissues and body fluids, placenta and fetus. Cross BBB (except sulfadimethoxine)
- ✓ A portion og absorbed drug is acetylated, glucuronidated (sulfadimethoxine) in liver.
- ✓ Excreted in to the urine, mainly by glomerular filtration.
- ✓ Sulfonamides and inactive metabolites are then excreted into the urine, mainly by glomerular filtration. In significant renal failure, the dosage of sulfonamides must be reduced.

Mechanism of Action & Antimicrobial Activity
Sulfonamide-susceptible organisms, unlike mammals, cannot use exogenous folate but must synthesize it from PABA. This pathway is thus essential for production of purines and nucleic acid synthesis. As structural analogs of PABA, sulfonamides inhibit ***dihydropteroate synthase*** and folate production. Sulfonamides inhibit both gram-positive and gram-negative bacteria, Nocardia sp, Chlamydia trachomatis, and some protozoa. Some enteric bacteria, such as Escherichia coli, Klebsiella pneumoniae, Salmonella, Shigella , and Enterobacter sp are also inhibited. It is interesting that rickettsiae are not inhibited by sulfonamides but are instead stimulated in their growth. Activity is poor against anaerobes. Pseudomonas aeruginosa is intrinsically resistant to sulfonamide antibiotics.

Combination of a sulfonamide with an inhibitor of dihydrofolate reductase (trimethoprim or pyrimethamine) provides synergistic activity because of sequential inhibition of folate synthesis



Picture 2

Resistance

Sulfonamide resistance may also occur as a result of mutations that (1) cause ***overproduction of PABA***, (2) cause production of a folic acid-synthesizing enzyme that has ***low affinity for sulfonamides***, or (3) ***impair permeability*** to the sulfonamide. Dihydropteroate synthase with low sulfonamide affinity is often encoded on a plasmid that is transmissible and can disseminate rapidly and widely. Sulfonamide-resistant dihydropteroate synthase mutants also can emerge under selective pressure

Clinical Uses

Sulfonamides are infrequently used as single agents. Many strains of formerly susceptible species, including meningococci, pneumococci, streptococci, staphylococci, and gonococci, are now resistant. The fixed-drug combination of trimethoprim sulfamethoxazole is the drug of choice for infections such as Pneumocystis jiroveci (formerly P carinii) pneumonia, toxoplasmosis, nocardiosis, and occasionally other bacterial infections.

Adverse Reactions

The most common adverse effects are fever, skin rashes, exfoliative dermatitis, photosensitivity, urticaria, nausea, vomiting, diarrhea, and difficulties referable to the urinary tract (see below). Stevens-Johnson syndrome, although relatively uncommon (< 1% of treatment courses), is a particularly serious and potentially fatal type of skin and mucous membrane eruption associated with sulfonamide use. Other unwanted effects include stomatitis, conjunctivitis, arthritis, hematopoietic disturbances, hepatitis.

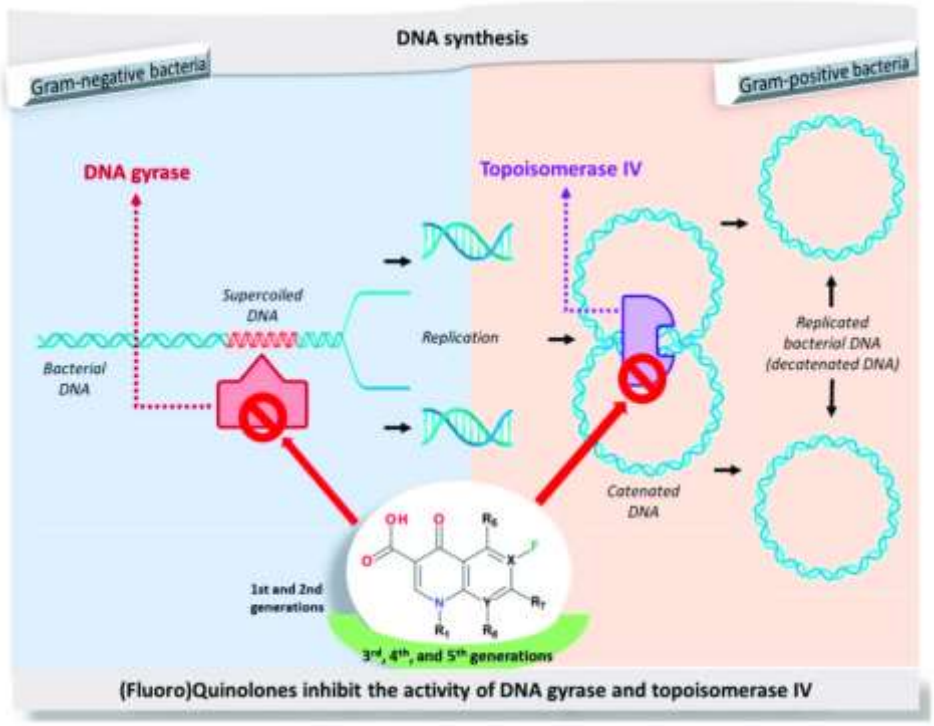
A. **Urinary Tract Disturbances** Sulfonamides may precipitate in urine, especially at neutral or acid pH, producing ***crystalluria***, hematuria, or even obstruction. This is rarely a problem with the more soluble sulfonamides (eg, sulfisoxazole). Sulfadiazine when given in large doses, particularly if fluid intake is poor, can cause crystalluria. Crystalluria is treated by administration of sodium bicarbonate to alkalinize the urine and fluids to increase urine flow. Sulfonamides have also been implicated in various types of nephrosis and in allergic nephritis.

B**. Hematopoietic Disturbances** Sulfonamides can cause hemolytic or aplastic anemia, granulocytopenia, thrombocytopenia, or leukemoid reactions. Sulfonamides may provoke hemolytic reactions in patients with glucose-6-phosphate dehydrogenase deficiency. Sulfonamides taken near the end of pregnancy increase the risk of kernicterus in newborns.

FLUOROQUINOLONES

The important quinolones are synthetic fluorinated analogs of nalidixic acid: Noefloxacin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, gemifloxacin . They are active against a variety of gram-positive and gram-negative bacteria.

Mechanism of Action 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. Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division.



Antibacterial Activity Earlier quinolones such as nalidixic acid did not achieve systemic antibacterial levels and were useful only in the treatment of lower urinary tract infections. Fluorinated derivatives (ciprofloxacin, levofloxacin, and others) have greatly improved antibacterial activity compared with nalidixic acid and achieve bactericidal levels in blood and tissues.

Fluoroquinolones were originally developed because of their excellent activity against ***gram-negative aerobic*** bacteria; they had limited activity against gram-positive organisms. Several newer agents have improved activity against gram positive cocci.

Norfloxacin is the least active of the fluoroquinolones against both gram-negative and gram-positive organisms. Ciprofloxacin, enoxacin, lomefloxacin, levofloxacin, ofloxacin, and pefloxacin comprise a second group of similar agents possessing excellent gram-negative activity and moderate to good activity against gram-positive bacteria. Methicillin-susceptible strains of S aureus are generally susceptible to these fluoroquinolones, but methicillin-resistant strains of staphylococci are often resistant. Streptococci and enterococci tend to be less susceptible than staphylococci, and efficacy in infections caused by these organisms is limited. Ciprofloxacin is the most active agent of this group against gram-negative organisms, P aeruginosa in particular. Levofloxacin, the L-isomer of ofloxacin, has superior activity against gram-positive organisms, including Streptococcus pneumoniae. Gatifloxacin, gemifloxacin, and moxifloxacin make up a third group of fluoroquinolones with improved activity against gram-positive organisms, particularly S pneumoniae and some staphylococci. Fluoroquinolones also are active against agents of atypical pneumonia (eg, mycoplasmas and

chlamydiae) and against intracellular pathogens such as Legionella and some mycobacteria, including Mycobacterium tuberculosis and Mycobacterium avium complex. Moxifloxacin also has modest activity against anaerobic bacteria. .

Resistance During fluoroquinolone therapy, resistant organisms emerge in about one of every 107–109 organisms, especially among staphylococci, P aeruginosa, and Serratia marcescens. Resistance is due to one or more point mutations in the quinolone binding region of the target enzyme or to a change in the permeability of the organism.

Pharmacokinetics After oral administration, the fluoroquinolones are well absorbed (bioavailability of 80–95%) and distributed widely in body fluids and tissues. The relatively long half-lives of levofloxacin, gemifloxacin, gatifloxacin, and moxifloxacin permit once-daily dosing. Oral absorption is impaired by divalent and trivalent cations, including those in antacids. Therefore, oral fluoroquinolones should be taken 2 hours before or 4 hours after any products containing these cations. Serum concentrations of intravenously administered drug are similar to those of orally administered drug. Most fluoroquinolones are eliminated by renal mechanisms, either tubular secretion or glomerular filtration.

Clinical Uses Fluoroquinolones (other than moxifloxacin, which achieves relatively low urinary levels) are effective in urinary tract infections caused by many organisms, including P aeruginosa. These agents are also effective for bacterial diarrhea caused by Shigella, Salmonella, toxigenic E coli, and Campylobacter. Fluoroquinolones (except norfloxacin, which does not achieve adequate systemic concentrations) have been used in infections of soft tissues, bones, and joints and in intraabdominal and respiratory tract infections, including those caused by multidrug-resistant organisms such as Pseudomonas and Enterobacter. Ciprofloxacin, levofloxacin, or moxifloxacin is occasionally used for treatment of tuberculosis and atypical mycobacterial infections.

These agents are suitable for eradication of meningococci from carriers and for prophylaxis of infection in neutropenic cancer patients. With their enhanced gram-positive activity and activity against atypical pneumonia agents (chlamydiae, Mycoplasma, and Legionella), levofloxacin, gatifloxacin, gemifloxacin, and moxifloxacin—so-called respiratory fluoroquinolones—are effective and used increasingly for treatment of upper and lower respiratory tract infections.

Adverse Effects Fluoroquinolones are generally well tolerated. The most common effects are nausea, vomiting, and diarrhea. Occasionally, headache, dizziness, insomnia, skin rash, or abnormal liver function tests develop. ***Photosensitivity*** has been reported with lomefloxacin and pefloxacin. Prolongation of the ***QTc*** interval may occur with gatifloxacin, levofloxacin, gemifloxacin, and moxifloxacin. Gatifloxacin has been associated with ***hyperglycemia in diabetic patients*** and with

hypoglycemia in patients also receiving oral hypoglycemic agents. Because of these serious effects (including some fatalities). Fluoroquinolones may damage ***growing cartilage and cause an arthropathy***. Thus, these drugs are not routinely recommended for patients under 18 years of age. Tendonitis, a rare complication that has been reported in adults, is potentially more serious because of the risk of tendon rupture. Risk factors for tendonitis include advanced age, renal insufficiency, and concurrent steroid use. Fluoroquinolones should be avoided during pregnancy. Oral or intravenously administered fluoroquinolones have also been associated with peripheral neuropathy. Neuropathy can occur at any time during treatment with fluoroquinolones and may persist for months to years after the drug is stopped.

ANTI-MYCOBACTERIAL DRUGS

Mycobacteria are intrinsically resistant to most antibiotics. Because they grow more slowly than other bacteria, antibiotics that are most active against rapidly growing cells are relatively ineffective. Mycobacterial cells can also be dormant and thus completely resistant to many drugs or killed only very slowly. The lipid-rich mycobacterial cell wall is impermeable to many agents. Mycobacterial species are intracellular pathogens, and organisms residing within macrophages are inaccessible to drugs that penetrate these cells poorly. Finally, mycobacteria are notorious for their ability to develop resistance. Combinations of two or more drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of therapy. The response of mycobacterial infections to chemotherapy is slow, and treatment must be administered for months to years, depending on which drugs are used.

ANTI-TUBERCULOSIS DRUGS

The drugs for TB are most commonly divided into two groups: first-line drugs and second-line drugs. For most purposes, knowledge of the first-line drugs is adequate.

A) 1-ST LINE DRUGS: ISONIAZID, RIFAMPICIN, PYRAZINAMIDE, ETHAMBUTOL AND STRETPMYCIN
B) SECOND-LINE DRUG: AMIKACIN, CAPREOMYCIN, CYCLOSERINE, ETHIONAMIDE, KANAMYCIN, LEVOFLOXACIN, MOXIFLOXACIN, RIFABUTIN. RIFAPENTINE, STREPTOMYCIN, AMINOSALICYLIC ACID,

Isoniazid, along with rifampin, is one of the two most important TB drugs.

ISONIAZID

Isoniazid is the most active drug for the treatment of tuberculosis caused by susceptible strains. It is a small molecule (MW 137) that is freely soluble in water. The structural similarity to pyridoxine is shown below.

Mechanism of action: Isoniazid inhibits synthesis of mycolic acids, which are essential components of mycobacterial cell walls. Isoniazid is a prodrug that is activated by KatG, the mycobacterial catalase-peroxidase. The activated form of isoniazid forms a covalent complex with an acyl carrier protein (AcpM) and KasA, a beta-ketoacyl carrier protein synthetase, which blocks mycolic acid synthesis.

Antibacterial spectrum: Isoniazid is specific for treatment of M. tuberculosis, although M. kansasii may be susceptible at higher drug concentrations. Most NTM are resistant to INH. The drug is particularly effective against rapidly growing bacilli and is also active against intracellular organisms

Resistance: Resistance to isoniazid is associated with mutations resulting in overexpression of inhA, which encodes an NADH-dependent acyl carrier protein reductase; mutation or deletion of the katG gene; promoter mutations resulting in overexpression of ahpC, a gene involved in protection of the cell from oxidative stress; and mutations in kasA. Overproducers of inhA express low-level isoniazid resistance and cross-resistance to ethionamide. KatG mutants express high-level isoniazid resistance and often are not cross-resistant to ethionamide.

Pharmacokinetics: Isoniazid is readily absorbed after oral administration. Absorption is impaired if isoniazid is taken with food, particularly high-fat meals. Isoniazid undergoes N-acetylation and hydrolysis, resulting in inactive products. Metabolism of isoniazid, especially acetylation by liver N-acetyltransferase, is genetically determined (the fast acetylators exhibiting a 90-minute serum half-life, as compared to 3 to 4 hours for slow acetylators).

Adverse effects:

Hepatitis is the most serious adverse effect associated with isoniazid.

Peripheral neuropathy (manifesting as paresthesia of the hands and feet) appears to be due to a relative pyridoxine deficiency. This can be avoided by supplementation of 25 to 50 mg per day of pyridoxine (vitamin B6).

Central nervous system (CNS) adverse effects can occur, including convulsions in patients prone to seizures.

Hypersensitivity reactions with isoniazid include rashes and fever.

Isoniazid inhibits the metabolism of carbamazepine and phenytoin (can potentiate the adverse effects of these drugs).

RIFAMPIN is a semisynthetic derivative of rifamycin, an antibiotic produced by Streptomyces mediterranei. It is active in vitro against gram-positive and gram-negative cocci, some enteric bacteria, mycobacteria, and chlamydiae.

Mechanism of Action Rifampin binds to the β subunit of bacterial DNA-dependent RNA polymerase and thereby inhibits RNA synthesis. Rifampin is bactericidal for mycobacteria.

Resistance results from any one of several possible point mutations in rpoB, the gene for the β subunit of RNA polymerase. These mutations result in reduced binding of rifampin to RNA polymerase. Human RNA polymerase does not bind rifampin and is not inhibited by it.

Pharmacokinetics It readily penetrates most tissues and penetrates into phagocytic cells. It can kill organisms that are poorly accessible to many other drugs, such as intracellular organisms and those sequestered in abscesses and lung cavities. Rifampin is well absorbed after oral administration and excreted mainly through the liver into bile. Rifampin is distributed widely in body fluids and tissues. The drug is relatively highly protein-bound, and adequate cerebrospinal fluid concentrations are achieved only in the presence of meningeal inflammation.

Adverse Reactions Rifampin imparts a harmless orange color to urine, sweat, and tears (soft contact lenses may be permanently stained). Occasional adverse effects include rashes, thrombocytopenia, and nephritis. Rifampin may cause cholestatic jaundice and occasionally hepatitis, and it commonly causes light-chain proteinuria. If administered less often than twice weekly, rifampin may cause a ***flu-like syndrome*** characterized by fever, chills, myalgias, anemia, and thrombocytopenia. Its use has been associated with acute tubular necrosis. Rifampin strongly ***induces most cytochrome P450 isoforms*** (CYP1A2, 2C9, 2C19, 2D6, and 3A4), which increases the elimination of numerous other drugs including methadone, anticoagulants, cyclosporine, some anticonvulsants, protease inhibitors, some nonnucleoside reverse transcriptase inhibitors, contraceptives.

Ethambutol is a synthetic, water-soluble, heat-stable compound, the dextro-isomer of the structure shown below, dispensed as the dihydrochloride salt.

Mechanism of Action & Clinical Uses . Ethambutol inhibits mycobacterial arabinosyl transferases, which are encoded by the embCAB operon. Arabinosyl transferases are involved in the polymerization reaction of arabinoglycan, an essential component of the mycobacterial cell wall.

Resistance to ethambutol is due to mutations resulting in overexpression of emb gene products or within the embB structural gene. As with all antituberculous drugs, resistance to ethambutol emerges rapidly when the drug is used alone. Therefore, ethambutol is always given in combination with other antituberculous drugs.

Pharmacokinetics. Is well absorbed from the gut. After ingestion of 25 mg/kg, a blood level peak of 2–5 mcg/mL is reached in 2–4 hours. About 20% of the drug is excreted in feces and 50% in urine in unchanged form. Ethambutol accumulates in renal failure, and the dose should be reduced by half if creatinine clearance is less than 10 mL/min. Ethambutol crosses the blood-brain barrier only when the meninges are inflamed.

Adverse Reactions. Hypersensitivity to ethambutol is rare. The most common serious adverse event is ***retrobulbar neuritis,*** resulting in loss of visual acuity and red-green color blindness.

Pyrazinamide is a relative of nicotinamide, and it is used only for treatment of tuberculosis. It is stable and slightly soluble in water. It is inactive at neutral pH, but at pH 5.5 it inhibits tubercle bacilli at concentrations of approximately 20 mcg/mL. The drug is taken up by macrophages and exerts its activity against mycobacteria residing within the acidic environment of lysosomes.

Mechanism of Action. Pyrazinamide is converted to pyrazinoic acid—the active form of the drug—by mycobacterial pyrazinamidase, which is encoded by pncA. Pyrazinoic acid disrupts mycobacterial cell membrane metabolism and transport functions.

Resistance may be due to impaired uptake of pyrazinamide or mutations in pncA that impair conversion of pyrazinamide to its active form.

Adverse Reactions Major adverse effects include hepatotoxicity (in 1–5% of patients), nausea, vomiting, drug fever, and ***hyperuricemia.*** The latter occurs uniformly and is not a reason to halt therapy.

SECOND-LINE DRUGS FOR TUBERCULOSIS

The alternative drugs listed below are usually considered only in case of:

- resistance to first-line agents;
- failure of clinical response to conventional therapy
- serious treatment-limiting adverse drug reactions.

Ethionamide is chemically related to isoniazid and similarly blocks the synthesis of mycolic acids. It is poorly water soluble and available only in oral form. It is

metabolized by the liver. Ethionamide is hepatotoxic. Neurologic symptoms may be alleviated by pyridoxine. Resistance to ethionamide as a single agent develops rapidly in vitro and in vivo. There can be low-level crossresistance between isoniazid and ethionamide.

Cycloserine is an inhibitor of cell wall synthesis. As a cyclic analogue of D-alanine, cycloserine acts against two crucial enzymes important in the cytosolic stages of peptidoglycan synthesis: alanine racemase (Alr) and D-alanine:D-alanine ligase (Ddl).

The most serious toxic effects are peripheral neuropathy and central nervous system dysfunction, including depression and psychotic reactions. Pyridoxine, 150 mg/d, should be given with cycloserine because this ameliorates neurologic toxicity.

Aminosalicylic Acid (PAS) Aminosalicylic acid is a folate synthesis antagonist that is active almost exclusively against M tuberculosis. It is structurally similar to p-amino-benzoic acid (PABA) and to the sulfonamides.

.Aminosalicylic acid is readily absorbed from the gastrointestinal tract. The drug is widely distributed in tissues and body fluids except the cerebrospinal fluid. Aminosalicylic acid is rapidly excreted in the urine, in part as active PAS and in part as the acetylated compound and other metabolic products. Very high concentrations of aminosalicylic acid are reached in the urine, which can result in ***crystalluria.*** Aminosalicylic acid is used infrequently because other oral drugs are better tolerated. Gastrointestinal symptoms are common and may be diminished by giving the drug with meals and with antacids. Peptic ulceration and hemorrhage may occur. Hypersensitivity reactions manifested by fever, joint pains, skin rashes, hepatosplenomegaly, hepatitis, adenopathy, and granulocytopenia often occur after 3–8 weeks of PAS therapy, making it necessary to stop administration temporarily or permanently.

Kanamycin & Amikacin- aminoglycoside antibiotics . Kanamycin had been used for treatment of tuberculosis caused by streptomycin-resistant strains, but the availability of less toxic alternatives (eg, capreomycin and amikacin) has rendered it obsolete. Amikacin is playing a greater role in the treatment of tuberculosis due to the prevalence of multidrug-resistant strains. .

Fluoroquinolones In addition to their activity against many gram-positive and gram-negative bacteria, ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin inhibit strains of M tuberculosis at concentrations less than 2 mcg/mL. . Fluoroquinolones are an important addition to the drugs available for tuberculosis, especially for strains that are resistant to first-line agents.

Resistance, which may result from one of several single point mutations in the gyrase A subunit, develops rapidly if a fluoroquinolone is used as a single agent; thus, the drug must be used in combination with two or more other active agents. .

TREATMENT REGIMEN OF TUBERCULOSIS:

1. Unsupervised regimen: drugs are taken by the patient himself daily. The drugs are isoniazid (INH) and rifampicin for 6 months, plus pyrazinamide for the first 2 months.

2. DOTs (directly observed treatment short course). Drugs are given under supervision of a health provider to improve compliance: Thrice weekly INH and rifampicin for 6 months, plus pyrazinamide for the first 2 months.

- With both regimen , ethambutol or streptomycin must be added if there is a possibility of drug resistant organism or if the patient is severely ill with extensive active lesions

- The initial 2 months three drugs treatment phase aim to reduce number of bacilli as rapidly as possible and render the sputum noninfectious. The use of rifampicin and INH for 4 additional months aims to eliminate the remaining intracellular bacteria and prevent relapse.

Chemoprophylaxis for tuberculosis For symptom- free persons in contact with disease, who develop a positive tuberculin test.

- INH twice weekly for 9 months

- Rifampicin daily for 4 months

DRUGS USED IN LEPROSY .

DAPSONE & OTHER SULFONES Several drugs closely related to the sulfonamides have been used effectively in the long-term treatment of leprosy. The most widely used is dapsone (diaminodiphenylsulfone). Like the sulfonamides, it inhibits folate synthesis. Resistance can emerge in large populations of M leprae, eg, in lepromatous leprosy, particularly if low doses are given. Therefore, the combination of dapsone, rifampin, and clofazimine is recommended for initial therapy of lepromatous leprosy. A combination of dapsone plus rifampin is commonly used for leprosy with a lower organism burden. Dapsone may also be used to prevent and treat Pneumocystis jiroveci pneumonia in AIDS patients.

Sulfones are well absorbed from the gut and widely distributed throughout body fluids and tissues. Dapsone’s half-life is 1–2 days, and drug tends to be retained in skin, muscle, liver, and kidney. Skin heavily infected with M leprae may contain

several times more drug than normal skin. Sulfones are excreted into bile and reabsorbed in the intestine.

Dapsone is usually well tolerated. Many patients develop some hemolysis, particularly if they have ***glucose-6phosphate dehydrogenase*** deficiency. ***Methemoglobinemia*** is common but usually is not a problem clinically. Gastrointestinal intolerance, fever, pruritus, and various rashes occur. During dapsone therapy of lepromatous leprosy, erythema nodosum leprosum often develops. It is sometimes difficult to distinguish reactions to dapsone from manifestations of the underlying illness. Erythema nodosum leprosum may be suppressed by thalidomide.

RIFAMPIN Rifampin in a dosage of 600 mg daily is highly effective in leprosy and is given with at least one other drug to prevent emergence of resistance.

CLOFAZIMINE Clofazimine is a phenazine dye used in the treatment of multibacillary leprosy, which is defined as having a positive smear from any site of infection. Its mechanism of action has not been clearly established.

DIUCIFONE is used for treatment of leprosy patients, as well as in treatment of a number of diseases accompanied by immunodeficiency, including dermatosis (skin diseases - psoriasis, scleroderma, etc.); rheumatoid arthritis (infectious allergic disease of collagenosis group characterized by chronic progressive joint inflammation); tuberculosis; tuberculosis and malignant arthritis. Rheumatoid arthritis (an infectious and allergic disease of the collagenosis group, characterized by chronic progressive inflammation of the joints); tuberculosis; chronic nonspecific lung diseases, etc..

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