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MEDICINAL CHEMISTRY - III

UNIT 3

TOPIC :

- **Miscellaneous :** *Furazolidine, Nitrofurantoin*, Methanamine.

Miscellaneous Urinary Tract Anti-Infective Agents

- Miscellaneous urinary tract anti-infectives are drugs used to treat UTIs that do not belong to the main antibiotic classes (like quinolones, sulfonamides, or beta-lactams).
- They have specific activity in the urinary tract due to high renal excretion or selective bacterial targeting.

Common Drugs

- **Nitrofurantoin**
- **Fosfomycin**
- **Methenamine**

Mechanism of Action

A. Nitrofurantoin

- Reduced by bacterial flavoproteins
- Produces reactive intermediates → damages DNA, proteins, and cell wall
- Effective mainly in urinary tract (rapid renal excretion)
- Bactericidal at urinary concentrations

B. Fosfomycin

- Inhibits enolpyruvate transferase
- Blocks formation of N-acetylmuramic acid → prevents peptidoglycan synthesis
- Bactericidal against Gram-negative and some Gram-positive bacteria

C. Methenamine

- Hydrolyzed in acidic urine to formaldehyde
- Denatures bacterial proteins
- Effective as urinary antiseptic (not systemic)

Spectrum of Activity

- Nitrofurantoin → E. coli, Enterococcus, Staphylococcus saprophyticus
- Fosfomycin → E. coli, Enterococcus, Klebsiella, Proteus
- Methenamine → Broad-spectrum urinary antiseptic, mainly prophylactic

Therapeutic Uses

- Nitrofurantoin → Uncomplicated UTIs, cystitis
- Fosfomycin → Single-dose therapy for uncomplicated UTIs
- Methenamine → Prophylaxis in recurrent UTIs

Adverse Effects

Drug	Adverse Effects
Nitrofurantoin	GI disturbances, pulmonary reactions, peripheral neuropathy (long-term)
Fosfomycin	Mild GI upset, diarrhea
Methenamine	Nausea, bladder irritation, hematuria (rare)

Contraindications

- Nitrofurantoin → Renal impairment (CrCl < 30 mL/min)
- Methenamine → Renal or hepatic failure
- Fosfomycin → Generally safe, avoid in hypersensitivity

Advantages

- Highly effective in urinary tract infections
- Nitrofurantoin & Fosfomycin → concentrate in urine
- Methenamine → Prevents recurrent UTIs

Furazolidine

- Furazolidine is a synthetic nitrofuran derivative with broad-spectrum antibacterial and antiprotozoal activity.
- It is bactericidal and amoebicidal, primarily used for gastrointestinal infections.
- Furazolidine acts by interfering with bacterial enzyme systems and DNA synthesis.

Classification

Based on Chemical Class

- Nitrofuran derivative

Based on Antibacterial Action

- Bactericidal

Based on Use

- Antidiarrheal and antiprotozoal agent

Structure

- Contains a furan ring with a nitro group at C-5.
- Hydrazine or side chain attached at C-2 contributes to activity.

Molecular formula: $C_8H_7N_3O_5$

Structural Characteristics

- Nitro group → essential for antimicrobial activity
- Furan ring → facilitates interaction with bacterial enzymes

Nomenclature

- Fura → furan ring
- Zolidine → substituted hydrazone moiety
- Available as oral tablets or suspension

Mechanism of Action

- Furazolidine is reduced in the bacterial cell by nitroreductase enzymes.
- Generates reactive intermediates that bind to bacterial proteins and DNA.
- Inhibits enzyme activity and DNA synthesis, leading to bacterial and protozoal cell death.
- Hence, furazolidine is bactericidal and antiprotozoal.

Spectrum of Activity

- Gram-positive bacteria: *Staphylococcus aureus, Streptococcus* spp.
- Gram-negative bacteria: *Escherichia coli, Salmonella spp., Shigella spp.*
- Protozoa: *Giardia lamblia, Entamoeba histolytica*

Uses

- Diarrhea and dysentery caused by bacteria or protozoa
- Giardiasis
- Amebiasis (intestinal)
- Occasionally used for prophylaxis in travelers' diarrhea

Adverse Effects

- Gastrointestinal: nausea, vomiting, abdominal discomfort
- Rare: allergic reactions, fever
- Can cause dark urine
- Avoid alcohol → may cause disulfiram-like reaction
- Contraindicated in pregnancy and infants

Chemical Degradation

- Sensitive to light and moisture
- Stable in acidic medium
- Store in cool, dry, and dark place

Structure–Activity Relationship (SAR)

- Nitro group at C-5 → essential for antimicrobial activity
- Furan ring → facilitates enzyme interaction
- Reduction in bacterial cell → formation of reactive intermediates → DNA and protein damage

Nitrofurantoin

- Nitrofurantoin is a synthetic nitrofuran derivative used primarily as a urinary tract antiseptic.
- It is bactericidal in urine and acts by interfering with bacterial enzyme systems and DNA synthesis.
- Nitrofurantoin is effective mainly against Gram-positive and Gram-negative urinary pathogens and is concentrated in the urine due to renal excretion.

Classification

Based on Chemical Class

- Nitrofuran derivative

Based on Antibacterial Action

- Bactericidal (in urine)
- Bacteriostatic at low concentrations

Based on Use

- Urinary tract anti-infective agent

Structure

- Contains a furan ring with a nitro group at C-5.
- Hydantoin or substituted side chain at C-2 contributes to activity.

Molecular formula: $C_8H_6N_4O_5$

Structural Characteristics

- Nitro group → essential for antibacterial activity
- Furan ring → facilitates interaction with bacterial enzymes
- Side chain → influences urinary excretion and activity

Nomenclature

- Nitro → nitro group

- Furantoin → furan ring + hydantoin derivative
- Available as oral capsules, tablets, and suspension

Mechanism of Action

- Nitrofurantoin is reduced by bacterial nitroreductases.
- Generates reactive intermediates that inhibit bacterial enzymes.
- Interferes with DNA, RNA, and protein synthesis, leading to bacterial cell death.
- Hence, nitrofurantoin is bactericidal in urine.

Spectrum of Activity

- Gram-negative bacteria: *Escherichia coli, Klebsiella spp., Enterobacter spp.*
- Gram-positive bacteria: *Staphylococcus aureus, Enterococcus spp.*
- Minimal activity against anaerobes and systemic infections

Uses

- Acute uncomplicated urinary tract infections (UTIs)
- Chronic UTI prophylaxis
- Cystitis caused by susceptible bacteria

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Pulmonary reactions (rare): acute or chronic pneumonitis
- Peripheral neuropathy (rare, especially in renal impairment)
- Dark-colored urine
- Hypersensitivity reactions: rash, fever

Chemical Degradation

- Sensitive to light and moisture
- Stable in acidic conditions
- Store in cool, dry, and dark place

Structure–Activity Relationship (SAR)

- Nitro group at C-5 → essential for bacterial enzyme inhibition
- Furan ring → facilitates interaction with bacterial enzymes
- Side chain at C-2 → improves urinary excretion and antibacterial activity

- Reduction in bacterial cell → formation of reactive intermediates → DNA, RNA, and protein damage

Methenamine

- Methenamine (also called hexamethylenetetramine) is a urinary antiseptic used to prevent and treat urinary tract infections (UTIs).
- It is bactericidal in acidic urine and works by releasing formaldehyde, which kills bacteria.
- Methenamine is considered a prodrug, inactive in blood but active in acidic urine.

Classification

Based on Chemical Class

- Urinary tract antiseptic
- Prodrug of formaldehyde

Based on Antibacterial Action

- Bactericidal in acidic urine
- Broad spectrum against Gram-positive and Gram-negative bacteria in urine

Based on Use

- Prophylactic and treatment agent for UTIs

Structure

- Methenamine is a hexamethylenetetramine: a tetraaza cyclohexane ring

Molecular formula: $C_6H_{12}N_4$

Structural Characteristics

- Stable at neutral pH
- Breaks down to formaldehyde in acidic environment (urine)

Nomenclature

- Methenamine → derived from methylene and amine groups
- Available as oral tablets or capsules

Mechanism of Action

- Methenamine is hydrolyzed in acidic urine to release formaldehyde.
- Formaldehyde denatures bacterial proteins and damages bacterial DNA.
- Leads to bacterial cell death in the urinary tract.
- Hence, methenamine is a urinary bactericidal antiseptic.

Spectrum of Activity

- Gram-negative bacteria: *Escherichia coli, Klebsiella spp., Proteus spp.*
- Gram-positive bacteria: *Staphylococcus aureus, Enterococcus spp.*
- Inactive in systemic infections because it is not bactericidal in blood or neutral pH

Uses

- Chronic urinary tract infection prophylaxis
- Recurrent UTIs
- Adjunctive therapy for UTIs in patients not responding to conventional antibiotics

Adverse Effects

- Gastrointestinal: nausea, vomiting, dyspepsia
- Rare: rash, headache
- Avoid in renal impairment (urine must be acidic for activity)
- Contraindicated in liver disease with impaired urea metabolism
- Monitor urine pH to ensure efficacy

Chemical Degradation

- Stable in neutral pH, decomposes in acidic conditions to release formaldehyde
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- Tetramine ring → prodrug form

- Acid hydrolysis in urine → releases formaldehyde (active moiety)
- Activity depends on urine pH → must be acidic (pH < 5.5) for bactericidal effect
- Broad-spectrum antibacterial activity limited to urinary tract