URINARY TRACT ANTISEPTICS/ANTIMICROBIALS

Escherichia coli is the most common pathogen, causing about 80 percent of uncomplicated upper and lower UTIs. Staphylococcus saprophyticus is the second most common bacterial pathogen causing UTIs, with other common causes including Klebsiella pneumoniae and Proteus mirabilis.

Urinary tract antiseptics, including *methenamine*, *nitrofurantoin*, and the quinolone *nalidixic acid*, do not achieve antibacterial levels in the circulation, but because they are concentrated in the urine, microorganisms at that site can be effectively eradicated.

Methenamine

1. Mechanism of action:

methenamine decompose at an acidic pH of 5.5 or less in the urine, thus producing formaldehyde which acts locally and is toxic to most bacteria. Bacteria do not develop resistance to formaldehyde. *Methenamine* is frequently formulated with a weak acid, such as mandelic acid or hippuric acid.

2. Antibacterial spectrum:

Methenamine is primarily used for chronic suppressive therapy. Urea-splitting bacteria alkalinize the urine, (such as Proteus species), so are usually resistant to the action of *methenamine*.

It is most useful when the causative organism is E. coli.

Pharmacokinetics:

Methenamine is administered orally. *Methenamine* is distributed throughout the body fluids, but no decomposition of the drug occurs at pH 7.4. , thus systemic toxicity does not occur.

The drug is eliminated in the urine.

Adverse effects:

The major side effect is gastrointestinal distress.

At higher doses, albuminuria, hematuria, and rashes may develop.

Methenamine mandelate is **contraindicated** in patients with renal insufficiency, because mandelic acid may precipitate.

In addition to formaldehyde, ammonium ion is produced in the bladder. Because the liver rapidly metabolizes ammonia to form urea, *methenamine* is **contraindicated** in patients with hepatic insufficiency (elevated levels of ammonium ions would be toxic to the CNS).

Sulfonamides must not be used concomitantly with *methenamine*. The combination increases the risk of crystalluria.

It is effective :

1. in treating UTIs (as well as prostatic and vaginal infections)
2. and respiratory tract infections (Haemophilis influenzae and Legionella Pneumophilia) as well as in Pneumocystis jiroveci pneumonia
3. and Gastrointestinal infections including *ampicillin-* or *chloramphenicol*-resistant salmonella infections, shigellosis,
4. meningitis caused by Listeria monocytogenes.
5. skin and soft tissue infections caused by MRSA.
6. It is the drug of choice for infections caused by Nocardia species.

Resistance

Resistance is less frequently encountered than resistance to either of the drugs alone, because it would require that the bacterium have simultaneous resistance to both drugs.

Pharmacokinetics

Trimethoprim is more lipid soluble than *sulfamethoxazole* and has a greater volume of distribution. Administration of one part *trimethoprim* to five parts of the sulfa drug produces a ratio of the drugs in the plasma of twenty parts *sulfamethoxazole* to one part *trimethoprim*. This ratio is optimal for the antibiotic effect.

Trimethoprim concentrates in the relatively acidic prostatic and vaginal fluids, thus used in infections at these sites. Both parent drugs and their metabolites are excreted in the urine.

Adverse effects

1. Dermatologic: Reactions involving the skin are very common.

2. Gastrointestinal: Nausea, vomiting, as well as, glossitis and stomatitis.

3. Hematologic : Megaloblastic anemia, leukopenia, and thrombocytopenia may occur. Hemolytic anemia may occur in patients with glucose 6-phosphate dehydrogenase deficiency due to the *sulfamethoxazole*.

Drug interactions:

Prolonged prothrombin times occur in patients receiving both *sulfamethoxazole* and *warfarin*. The plasma half-life of *phenytoin* may be increased (inhibition of its metabolism). *Methotrexate* levels may rise (displacement from albumin-binding sites by *sulfamethoxazole*.)

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TRIMETHOPRIM

Trimethoprim, a potent inhibitor of bacterial dihydrofolate reductase, exhibits an antibacterial similar to that of the sulfonamides.

Mechanism of action

The active form of folate (tetrahydro-folate) is formed through reduction of dihydrofolic acid by dihydrofolate reductase. This enzymatic reaction is inhibited by *trimethoprim*, leading to a decreased availability of the tetrahydrofolate coenzymes required for purine, pyrimidine, and amino acid synthesis. The bacterial reductase has a much stronger affinity for *trimethoprim* than does the mammalian enzyme, which accounts for the drug's selective toxicity.

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 UTIs and in the treatment of bacterial prostatitis (although fluoroquinolones are preferred) and vaginitis.

Resistance

1. presence of an altered dihydrofolate reductase that has a lower affinity for *trimethoprim*.
2. Overproduction of the enzyme may also lead to resistance.

Pharmacokinetics

Because the drug is a weak base, higher concentrations of *trimethoprim* are achieved in the relatively acidic prostatic and vaginal fluids. Most excreted unchanged through the kidney.

Adverse effects

Trimethoprim can produce the effects of folic acid deficiency. These effects include megaloblastic anemia, leukopenia, and granulocytopenia.

COTRIMOXAZOLE

The combination of *trimethoprim* with *sulfamethoxazole* [*cotrimoxazole*], shows greater antimicrobial activity than equivalent quantities of either drug used alone (synergistic activity)

Antibacterial spectrum

Includes : Gram positive : Listeria monocytogenes. Gram negative rods (E coli, H influenza, Salmonella typhi, Legionella Pneumophilia, Shigella, Proteus mirablis). Other : Pneumocystis jiroveci.

Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs.

Pharmacokinetics

1. Administration: Most sulfa drugs are well absorbed.

Because of the risk of sensitization, sulfas are not usually applied topically. However, creams of *silver sulfadiazine* or *mafenide acetate* are effective in reducing burn-associated sepsis.

Distribution:

Sulfa drugs are bound to serum albumin in the circulation, the smaller the pKa value, the greater the EXTENT OF binding.

Sulfa drugs penetrate well into cerebrospinal fluid. They can also pass the placental barrier.

Metabolism:

The sulfa drugs are acetylated, primarily in the liver to inactive metabolite, metabolite precipitate at neutral or acidic pH. This causes crystalluria.

Excretion: Sulfa drugs are eliminated by glomerular filtration. Depressed kidney function necessitates dose adjustment.

Adverse effects

1. Crystalluria: Nephrotoxicity develops as a result of crystalluria. Agents, such as *sulfisoxazole* and *sulfamethoxazole* are more soluble at urinary pH than are the older sulfonamides (for example, *sulfadiazine*) and are less liable to cause crystalluria.

2. Hypersensitivity: Hypersensitivity reactions include rashes, angioedema, and Stevens-Johnson syndrome.

3. Hemopoietic disturbances: Hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase deficiency. Granulocytopenia and thrombocytopenia can also occur.

4. Kernicterus: is a bilirubin-induced brain dysfunction. Bilirubin is a highly neurotoxic substance. This disorder may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin pass into the CNS, because the baby's blood brain barrier is not fully developed.

5. Drug interaction: potentiation of the effect of *warfarin* (displacement from binding sites on serum albumin). Free *methotrexate* levels may also rise through displacement.

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. Because sulfonamides condense with formaldehyde, they should not be given to patients receiving *methenamine* for UTIs.