Name of Unit	Drugs acting on Endocrine System, Drugs for Erectile Dysfunction, Oral Contraceptives, Corticosteroids & Thyroid and Anti-Thyroid Drugs
Subject /Course	Medicinal Chemistry-II
Subject/Course ID	BP 501T
Class: B.Pharm. Semester	5th
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Learning Outcome of Module 04

LO	Learning Outcome	Course Outcome Code
LO1	To understand the classification, uses & mechanism of action of Drugs acting on Endocrine System, Drugs for Erectile Dysfunction, Oral Contraceptives, Corticosteroids & Thyroid and Anti-Thyroid Drugs	BP501.1
LO2	To understand the chemical synthesis of selected drugs.	BP501.3
LO3	To understand the Structural Activity Relationship of different class of drugs.	BP501.4
LO4	To understand the biological targets for medicinal compounds	BP501.2

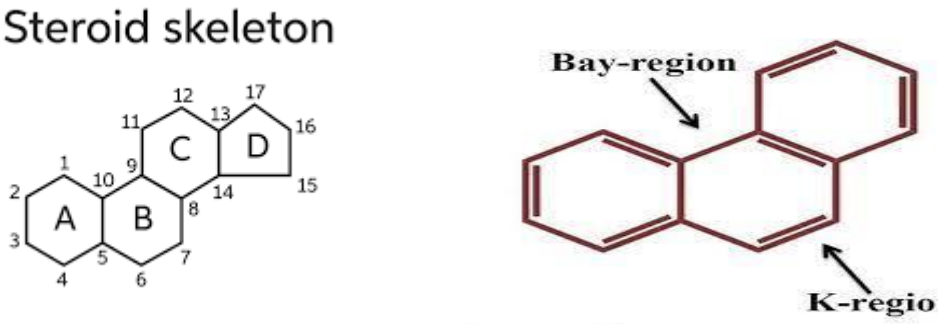
Content Table

STEROIDS

Nomenclature of Steroids

Steroids are made up of four fused rings, i.e., A, B, C, and D. These hydrocarbons are chemically **cyclopentanoperhydrophenanthrenes** and have a **5-membered cyclopentane ring** (D) and **three phenanthrene rings**. A perhydrophenanthrene (rings A, B, and C) is the saturated derivative of phenanthrene.

The polycyclic hydrocarbon is termed **5α-cholestane**. It is used for numbering system of a steroid. It is represented with **5α** since the hydrogen atom at position 5 is on the opposite side of the rings from the angular methyl groups at positions.



18 and 19 on the β side of the molecule. The term **cholestane** is used for a steroid with 27 carbons including a side chain of 8 carbons at position 17 on the β side. Functional groups on the β side of the molecule are shown by solid lines , while the groups on α side are shown by dotted lines. Side chains a t position 17 are always β unless shown by dotted lines or in the steroid nomenclature

Stereochemistry of Steroids

All steroids have a common tetra cyclic nucleus (shown below). The rings A, B and C are 6-membered, while the ring D is 5-membered. The sequence of numbering is shown below. In the structure below, the carbons 5, 8, 9, 10, 13 and 14 are dissimilar asymmetric centers and there is a possibility of having 2^6 =64 stereo isomers.

The situation seems slightly complex and the different functional groups present increases the steric complexity. The rings A/B i n the naturally occurring saturated steroid derivatives are *cis* or *trans* fused, the rings B/C are *trans* fused and the rings C/D are *trans* fused; however in aglycones of cardiac glycosides, the rings C/D are *cis* fused. It has been accepted that a group or hydrogen at a certain position, if shown by continuous thick line or wedge is above the nucleus plane and is indicated as

beta (□); while, a group shown by dotted line is below the nucleus plane and is indicated as alpha (□). **Androstane** is a simple parent hydrocarbon with 19 carbons.

In the structures of **5□- and 5□-androstane** (shown above), rings B/C and C/D are *trans* fused, while the rings A/B are *trans* fused in 5 □-androstane and *cis* fused in 5□-androstane. **Testosterone** (male sex hormone) is the main derivative of androstane.

Estrane has 18 carbons. No angular methyl group is attached to its position 10. The 5□-estrane is also called **19-nor-5□-androstane**. The term **nor** indicates that it has one carbon less; and in this case 19 -carbon (methyl group at 10) is absent. **Estradiol** (the oestrogenic hormone) is derived from estrane. The pregnane hydrocarbon has 21 carbons and position 17 has a two -carbon side chain. **Progesterone** (the progestational hormone) and the **adrenocortical hormones** are pregnane derivatives.

The hydrocarbon **5□-cholane** and **5□-cholestane** are shown below. Cholane has 24 carbons and 5-carbon branched chain at position 17. Cholestane comprises of 27 carbons, and has a 8 -carbon branched chain at position 17. The branching and stereochemistry of the side chains at position 20 and 17 □-disposition of attachment are to be noted. The bile acids are structurally related to cholane and cholesterol (derivative of hydrocarbon cholestane).

Arrangement of various atoms or groups in space is without regard to arrangements that differ after rotation around one or more single bonds. The conformational perspectives of the steroid nucleus can be indicated as the arrangements of molecular atoms in space that is interconverted by rotations about single bonds. The conformational aspects are explained by examining the shapes of **5□-cholestan-3□-ol** and **5□-cholestan-3□-ol**, in which t he rings B and C are locked and both have chair conformations.

The ring A has the flexibility to take boat conformation; however it also has chair conformation. The r ing D is slightly puckered. The conformations of C—H, C—CH3 and C—OH bonds are observed. A bond may be axial (a), parallel to the axis of symmetry of the ring, or equatorial (e), radiating in the plane of the ring.The 5□- and 5 □-cholestan-3□-ol vary with respect to the ir configurations at position 5. In the former, the rings A/B are *trans* fused and in the latter the rings A/B are *cis* fused.

Due to this difference the conformations get disturbed at different ring A positions and this can be seen at positions 3, 5, and 10. The hydroxyl groups at position 3 in both have the same configuration (□), but conformationally the 3□-OH are equatorial and 3 □-H are axial in 5 □-cholestan-3□-ol, while the condition is just the reverse in 5□-cholestan-3□-ol. In 5□-cholestan-3□-ol, 5□-H and 10□-CH3 are axial in relation to rings A and B; while in 5□-cholestan-3□-ol, 5□-H is axial with respect to ring A

and equatorial with respect to ring B; in the same molecule, 10□-CH3 is equatorial with respect to ring A and axial with respect to ring B. Conformational analysis provides a description of 3-D forms of the steroids.

Metabolism of Steroids

The metabolic conversion of a biologically active compound into an inactive one is termed **inactivation**, which occurs at many stages of hormone action.

Peripheral inactivation (**e.g.**, by liver enzymes) is needed to confirm steady state levels of plasma hormones as steroids are continuously released into the blood circulation. When a hormone acts as a chemical signal , its half -life in the bloodstream is limited so that any alteration in secretion rate is reflected by altered plasma concentration (when secretion rates are reduced) . Hormone inactivation also occurs in target tissues, particularly after the hormone has triggered significant biological effects to make sure that the hormone action is terminated.

Liver is the major site of peripheral steroid inactivation and catabolism. However, certain catabolic activities occur in the kidney also Generally, the inactive hormones are eliminated in urinary as conjugated metabolites. Steroids after inactivation are not recycled, but are eliminated from the human body. This elimination (**e.g.**, as urinary excretion products) needs conversion to hydrophilic compounds for confirming their solubility in biological fluids at high concentrations.

The f ollowing reactions are involved depending on the structure of the starting steroid:

1) Reduction of a double bond at C-4 and reduction of an oxo (keto) group at C-3 to yield a secondary alcoholic group.
2) Reduction of an oxo group at C-20 to yield a secondary alcoholic group.
3) Oxidation of a 17β-hydroxyl group.
4) Hydroxylation at various positions of the steroid nucleus **e.g.,** 7-hydroxylation of 5α-reduced androgens.
5) Sulphate and/or glucuronide conjugation.

Classification

Steroids are classified as follows:

1) Sex Hormones: Androgens, oestrogens, and Progesterone.

2) Glucocorticoids (GCs): These are a class of steroid hormones which bind to the Glucocorticoid Receptor (GR found in most of the vertebrate animal cells. The name **glucocorticoid** (glucose + cortex + steroid) has been derived

from its role in regulating glucose metabolism, its synthesis in the adrenal cortex, and its steroidal structure. **Examples** of glucocorticoids are **hydrocortisone**, **11-dehydrocorticosterone**, and **corticosterone**.

3) Mineralocorticoids (MCs): The essential natural mineralocorticoids are **aldosterone** and **desoxycorticosterone**. Their effects on electrolyte and water metabolism and on cardiovascular system are identical; however, aldosterone is 30 times more potent than desoxycorticosterone. **Examples** of mineralocorticoids are **aldeosterone**, **11-deoxycorticosterone**, and **11-deoxy-17-oxycorticosterone**.

4) Cardiac Glycosides: Digitoxin and Digoxin.

SEX HORMONES

Sex hormones are synthesised by the gonads. These hormones are required for conception, e embryonic maturation, and development of primary and secondary sexual characteristics at the time of puberty. The activity of sex hormones on target cells is regulated by the receptors.

Testosterone is a male sex hormone. It is essential for sexual and re productive development. It belongs to a class of male hormones known as **androgens**; this class is also referred to as **steroids** and **anabolic steroids.** Testosterone is involved in the development of male sex organ s before birth and in the development of secondary sexcharacteristics (deepening of voice, increased penis and testes size, and growth of facial and body hair) at puberty.

Classification

The sex hormones are classified as follows:

1) **Androgens:** This group of hormones affects the growth and development of the male reproductive system.

Androgens are divided into:

i) **Naturally Occurring Androgens:** Testosterone, Dihydrotestosterone, Dehydroepiandrosterone and Androsterone.

ii) **Synthetic Androgens :** Methyl testosterone, Fluoxymesterone, Testosterone undecanoate and

Mesterolone.

2) Oestrogens: These are the main female sex hormone s. Oestrogens are divided into:

i) **Natural Oestrogens**

a) Oestradiol (the most common type in women of child bearing age),

b) Oestrone (the only oestrogen body makes after menopause), and

c) Oestriol (the main oestrogen during pregnancy).

ii) **Synthetic Oestrogens**

a) **Steroidal:** Ethinylestradiol, Mestranol and Tibolone.

b) **Non-Steroidal:** Diethylstilbestrol (stilbestrol), Hexestrol, and Dienestrol.

3) **Progesterone:** It is one of the hormones in the bodies which stimulates and regulates many functions. Progesterone is divided into:

i) **Natural Progestin:** Progesterone

ii) **Synthetic Progestins**

a) **Progesterone Derivatives**

Older Compounds: Medroxyprogesterone acetate (weak androgenic), Megestrol acetate, Dydrogesterone and Hydroxyprogesterone caproate (long acting injection).

Newer Compound: Nomegestrol acetate.

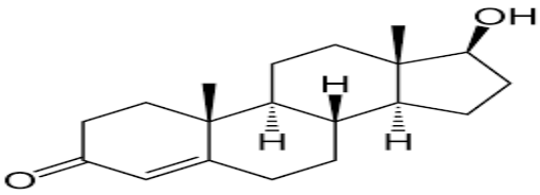
b) **19-Nortestosterone Derivatives**

Older Compounds: Norethindrone (Norethisterone), Norethynodrel, Ethynodiol diacetate, Lynestrenol (Ethinleystrenol), Allylestrenol, Norgestrel (Gonane) and Levonorgestrel.

Newer Compounds: Desogestrel, Norgestimate and Gestodene.

DRUGS

1. **Testosterone**



Testosterone is a steroid sex hormone present in males as well as in females. It is produced by the Leydig (interstitial) cells of the testes in males, if stimulated by Luteinizing Hormone (LH).

Mechanism of Action: Testosterone acts by the following two mechanisms:

1) It activates the androgen receptor (directly or as DHT), and

2) It converts to estradiol and activates certain oestrogen receptors.

Free testosterone (T) is transported into the cytoplasm of target tissue cells, and binds to the androgen receptor or reduces to 5α-Dihydrotestosterone (DHT) by the cytoplasmic enzyme 5α-reductase. DHT binds to the same androgen receptor more strongly than the free testosterone; thus, its androgenic potency is 2.5 times more than that of testosterone.

Uses

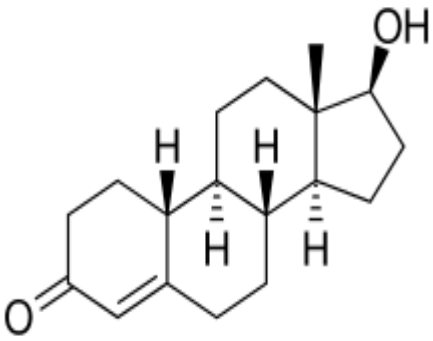
1) It is used as a replacement of reduced or absent endogenous testosterone.

2) It is used in males for management of congenital or acquired hypogonadism, hypogonadism related to HIV Infection, and male climacteric (andropause).

3) It is used in females for palliative treatment of androgen -responsive, advanced, inoperable, metastatis (skeletal) carcinoma of the breast in women after 1-5 years of their menopause.

2. Nandrolone

Nandrolone is a synthetic Anabolic-Androgenic Steroid (AAS) obtained from testosterone.



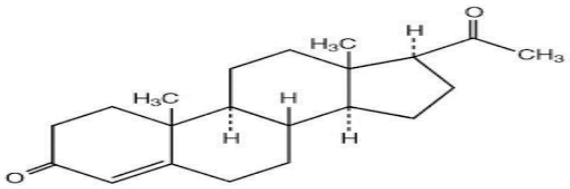
Mechanism of Action:

Nandrolone binds to testosterone receptors present in the cytoplasm of cells in androgen responsive organs and tissues. The resultant hormone-receptor complex binds with DNA to enhance transcription of DNA and formation of mRNA. This modifies the protein synthesis. Nandrolone produces anabolic effect s on skeleton and skeletal muscles.

Uses

It is used for the treatment of chronic wasting diseases and for the management of anaemia and osteoporosis in postmenopausal women.

3. Progesterone



Progesterone is the main progestational steroid which is released by the corpus luteum and placenta. It works on the uterus, mammary glands, and brain.

Mechanism of Action

Progesterone binds to and activates the Progesterone Receptor (PR) expressed in the female reproductive tissue and in the CNS. The resultant complex helps in the signaling of stimuli to prepare the endometrium for pregnancy.

When progesterone binds to PR, it modulates the expression of genes governing the development, differentiation, and proliferation of target tissues. In humans, PR is highly expressed in the stromal (connective tissue) cells during the secretory phase and during pregnancy.

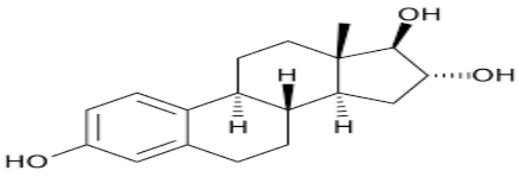
Uses

1) It is used as a supplementation or replacement as part of an Assisted Reproductive Technology (ART) treatment of infertile women n with progesterone deficiency.

2) It is also used for the treatment of secondary amenorrhea, and for reducing endometrial hyperplasia and risk of endometrial carcinoma in postmenopausal women receiving oestrogen replacement therapy.

3) It is used in abnormal uterine bleeding because of hormonal imbalance in the absence of organic pathology like fibroids or uterine cancer.

4. estriol



estriol is a hydroxylase metabolite of oestradiol or oestrone having a hydroxyl group at C3 -β, 16-α, and 17 -βposition. It is the principal urinary oestrogen. It is formed in large quantities by the placenta during pregnancy.

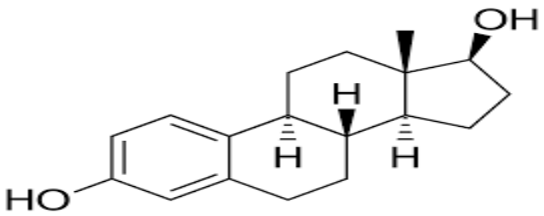
Mechanism of Action

The levels of oestriol are measured to determine a foetus's general health. The adrenal cortex of foetus produces Dehydroepiandrosterone Sulphate (DHEA-S),which is converted to oestriol by the placenta. If a pregnant woman has abnormally low levels of unconjugated oestriol, there might be a problem in child development. Oestriol interacts with the target cell receptor. When the oestrogen receptor has bound its ligand, it can enter the target cell nucleus, and regulate gene transcription to stimulate mRNA formation. The mRNA and ribosomes interact to produce specific proteins that express the effect of oestriol on the target cell.

Uses

It is used for testing the general health of an unborn foetus.

5. estradiol



Oestradiol (17β-oestradiol) is a naturally occurring hormone which circulates endogenously in the human body. It is the most potent form of mammalian oestrogenic steroids. It is the major female sex hormone.

Mechanism of Action

Oestrogen mediates its effects through potent agonist of the Oestrogen Receptor (ER), found in the tissues of breasts, uterus, ovaries, skin, prostate, bone, fat, and brain. Oestradiol binds to the sub-types of ER, i.e., Oestrogen Receptor Alpha (ERα) and Oestrogen Receptor Beta (ERβ). It also acts as a potent agonist of G Protein-coupled Oestrogen Receptor (GPER), which is a major mediator of the cellular effects of oestradiol.

Uses

1) It is used in moderate to high vasomotor symptoms, vulvar and vaginal atrophy because of menopause.

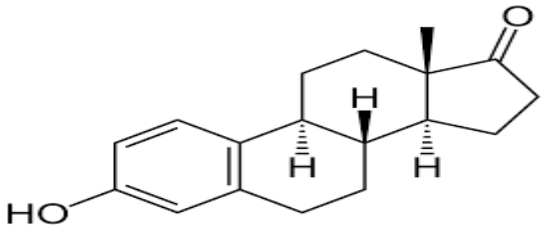
2) It is also used for the treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

3) It is indicated for the prevention of post-menopausal osteoarthritis.

4) It is also given in the treatment of breast cancer in selected women and men with metastatic disease.

5) Advanced androgen-dependent carcinoma of the prostate is also treated with estradiol.

6. Estrone



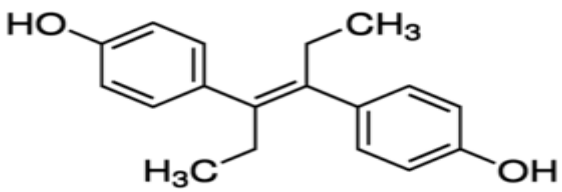
estrone is a mammalian oestrogen. It is an aromatised C -18 steroid with a 3 -hydroxyl group and a 17 -ketone. It is produced from androstenedione or testosterone by oestradiol *in vivo*. Mainly, it is formed in the ovaries, placenta and peripheral tissues (mainly adipose tissue) by the conversion of androstenedione.

Mechanism of Action: Oestrone enters the cells of responsive tissues e.g**.,** female organs, breasts, hypothalamus, and pituitary) to interact with the oestrogen receptors. Hormone -bound oestrogen receptors translocate to the nucleus of cells and bind to Oestrogen Response elements (ERE) of genes. This binding alters the transcription rate of affected genes. Oestrone also increase the hepatic synthesis of sex hormone binding globulin, thyroid -binding globulin, and other serum proteins. It suppresses the release of follicle -stimulating hormone from anterior pituitary.

Uses

It is used for treating pre-menopausal and post-menopausal symptoms.

7. Diethylstilbestrol



Diethylstilbestrol is a non -steroidal oestrogen. It is used for treating menopausal and post-menopausal disorders.

Mechanism of Action:

Diethylstilbestrol is a synthetic, non -steroidal form of oestrogen. It is a well -known teratogen and carcinogen. It inhibits the hypothalamic -pituitary-gonadal axis, thus blocks the testicular synthesis of testosterone, lowers the plasma levels of testosterone, and induces a chemical castration.

Uses

1) It is used for treating prostate cancer.

2) It was used formerly for preventing miscarriage or premature delivery in pregnant women prone to Miscarriage or premature delivery.

Drugs for Erectile Dysfunction

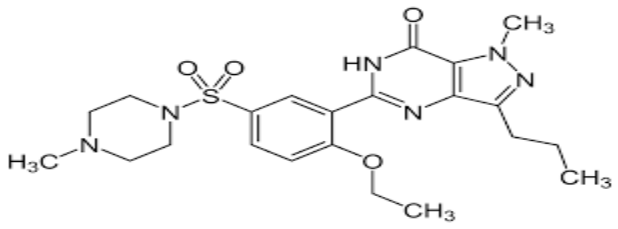
Introduction

The National Institutes of Health defined Erectile Dysfunction (ED) as the inability to attain or maintain an erection sufficient for satisfactory sexual performance. There is no ideal first-line diagnostic test for ED and routine screening is also not suggested. Mostly, the patient history and physical examination are enough for diagnosing ED. Erectile dysfunction is caused due to organic causes (**e.g.,** vascular, neurogenic, hormonal, anatomic, and drug g-induced), psychology causes, or both. Sexual erectile response is caused by the interaction between neurotransmitter, biochemical, and vascular smooth muscle responses stimulated by

Parasympathetic and sympathetic neuronal triggers that integrate physiologic stimuli of the penis with sexual sensitivity and desire. Nitric oxide produced from the endothelial cells after parasympathetic stimuli triggers a molecular cascade which causes smooth muscle relaxation and arterial influx of blood into the corpus cavernosum. This causes compression of venous return that result in erection.

Drugs Used

1. **Sildenafil**



Sildenafil is a vasoactive agent. It is used for treating e erectile dysfunction and reducing the symptoms of Pulmonary Arterial Hypertension (PAH).

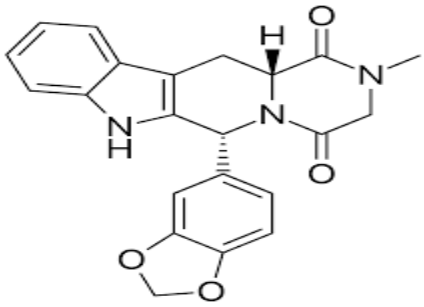
Mechanism of Action

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), which causes cGMP degradation in the corpus cavernosum of penis. Sildenafil does not produce any direct relaxant effect t on isolated human corpus cavernosum. Rather, it enhances the relaxant effect of Nitric Oxide (NO) on this tissue. When sexual stimulation the NO/cGMP pathway is activated, sildenafil causes inhibition of PDE5, thus increasing cGMP levels in corpus cavernosum. Therefore, sexual stimulation is required so that sildenafil can exert its pharmacological effects.

Uses

It is a phosphodiesterase -5 inhibitor, and is mainly used in the treatment of erectile dysfunction and pulmonary hypertension.

2. Tadalafil



Tadalafil is an orally administered drug. It is used for treating erectile dysfunction.

Mechanism of Action

Tadalafil inhibits the cGMP specific PDE5 that causes cGMP degradation in the corpus cavernosum of penis. Relaxation of penile arteries and corpus cavernosal smooth muscle increases the penile blood flow, thus causing penile erection during sexual stimulation. This effect is stimulated by the release of Nitric Oxide (NO) from nerve terminals and endothelial cells, which further stimulates cGMP synthesis in smooth muscle cells. The c GMP relaxes the smooth muscle s and increases the blood flow in corpus cavernosum. Inhibition of PDE5 by Tadalafil enhances the erectile function by increasing the amount of cGMP.

Uses

1) It is used for treating erectile dysfunction.

2) It raises the blood flow to penis, thus resulting in sexual stimulation.

3) It is also used for treating the signs and symptoms of Benign Prostatic Hyperplasia (BPH).

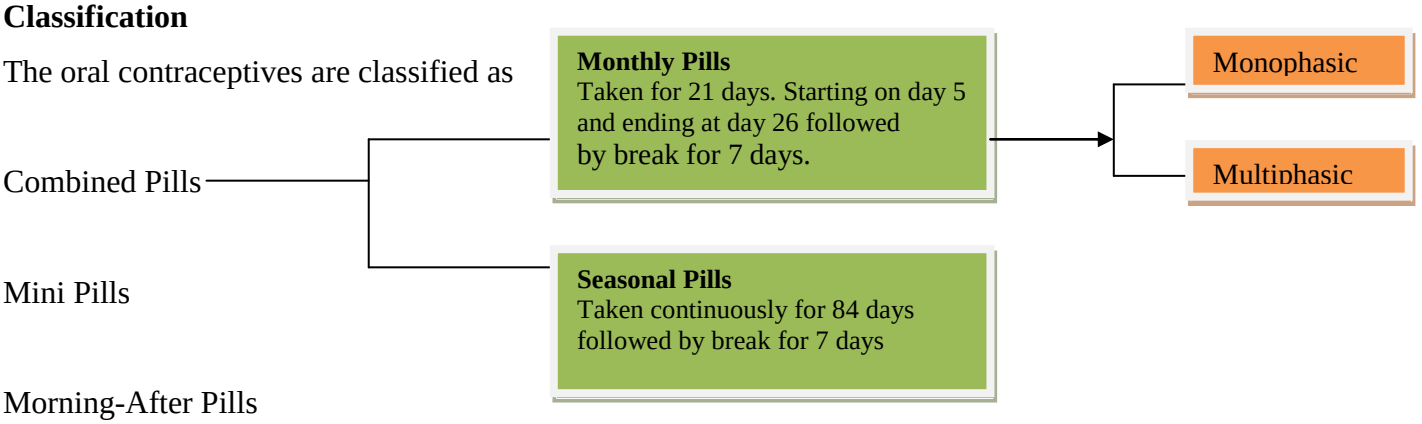
ORAL CONTRACEPTIVES

Introduction

Oral contraceptives (or **birth-control pills**) are used for preventing pregnancy. The combination of oestrogen and progestin (female sex hormones) is used to prevent ovulation, i.e., release of eggs from the ovaries. These hormones also change the uterus lining for inhibiting pregnancy. These hormones prevent the development and changes occurring at the mucus lining of the cervix (opening of the uterus) thus prevent the entry of sperms. Oral contraceptives are highly effective methods of birth control. However, they do not inhibit the Human Immunodeficiency Virus (HIV, the virus that causes AIDS) and other sexually transmitted diseases.

Classification

The oral contraceptives are classified as



Combined Oral Contraceptives (COCs) are found in either monophasic or multiphasic packaging:

1) **Monophasic Formulations:** Each hormone-containing pill has similar dose of the oestrogen and progestin as other active pills.

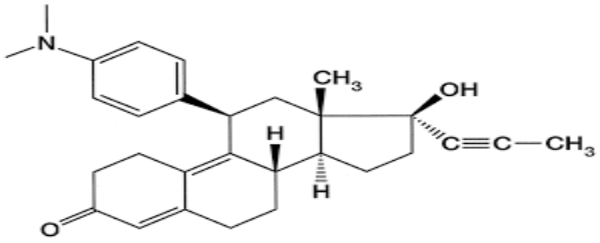
2) **Multiphasic Formulations:** The quantity of hormones changes in the active pills.

i) **Biphasic Formulations:** These have two different combinations of oestrogen and progestin in the packet of pills.

ii) **Triphasic Formulations:** These have three different combinations. Sometimes, in stepwise progression of the cycle, the progestin content increases. However, some other formulations also change the quantity of oestrogen given during the cycle. One formulation has constant progestin dose, whereas the amount of oestrogen is increased later in the cycle.

DRUGS USED

1. Mifepristone



Mifepristone is a progestational and glucocorticoid hormone antagonist. It inhibits progesterone, and this releases endogenous prostaglandins from the endometrium or deciduas. As a result, b leading occurs in the luteal phase and in early pregnancy.

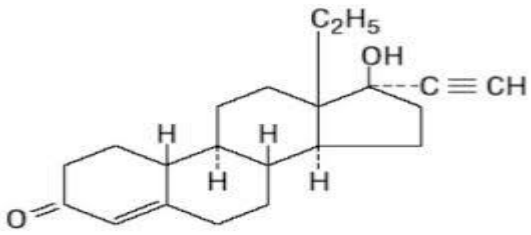
Mechanism of Action

Mifepristone exhibits anti-progestational activity as it competitively interacts with progesterone at the progesterone-receptor sites. Several studies have been conducted in mouse, rats, rabbits, and monkeys using oral doses of mifepristone. The results have revealed that it inhibits the activity of endogenous or exogenous progesterone, thus terminating the pregnancy.

Uses

1) It is used for the medical termination of intrauterine pregnancy (49 days' pregnancy).
2) It is also used for controlling hyperglycaemia secondary to hypercortisolism in adult s having Endogenous Cushing's syndrome, type 2 diabetes mellitus, glucose intolerance on whom Surgery cannot be conducted, or who had unsuccessful surgery.

2. Norgestrel



Norgestrel is a synthetic steroidal progestin. It is used with ethinyl estradiol for, oral contraception. It is made up of a racemic mixture of two stereoisomers, i.e., dextronorgestrel and levonorgestrel; of which only the levorotary enantiomer (levonorgestrel) is biologically active.

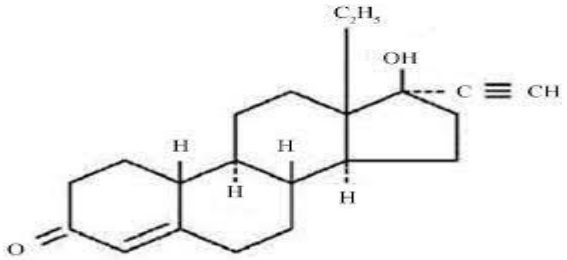
Mechanism of Action:

Norgestrel binds to the progesterone and estrogen receptors found in the female reproductive tract, mammary gland, hypothalamus, and pituitary gland. After binding, the progestins (like levonorgestrel) delay the release of Gonadotropin Releasing Hormone (GnRH) from hypothalamus and block the preovulatory flow of Luteinizing Horm one (LH). This in turn inhibits ovulation and prevents pregnancy.

Uses

It is used with ethinyl estradiol for preventing pregnancy in women who use this product as a contraception method.

3. Levonorgestrel



Levonorgestrel is a synthetic progestational hormone. It s actions are similar to those of progesterone , and its potency is twice as that of its racemic (+)-isomer(norgestrel). It is used for contraception and control menstrual disorders. It is also used for treating endometriosis.

Mechanism of Action

Levonorgestrel binds to the progesterone and estrogen receptors. The female reproductive tract, mammary gland, hypothalamus, and pituitary gland are the target organs for this drug. After binding to the receptors, pro gestins like levonorgestrel delay the release of Gonadotropin Releasing Hormone (GnRH) from hypothalamus and block the pre -ovulatory flow of Luteinizing Hormone (LH).

Uses

1) It is used for treating menopausal and post-menopausal disorders.

2) It is used either alone or with other hormones as an oral contraceptive.

CORTICOSTEROIDS

Introduction

Corticosteroids are the class of steroid hormones that include the hormone synthesized in the adrenal cortex of vertebrates, and the synthetic analogues of these hormones. They have a large range of physiological processes such as stress response, immune response, and regulation of inflammation, carbohydrate

metabolism, protein catabolism, blood electrolyte levels, and behaviour. **Examples** of some common natural hormones include corticosterone (C21H30O4), cortisone (C21H28O5, 17-hydroxy-11-ehydrocorticosterone), and aldosterone.

Classification

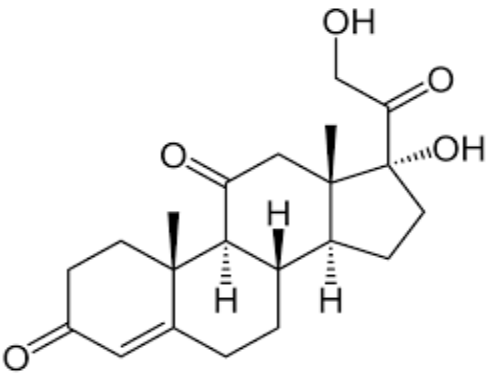
Two types of corticosteroids are given below:

1) Glucocorticoids: They control carbohydrate, fat and protein metabolism. They show anti-Inflammatory actions by inhibiting the phospholipid release, reducing the eosinophil action, and some other mechanisms.

2) Mineralocorticoids: They regulate the electrolyte and water levels by stimulating sodium retention in the kidneys.

DRUGS USED

1. **Cortisone**



Cortisone is a naturally occurring glucocorticoid. It is used in replacement therapy for adrenal insufficiency. It is also used as an anti -inflammatory agent. It is an inactive compound, and converts in the liver to hydrocortisone (its active metabolite).

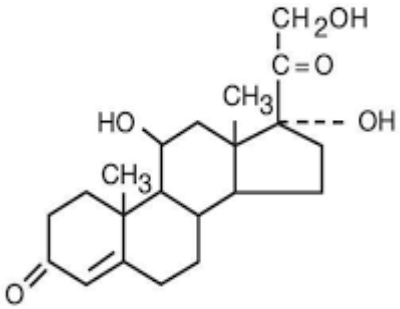
Mechanism of Action

Cortisone is an adrenocortical steroid. It inhibits the accumulation of inflammatory cells at inflammation sites. It also inhibits phagocytosis, synthesis and release of lysosomal enzyme, and release of inflammation mediators.

Uses

Cortisone is used in replacement therapy for adrenal insufficiency and as an anti -inflammatory agent. It is also used in rheumatoid arthritis, severe shock, allergic conditions, and chronic lymphatic leukaemia.

2. Hydrocortisone



$C_{21}H_{30}O_5$

362.47

Hydrocortisone is a synthetic or semi -synthetic analogue of natural hydrocortisone hormone. It is formed by the adrenal glands and exhibits primary glucocorticoid and minor mineralocorticoid effects.

Mechanism of Action

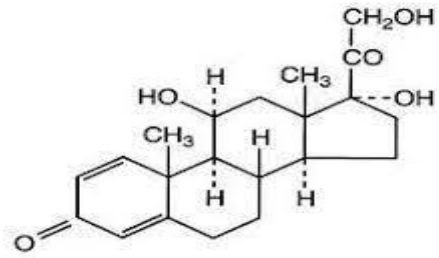
Hydrocortisone binds to the cytosolic glucocorticoid receptor. The resultant receptor-ligand complex translocates into the cell nucleus and binds to Glucocorticoid Response Elements (GRE), present in the promoter region of the target genes. Then, the DNA bound receptor interacts and the basic transcription factors interact and increase the expression of certain target genes. The anti -inflammatory actions of corticosteroids involve lipocortins and phospholipase A2inhibitory proteins, which inhibit arachidonic acid and control prostaglandins and leukotrienes biosynthesis.

Uses

1) Its synthetic counterpart is used either as injectable or topically for treating inflammation, allergy, arthritis, lupus, severe psoriasis, ulcerative colitis, collagen diseases, Crohn's disease, asthma, adrenocortical deficiency, shock, and some neoplastic conditions.

2) It is also used for the treatment of adrenal insufficiency and Addison's disease.

3. Prednisolone



Prednisolone is a glucocorticoid having the general properties of corticosteroids. It is the drug of choice in conditions where routine systemic corticosteroid therapy is indicated, except in adrenal deficiency states.

Mechanism of Action

Prednisolone inhibits leukocyte infiltration at the inflammation sites, interferes with inflammation mediators, and suppresses humoral immune responses. It reduces inflammatory reaction by preventing capillary dilatation and permeability of vascular structures. It prevents the accumulation of polymorphonuclear l eukocytes and macrophages, and reduces the release of vasoactive kinins. Prednisolone is a glucocorticoid receptor agonist.

Uses

1) It is used in the treatment of primary or secondary adrenocortical insufficiency (like Congenital adrenal hyperplasia and thyroiditis).

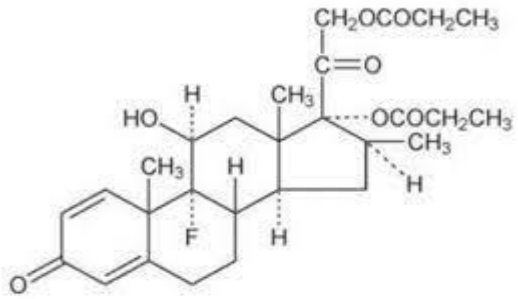
2) It is also used in psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, bursitis, acute gouty arthritis and epicondylitis.

3) It is also given in systemic lupus erythematosus, pumping us and acute rheumatic carditis.

4) It can be used for the treatment of leukaemia, lymphomas, thrombocytopenia purpurea and Autoimmune haemolytic anaemia.

5) It is also used in the treatment of celiac disease, insulin resistance, ulcerative colitis, and liver disorders.

4. Betamethasone



Betamethasone is a glucocorticoid. It is administered orally, parenterally, by local injection, inhalation, or used topically for treating many disorders in which corticosteroids are used.

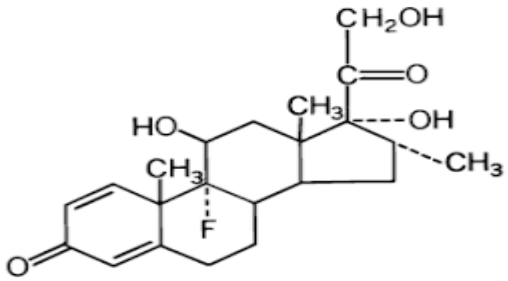
Mechanism of Action

Betamethasone is a glucocorticoid receptor agonist. It binds to GRE and the resultant complex changes the genetic expression. The anti –inflammatory activities of corticosteroids involve lipocortins (phospholipase A2 inhibitory proteins) which inhibit arachidonic acid and control the biosynthesis of prostaglandins and leukotrienes. Corticosteroids decrease the function of lymphatic system, reduce the concentration of immunoglobulin and precipitation of lymphocytopenia, and interfere with antigen-antibody binding. As a result, the immune system is suppressed.

Uses

1) It is used topically in many creams, foams lotions, and ointments for relieving inflammatory and Pruritic manifestations of cortic osteroidresponsive dermatoses.
2) It is systemically used in endocrine disorders, rheumatic disorders, collagen diseases,dermatological diseases, allergic states, ophthalmic diseases, respiratory diseases, hematologic disorders, neoplastic Diseases, oedematous states, gastrointestinal diseases, tuberculosis, meningitis, and trichinosis.

5. Dexamethasone



Dexamethasone is a potent synthetic glucocorticoid. It is used as an anti -inflammatory and immune suppressant.

Mechanism of Action

Dexamethasone is a glucocorticoid agonist. In free form, it crosses the cell membranes and binds to specific cytoplasmic glucocorticoid receptors. The resultant complex binds to DNA elements (glucocorticoid response elements) and modifies the transcription process and thus protein synthesis. As a result, leukocyte infiltration at the inflammation site is inhibited, the function of inflammatory mediators is restricted, humoral immune responses are suppressed and oedema or scasru tei sis reduced.

Uses

1) **Injection:** It is used for treating endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, oedematous states, and cerebral odema.

2) **Ophthalmic Ointment and Solution:** It is used for treating the steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

3) **Ophthalmic Solution:** It is used for treating steroid responsive inflammatory situations of the nexternal auditory meatus.

4) **Topical Cream:** It is used in the treatment of inflammatory and pruritic manifestations of corticosteroid- responsive dermatoses.

5) **Oral Aerosol:** It is used for treating bronchial asthma and associated corticosteroid responsive bronchospastic states intractable to suitable trial of conventional therapy.

6) **Intranasal Aerosol:** It is used for treating allergic or inflammatory nasal conditions, and nasal Polyps.

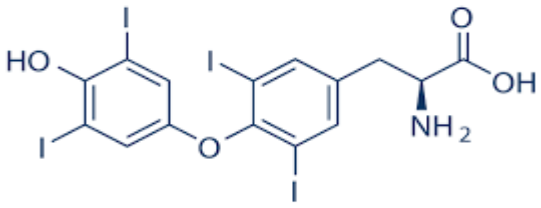
THYROID AND ANTI-THYROID DRUGS

Introduction

Thyroxine (T4) and **tri-iodothyronine (T3)** are the two hormones synthesised by thyroid gland. The similar feature of these two thyroid hormones is their high iodine concentration. Both the hormones are tyrosine derivatives. **Thyroxine** (T4) is the **major form of thyroid hormone** in blood. Its half-life is longer than that of T3. The ratio of T4 to T3 released in the blood lies between 14:1 to 20:1. The T4 converts into T3 (active and 3-4 times more potent than T4) in the cells by deiodinases (5'-iodinase enzyme). Further, they undergo decarboxylation and deiodination to form iodothyronamine (T1a) and thyronamine (T 0a). All the three isoforms of deiodinases are enzymes containing selenium. Therefore, selenium is required in the diet for production of T3. The receptors for thyroid hormones are intracellular DNA -binding proteins, which work as hormone -responsive transcript ion factor. These receptors are almost conceptually same as the steroid hormone receptors.

DRUGS USED

1. **L- Thyroxine**



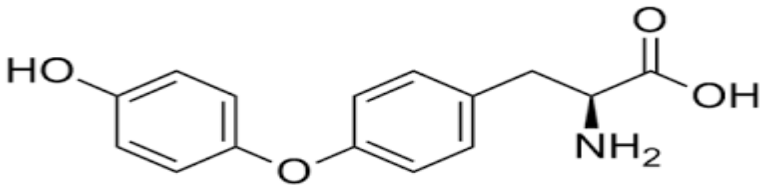
Mechanism of Action

L-Thyroxine acts like the endogenous thyroid hormone, thyroxine (T 4, a tetra -iodinated tyrosine derivative). In liver and kidneys, T4 converts into its active metabolite, T3. The solubility of thyroid hormones increases when they attach to thyroid hormone binding proteins, thyroxin e-binding globulin, and thyroxine-binding prealbumin (transthyretin).

Uses

It is used either alone or with anti -thyroid drugs for treating hypothyroidism, goitre, chronic lymphocytic thyroiditis, myxoedema, coma, and stupor.

2. **L-Thyronine**



Mechanism of Action

L-Thyronine replaces the endogenous thyroid hormone and produces its physiological effects by controlling DNA transcription and protein synthesis. This effect is the result of binding of liothyronine to the thyroid receptors attached to DNA. Exogenous liothyronine can produce all the normal effects of T3 hormone. Hence, it increases energy expenditure, accelerates the rate of cellular oxidation stimulating growth, maturation, and metabolism of body tissues, aids in myelinat ion of nerves and development of synaptic processes in the nervous system, and enhances carbohydrate and protein metabolism.

Uses

1) It is used as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) Congenital of acquired hypothyroidism.
2) It is used as an adjunct to surgery and radioiodine in thyroid cancer.
3) It is used as a diagnostic agent in suppression tests for mild hyperthyroidism or thyroid gland autonomy.

ANTI-TYROID DRUG

Introduction

Anti-thyroid drugs are the hormone antagonists that act on thyroid hormones. Carbimazole, methimazole, and propylthiouracil are the examples of common anti-thyroid drugs. Potassium perchlorate is a rarely used anti-thyroid agent.

Classification

The anti-thyroid drugs are classified as follows:

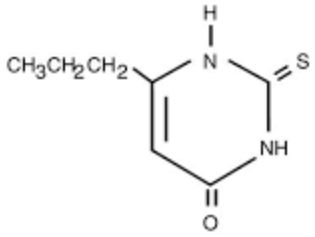
1) **Inhibit Hormone Synthesis (Anti-Thyroid Drugs):** Propylthiouracil, Methimazole, and Carbimazole.

2) **Inhibit Iodide Trapping (Ionic Inhibitors):** Thiocyanates (–SCN), Perchlorates ($–ClO_4$), and Nitrates (– NO_3).

3) **Inhibit Hormone Release:** Iodine, Iodides of Na and K, and Organic iodide.

4) **Destroy Thyroid Tissue:** Radioactive iodine (131I, 125I, 123I).

1. **Propylthiouracil**



Molecular Weight: 170.23 $C_7H_{10}N_2OS$

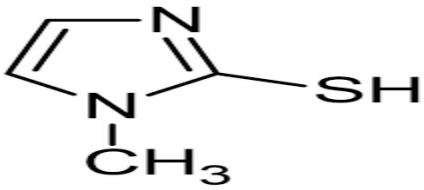
Mechanism of Action

Propylthiouracil inhibits iodide conversion to iodine by binding to thyroid peroxidase. This enzyme converts iodide to iodine (via hydrogen peroxide as a cofactor) and also catalyses the attachment of the resulting iodide and 5 positions of the phenol rings of tyrosine in thyroglobulin. T4 and T3 (the major hormones of the thyroid gland) are released by the degradation of thyroglobulin. Thus, propylthiouracil inhibits the production of new thyroid hormones.

Uses

It is used for treating hyperthyroidism.

2. **Methimazole**



Mechanism of Action

Same as Propylthiouracil.

Uses

Methimazole is used for treating hyperthyroidism, goiter, psoriasis, and Grave's disease.