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NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
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Bachelor of Pharmacy
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NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
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Bachelor of Pharmacy
Medicinal Chemistry II
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
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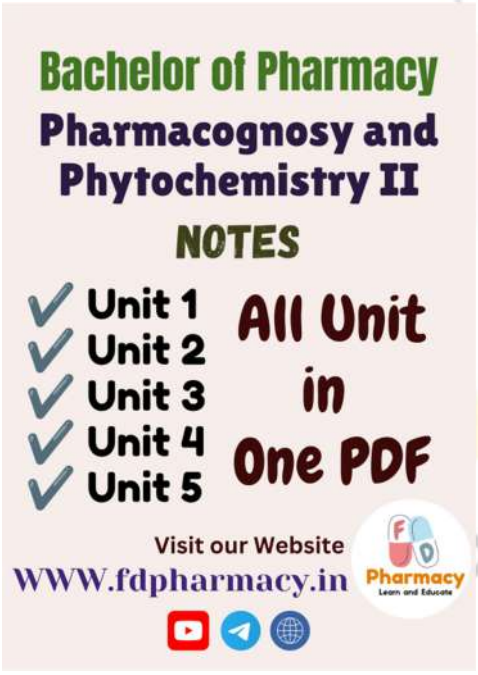
Bachelor of Pharmacy
Pharmacognosy and Phytochemistry II
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
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Bachelor of Pharmacy
Pharmacology II
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
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MEDICINAL CHEMISTRY - II

UNIT 4

TOPIC :

- **Corticosteroids :** Cortisone, Hydrocortisone, Prednisolone, Betamethasone, Dexamethasone

Corticosteroids

- Corticosteroids are steroid hormones produced by the adrenal cortex.
- They are classified into:
  1. Glucocorticoids – regulate carbohydrate metabolism and immune response
  2. Mineralocorticoids – regulate electrolyte and water balance
- Synthetic corticosteroids are widely used in inflammation, autoimmune disorders, allergies, and adrenal insufficiency.

Classification

Class	Examples	Primary Action
Glucocorticoids	Hydrocortisone, Prednisone, Dexamethasone	Anti-inflammatory, immunosuppressive
Mineralocorticoids	Aldosterone, Fludrocortisone	Sodium retention, potassium excretion
Mixed Action	Cortisone	Moderate glucocorticoid + mineralocorticoid effects

Mechanism of Action

1. Glucocorticoids:
   - Bind cytoplasmic glucocorticoid receptors → translocate to nucleus
   - Regulate transcription of anti-inflammatory proteins (e.g., lipocortin)
   - Suppress pro-inflammatory cytokines and immune cell activation
2. Mineralocorticoids:
   - Bind mineralocorticoid receptors in renal distal tubules
   - Increase Na^+ reabsorption and K^+ excretion → water retention

Pharmacological Effects

A. Glucocorticoids

- Metabolic: ↑ gluconeogenesis, ↑ protein catabolism, ↑ lipolysis
- Anti-inflammatory: Inhibit phospholipase A2 → ↓ prostaglandins & leukotrienes
- Immunosuppressive: Reduce T-cell proliferation and cytokine production
- CNS: Mood elevation or euphoria
- CVS: Maintain vascular tone

B. Mineralocorticoids

- ↑ Na^+ reabsorption → ↑ water retention → ↑ blood pressure
- ↑ K^+ and H^+ excretion → electrolyte balance

Therapeutic Uses

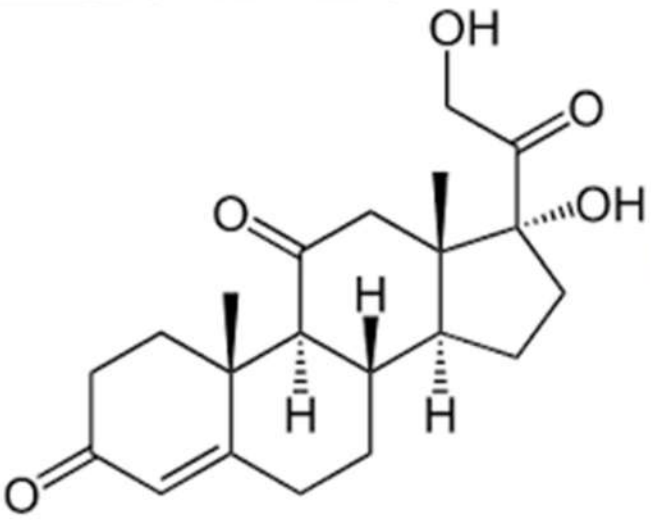
Class	Clinical Use
Glucocorticoids	Asthma, rheumatoid arthritis, lupus, inflammatory bowel disease, organ transplantation, adrenal insufficiency
Mineralocorticoids	Addison's disease, salt-wasting conditions
Short-term use	Acute allergic reactions, shock, cerebral edema
Chronic use	Hormone replacement, autoimmune diseases

Cortisone

- Cortisone is a glucocorticoid steroid hormone naturally produced by the adrenal cortex.
- It is a prodrug, converted in the liver to cortisol (hydrocortisone), which exerts the anti-inflammatory and immunosuppressive effects.
- Synthetic cortisone is used in treating adrenal insufficiency, inflammatory disorders, and autoimmune diseases.
- Administered orally, intramuscularly, or intravenously.

Chemical Structure

- Chemical name: 17α,21-Dihydroxy-3,11-dioxopregn-4-ene- corticoid
- Molecular formula: $C_{21}H_{28}O_5$
- Molecular weight: 360.44 g/mol
- Chemical class: Glucocorticoid; corticosteroid
- Structural



Mechanism of Action

- Target: Glucocorticoid receptors (GR) in cytoplasm of target cells

Stepwise Mechanism:

1. Cortisone is converted to cortisol by 11β-hydroxysteroid dehydrogenase in the liver.
2. Cortisol binds to cytoplasmic glucocorticoid receptors, forming a hormone-receptor complex.

3. The complex translocates into the nucleus → binds glucocorticoid response elements (GREs) on DNA.
4. Modulates transcription of target genes → anti-inflammatory and immunosuppressive effects:
    - Suppresses pro-inflammatory cytokines
    - Inhibits leukocyte migration and function
    - Reduces vascular permeability
    - Alters carbohydrate, protein, and fat metabolism

Synthesis

1. Starting material: Corticosterone or similar steroid intermediates
2. Step 1: Oxidation at C11 to form ketone
3. Step 2: Oxidation at C3, introduction of C4–C5 double bond
4. Step 3: Purification and crystallization → pharmaceutical-grade cortisone

Uses

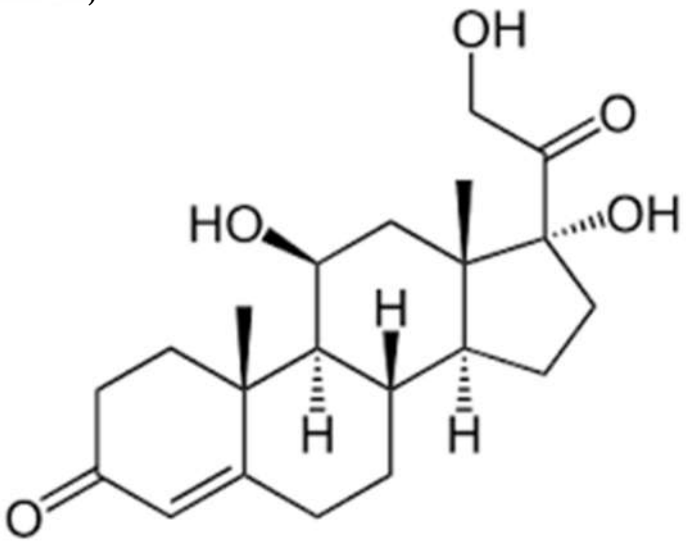
- Therapeutic Uses:
    1. Adrenal insufficiency (Addison's disease)
    2. Anti-inflammatory therapy (arthritis, bursitis, asthma)
    3. Allergic conditions (anaphylaxis, severe dermatitis)
    4. Autoimmune disorders (lupus, multiple sclerosis)
    5. Adjunct therapy in certain cancers (lymphomas)

Hydrocortisone

- Hydrocortisone (also known as cortisol) is a natural glucocorticoid steroid hormone produced by the adrenal cortex.
- It exhibits anti-inflammatory, immunosuppressive, and metabolic effects.
- Clinically used for adrenal insufficiency, inflammatory disorders, and allergic reactions.
- Available in oral, topical, and parenteral formulations.

Chemical Structure

- Chemical name: 11β,17α,21-Trihydroxypregn-4-ene-3,20-dione
- Molecular formula: $C_{21}H_{30}O_5$
- Molecular weight: 362.46 g/mol
- Chemical class: Glucocorticoid; corticosteroid
- Structural



Mechanism of Action

- Target: Glucocorticoid receptors (GR) in cytoplasm of target cells

Stepwise Mechanism:

1. Hydrocortisone binds to cytoplasmic glucocorticoid receptors → forms hormone-receptor complex.
2. Complex translocates into the nucleus → binds glucocorticoid response elements (GREs) on DNA.

3. Modulates transcription of target genes → physiological effects:
    - Anti-inflammatory: Suppresses cytokines, chemokines, leukocyte migration
    - Immunosuppressive: Reduces immune responses
    - Metabolic: Increases gluconeogenesis, protein catabolism, fat redistribution
    - Cardiovascular: Maintains vascular tone and responsiveness

Synthesis

1. Starting material: Pregnenolone or related steroid precursors
2. Step 1: Hydroxylation at C11, C17, and C21
3. Step 2: Ketone formation at C3 and C20, double bond at C4–C5
4. Step 3: Purification → pharmaceutical-grade hydrocortisone

Uses

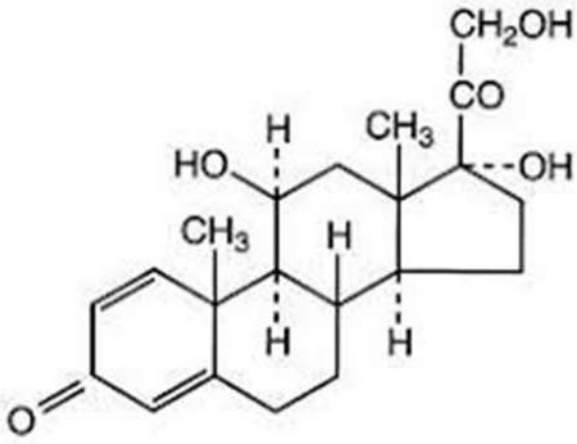
- Therapeutic Uses:
    1. Adrenal insufficiency (Addison's disease, adrenal crisis)
    2. Anti-inflammatory therapy (arthritis, asthma, dermatitis)
    3. Allergic conditions (anaphylaxis, severe eczema)
    4. Autoimmune diseases (lupus, multiple sclerosis)
    5. Shock or severe inflammation in ICU settings

Prednisolone

- Prednisolone is a synthetic glucocorticoid corticosteroid derived from cortisol (hydrocortisone).
- It exhibits potent anti-inflammatory, immunosuppressive, and metabolic effects.
- Prednisolone is more potent than hydrocortisone (≈4–5 times) with less mineralocorticoid activity, reducing fluid retention.
- Administered orally, intravenously, intramuscularly, and topically for various inflammatory and autoimmune conditions.

Chemical Structure

- Chemical name: 11β,17α,21-Trihydroxypregna-1,4-diene-3,20-dione
- Molecular formula: $C_{21}H_{28}O_5$
- Molecular weight: 360.44 g/mol
- Chemical class: Synthetic glucocorticoid; corticosteroid
- Structural



Mechanism of Action

- Target: Glucocorticoid receptors (GR) in cytoplasm of target cells

Stepwise Mechanism:

1. Prednisolone binds to cytoplasmic glucocorticoid receptors → forms hormone-receptor complex.

2. Complex translocates into the nucleus → binds glucocorticoid response elements (GREs) on DNA.
3. Modulates transcription of target genes → physiological effects:
    - Anti-inflammatory: Suppresses cytokine and prostaglandin synthesis, inhibits leukocyte migration
    - Immunosuppressive: Reduces T-cell and B-cell activity
    - Metabolic: Increases gluconeogenesis, protein catabolism, and lipolysis
    - Other: Maintains vascular tone, stabilizes lysosomal membranes

Synthesis

1. Starting material: Cortisone or hydrocortisone
2. Step 1: Introduction of C1–C2 double bond (dehydrogenation) → increases glucocorticoid potency
3. Step 2: Purification → Prednisolone in pharmaceutical grade

Uses

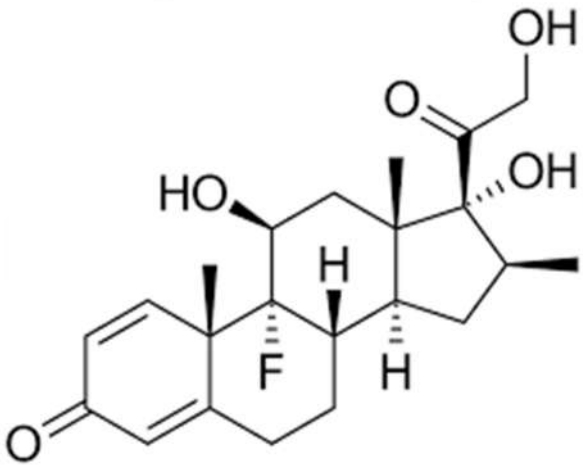
- Therapeutic Uses:
    1. Inflammatory disorders (arthritis, asthma, dermatitis)
    2. Autoimmune diseases (lupus, multiple sclerosis)
    3. Allergic conditions (anaphylaxis, severe urticaria)
    4. Adrenal insufficiency (alternative to hydrocortisone)
    5. Certain cancers (lymphoma, leukemia, as part of chemotherapy protocols)

Betamethasone

- Betamethasone is a synthetic glucocorticoid corticosteroid with potent anti-inflammatory and immunosuppressive activity.
- It is more potent than hydrocortisone and prednisolone and has minimal mineralocorticoid activity, reducing fluid retention.
- Clinically used for inflammatory, allergic, dermatologic, and autoimmune disorders, as well as adrenal insufficiency.
- Available in oral, parenteral, topical, and inhalation formulations.

Chemical Structure

- Chemical name: 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione
- Molecular formula: $C_{22}H_{29}FO_5$
- Molecular weight: 392.47 g/mol
- Chemical class: Synthetic glucocorticoid; fluorinated corticosteroid
- Structural



Mechanism of Action

- Target: Glucocorticoid receptors (GR) in cytoplasm of target cells

Stepwise Mechanism:

1. Betamethasone binds to cytoplasmic glucocorticoid receptors → forms hormone-receptor complex.

2. Complex translocates into the nucleus → binds glucocorticoid response elements (GREs) on DNA.
3. Modulates transcription of target genes → physiological effects:
    - Anti-inflammatory: Suppresses cytokine, prostaglandin, and leukotriene synthesis, inhibits leukocyte migration
    - Immunosuppressive: Reduces T-cell and B-cell activity
    - Metabolic: Increases gluconeogenesis, protein catabolism, lipolysis
    - Other: Maintains vascular tone, stabilizes lysosomal membranes

Synthesis

1. Starting material: Cortisone, hydrocortisone, or other suitable steroid precursors
2. Step 1: Introduction of fluoro group at C9 → increases anti-inflammatory activity
3. Step 2: Introduction of 16β-methyl group → reduces mineralocorticoid effects
4. Step 3: Formation of C1–C2 double bond → enhances glucocorticoid potency
5. Purification: Crystallization → pharmaceutical-grade betamethasone

Uses

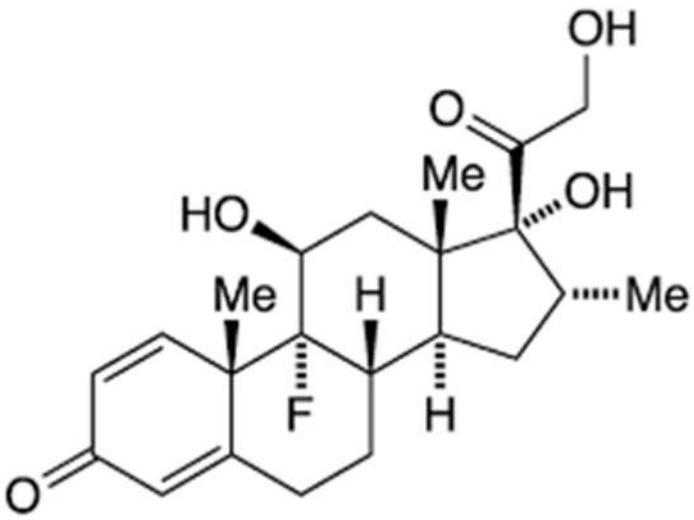
- Therapeutic Uses:
    1. Inflammatory disorders (arthritis, asthma, dermatitis)
    2. Allergic conditions (severe urticaria, anaphylaxis)
    3. Autoimmune diseases (lupus, multiple sclerosis)
    4. Adrenal insufficiency (replacement therapy)
    5. Dermatologic and ocular disorders (eczema, keratitis)
    6. Prenatal use to accelerate fetal lung maturation in preterm labor

Dexamethasone

- Dexamethasone is a synthetic fluorinated glucocorticoid corticosteroid with very potent anti-inflammatory and immunosuppressive activity.
- It has minimal mineralocorticoid activity, reducing fluid retention and hypertension risk.
- Widely used in inflammatory, allergic, autoimmune, and oncologic conditions, and in cerebral edema management.
- Available in oral, injectable, topical, and inhalation formulations.

Chemical Structure

- Chemical name: 9-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione
- Molecular formula: $C_{22}H_{29}FO_5$
- Molecular weight: 392.47 g/mol
- Chemical class: Synthetic glucocorticoid; fluorinated corticosteroid
- Structural



Mechanism of Action

- Target: Glucocorticoid receptors (GR) in cytoplasm of target cells

Stepwise Mechanism:

1. Dexamethasone binds to cytoplasmic glucocorticoid receptors, forming a hormone-receptor complex.

2. The complex translocates to the nucleus → binds glucocorticoid response elements (GREs) on DNA.
3. Modulates transcription of target genes → physiological effects:
    - Anti-inflammatory: Inhibits cytokine, prostaglandin, and leukotriene synthesis; reduces leukocyte migration
    - Immunosuppressive: Suppresses T-cell and B-cell function
    - Metabolic: Stimulates gluconeogenesis, protein catabolism, lipolysis
    - Other: Maintains vascular tone, stabilizes lysosomal membranes

Synthesis

1. Starting material: Cortisone, hydrocortisone, or other suitable steroid precursors
2. Step 1: Introduction of 9-fluoro group → enhances anti-inflammatory activity
3. Step 2: Introduction of 16α-methyl group → reduces mineralocorticoid effects
4. Step 3: Formation of C1–C2 double bond → increases glucocorticoid potency
5. Purification: Crystallization → pharmaceutical-grade dexamethasone

Uses

- Therapeutic Uses:
    1. Inflammatory disorders (arthritis, asthma, dermatitis)
    2. Allergic conditions (anaphylaxis, severe urticaria)
    3. Autoimmune diseases (lupus, multiple sclerosis)
    4. Cerebral edema (brain tumors, trauma)
    5. Oncologic uses (lymphoma, leukemia, as part of chemotherapy regimens)
    6. Adrenal insufficiency (replacement therapy)
    7. Severe COVID-19 or systemic inflammatory conditions