HORMONES AND HORMONE ANTAGONISTS-II

Sex hormones

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Oestrogen and Progesterone

* Sex hormones are the substances secreted by ovaries or testes that stimulate the development of secondary sexual characters.
* **Pharmacological Actions of oestrogen and progesterone:-** The oestrogens are feminising and are responsible for the normal development and maintenance of the female genital tract & secondary sex characteristics. Progesterone is secreted by the corpus luteum and by the placenta if pregnancy develops.
* **Mechanism of Action:**
* Oestrogens and progestin exert their effects in target tissues by a combination of cellular mechanisms. There are two forms of the oestrogen receptor, ER-alpha and ER-beta, and two forms of progesterone receptor, PR-alpha and PR-beta. Receptor binding by oestrogens and progestin can activate a classic pathway of steroid hormone gene transcription. Gene activation is mediated by ability of steroid hormone receptor complexes to recruit nuclear coactivator proteins to transcription complex.

Oestrogen-Physiologic Effects:

* FEMALE MATURATION- Oestrogens are required for normal sexual maturation and growth of female. They stimulate development of vagina, uterus, and uterine tubes as well as secondary sex characteristics. They stimulate stromal development and ductal growth in the breast and are responsible for accelerated growth phase and closing of epiphyses of long bones that occur at puberty. They contribute growth of axillary and pubic hair and alter distribution of body fat to produce typical female body contours.

* ENDOMETRIAL EFFECTS- When oestrogen production is properly coordinated with production of progesterone during normal menstrual cycle, regular periodic bleeding and shedding of endometrial lining occur. Continuous exposure to oestrogens for prolonged periods leads to hyperplasia of endometrium that is associated with abnormal bleeding patterns.

Oestrogen-Physiologic Effects:

* METABOLIC AND CARDIOVASCULAR EFFECTS- Oestrogens seem to be partially responsible for maintenance of normal structure and function of skin and blood vessels in women. Oestrogens also decrease rate of resorption of bone by promoting apoptosis of osteoclasts and by antagonizing osteoclastogenic and pro-osteoclastic effects of parathyroid hormone and interleukin-6. Oestrogens also stimulate adipose tissue production of leptin.

* EFFECTS ON BLOOD COAGULATION- Oestrogens enhance coagulation ability of blood. Many changes in factors influencing coagulation have been reported, including increased circulating levels of factors II, VII, IX, and X and decreased anti-thrombin-III. Increased plasminogen levels and decreased platelet adhesiveness is found.

Oestrogen - THERAPEUTIC APPLICATIONS:

* a. Oral Contraception-it is among most effective forms of birth control.
* b. Osteoporosis-One in four postmenopausal women have osteoporosis. Oestrogen replacement therapy can prevent bone loss. Oestrogen treatment is the most effective therapy for osteoporosis and reduces incidence of bone fractures in postmenopausal women.
* c. Hormone Replacement Therapy (HRT) refers to administration of oestrogen– progestin combinations.
* d. Cardiovascular Actions-Declining oestrogen levels associated with menopause are correlated with an increased risk of cardiovascular related deaths in women. The protective effects of oestrogens on the lipid profile are well recognized.

Oestrogen - THERAPEUTIC APPLICATIONS:

* e. Central Nervous System Effects-Insomnia and fatigue in many postmenopausal women may be related to reduce oestrogen levels. Oestrogen replacement therapy may be used to treat severe cases.
* f. Infertility-Anovulation, often related to altered ratios of oestrogen to progestin, can be treated with a variety of agents, including oestrogen–progestin replacement, clomiphene citrate, bromocriptine, FSH, LH, human chorionic gonadotropin, and GnRH.
* g. Induction of Ovulation-Anovulation can be due to an insufficient release of LH and FSH during mid phase of menstrual cycle. Induction of ovulation by clomiphene citrate is result of stimulation of FSH and LH release.

Oestrogen - Adverse Reactions:

* UTERINE BLEEDING- Oestrogen therapy is a major cause of postmenopausal uterine bleeding.
* CANCER-The relation of oestrogen therapy to cancer continues to be the subject of active investigation.
* OTHER EFFECTS-Nausea and breast tenderness are common and minimized by using smallest effective dose of oestrogen. Hyperpigmentation also occurs. Oestrogen therapy is associated with an increase in frequency of migraine headaches as well as cholestasis, gallbladder disease, and hypertension.
* **Contraindications:** Oestrogens should not be used in patients with oestrogen-dependent neoplasms such as carcinoma of endometrium or in those with carcinoma of breast. They should be avoided in patients with undiagnosed genital bleeding, liver disease, or a history of thromboembolic disorder. In addition, the use of oestrogens should be avoided by heavy smokers.

Oestrogen - Pharmacokinetics:

* When released into circulation, estradiol binds to alpha2 globulin (sex hormone-binding globulin [SHBG]) and with lower affinity to albumin. Bound estrogen is unavailable for diffusion. Estradiol is converted by liver to estrone and estriol and their 2-hydroxylated derivatives and conjugated metabolites and excreted in bile. Conjugates may be hydrolyzed in intestine to active, reabsorbable compounds. Estrogens are also excreted in small amounts in breast milk of nursing mothers.

Progestin -Physiologic Effects:

* a. Progesterone has little effect on protein metabolism. It stimulates lipoprotein lipase activity and favours fat deposition. The effects on carbohydrate metabolism are more marked. Progesterone increases basal insulin levels and the insulin response to glucose. In the liver, progesterone promotes glycogen storage, possibly by facilitating the effect of insulin. Progesterone also promotes ketogenesis.
* b. Progesterone can compete with aldosterone for mineralocorticoid receptor of renal tubule, causing a decrease in Na+ reabsorption. This leads to an increased secretion of aldosterone by adrenal cortex (e.g., in pregnancy).
* c. Progesterone increases body temperature in humans.

Progestin -Physiologic Effects:

* d. Progesterone alters function of respiratory centers. The ventilatory response to CO_2 is increased. This leads to a measurable reduction in arterial and alveolar PCO_2 during pregnancy and in luteal phase of the menstrual cycle.
* e. Progesterone and related steroids also have depressant and hypnotic effects on the brain.
* f. Progesterone is responsible for alveo-lobular development of secretory apparatus in the breast. It also participates in pre-ovulatory LH surge and causes maturation and secretory changes in endometrium that are seen following ovulation.
* g. Progesterone decreases plasma levels of many amino acids and leads to increased urinary nitrogen excretion.

Progestin - THERAPEUTIC APPLICATIONS:

* a. Used in for hormone replacement therapy and hormonal contraception.
* b. Useful in producing long-term ovarian suppression for other purposes.
* c. In treatment of dysmenorrhea, endometriosis, and bleeding disorders, when oestrogens are contraindicated, and for contraception.
* d. Progesterone and medroxyprogesterone have been used in the treatment of women who have difficulty in conceiving and who demonstrate a slow rise in basal body temperature.

Progestin - THERAPEUTIC APPLICATIONS:

* e. Preparations of progesterone and medroxyprogesterone have been used to treat premenstrual syndrome.
* f. Abortifacients and Emergency Contraceptives- Progesterone is a hormone required for the maintenance of pregnancy. Termination of early pregnancy is effected using the steroidal anti-progestin drug, mifepristone (RU486), which acts by blocking progestin binding to the progesterone receptor.
* **Pharmacokinetics-** Rapidly absorbed following administration by any route. Its half-life in plasma is approximately 5 minutes, and small amounts are stored temporarily in body fat. It is completely metabolized in one passage through liver. Metabolized to inactive products and are excreted mainly in urine.

Androgen

* Androgens are steroid hormones secreted primarily by testis, and testosterone is principal androgen secreted. Its primary function is to regulate differentiation and secretory function of male sex accessory organs. Androgens also possess protein anabolic activity that is manifested in skeletal muscle, bone, and kidneys.

* **PHARMACOLOGICAL ACTIONS**:

* Androgens produce both virilising and protein anabolic actions. The virilising actions of testosterone include irreversible effects that occur during embryogenesis, and excitatory actions at puberty that are responsible for secondary sexual development.

Androgen

*PHARMACOLOGICAL ACTIONS:

*In addition to effects on male reproductive function, androgens influence a number of other systems, associated with masculinity. These actions include growth of male-pattern facial, pubic, and body hair, lower vocal pitch resulting from a thickening and lengthening of vocal cords, and increase in rate of long bone growth.

*The protein anabolic actions of androgens on bone and skeletal muscle are responsible for larger stature of males than females. Androgens induce some degree of anabolism in other tissues, including bone marrow, liver, kidney, and heart.

Androgen

* **CLINICAL USES:**
* 1. Hypogonadism
* 2. Prepuberal Hypogonadism
* 3. Postpuberal Hypogonadism
* 4. Aging and Impotence
* 5. Anemia
* **Therapeutic Use of Androgens in Women:**
* 1. Endometriosis
* 2. Female Hypogonadism
* 3. Use of Androgens as Protein
* 4. Anabolic Agents

Oral contraceptive

* Contraception means interception in the birth process at any stage ranging from ovulation to ovum implantation. An ideal contraceptive agent should not only be safe but provide reversible suppression of fertility.
* **Classification:**
* 1. **Combination pills**
* a. Ethinyl estradiol (30 mcg)+ Norgestrel (300 mcg)
* b. Ethinyl estradiol (30 mcg)+ Levonorgestrel (150 mcg)
* c. Ethinyl estradiol (50 mcg)+ Norgestrel (0.5 mg)
* d. Ethinyl estradiol (30 mcg)+ desogestrel (150 mcg)
* e. Mestranol (50 mcg) + Norethindrone (1 mg)

Oral contraceptive

* 2. **Phased pills**
* a. Ethinyl estradiol (30-40-30 mcg)+ Levonorgestrel (50-75-125 mcg)
* b. Ethinyl estradiol (35-35-35 mcg) + Norethindrone (0.5-0.75-1.0 mg)
* 3. **Post coital (morning after) pills**
* a. Ethinyl estradiol (50 mcg)+ Levonorgestrel (0.25 mg)
* b. Levonorgestrel (0.75 mg)
* c. Mifepristone 600mg
* 4. **Mini pills (progestin only pills)**
* a. Norgestrel (75 mcg)
* b. Norethindrone (0.35 mg)

Oral contraceptive

* MECHANISM OF ACTION-The combinations of estrogens and progestins exert their contraceptive effect largely through selective inhibition of pituitary function that results in inhibition of ovulation. The combination agents also produce a change in cervical mucus, in uterine endometrium, and in motility and secretion in uterine tubes, all of which decrease the likelihood of conception and implantation.

* Pharmacologic Effects:

* Effects On OVARY-Chronic use of combination agents depresses ovarian function. Follicular development is minimal, and corpora lutea, larger follicles, stromal oedema, and other morphologic features normally seen in ovulating women are absent. The ovaries usually become smaller even when enlarged before therapy.

Oral contraceptive

* Pharmacologic Effects:

* Effects On UTERUS-After prolonged use, the cervix may show hypertrophy and polyp formation. There are also important effects on cervical mucus, making it more like post-ovulation mucus, i.e., thicker and less copious.

* Effects On BREAST-Stimulation of breasts occurs in most patients receiving oestrogen-containing agents. Enlargement is noted. The administration of oestrogens and combinations of oestrogens and progestins tends to suppress lactation.

Oral contraceptive

* **Clinical Uses:-**
* a. Oral contraception
* b. In post coital contraception
* c. Polycystic ovary syndrome
* d. Dysfunctional uterine bleeding
* e. Premature menopause
* f. Turner’s syndrome
* g. In the treatment of endometriosis

Oral contraceptive-Adverse Effects:

* MILD ADVERSE EFFECTS:
* 1. Nausea, mastalgia, breakthrough bleeding, and oedema
* 2. Changes in serum proteins and other effects on endocrine function
* 3. Headache is mild and often transient
* 4. Withdrawal bleeding sometimes fails to occur
* MODERATE ADVERSE EFFECTS:
* 1. Breakthrough bleeding
* 2. Weight Increased
* 3. skin pigmentation may occur
* 4. Acne may be exacerbated
* 5. Hirsutism
* 6. Ureteral dilation
* 7. Amenorrhea occurs

TO BE CONTINUED....