DRUGS IN REPRODUCTIVE & URINARY SYSTEMS - III

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LEARNING OUTCOMES

By the end of the lecture, students will be able to describe…

1. Testosterone and Anabolic Steroids
   - Clinical uses
   - Misuses
   - ADRs
2. Treatment of benign prostatic hyperplasia and carcinoma of prostrate
   - list the different classes of drugs used in the treatment and describe their mode of action

ANDROGENS - PHYSIOLOGY

Androgenic effects

- Develop and maintain male secondary sex characteristics
  e.g.: - Changes in external and internal genitalia
  - Changes in hair growth
  - Predisposition to acne
- Initiation and maintain spermatogenesis
- Stimulate libido
- Changes in cholesterol (↓ HDL, ↑LDL, ↑ TAG)
- Changes in mood - ↑ irritability/anger

ANDROGENS - PHYSIOLOGY

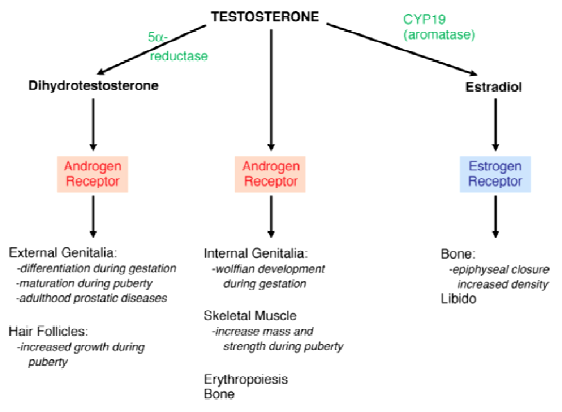
Anabolic effects

- ↑ Synthesis and ↓ breakdown of protein

↓

Muscle hypertrophy

- Na^+, K^+ and water retention
- ↑ Production of erythropoietin



PHARMACOKINETICS

- Well absorbed through gut & skin
- Undergo extensive hepatic metabolism
- Metabolized in liver → Less potent androgens
- Bound in the circulation to sex- hormone binding globulin & albumin

PREPARATIONS

- Esters of testosterone
  - E.g.: Testosterone enanthate
  - Testosterone propionate
  - } Due to extensive first pass metabolism given i.m.
- Testosterone patches
- Alkylated Testosterones
  - Fluoxymesterone
  - Methyltestosterone
  - Danazol
  - } Resist hepatic metabolism ↓ Given orally
- Anabolic steroids
  - Nandrolone , Stanozolol

CLINICAL INDICATIONS

a. Hypogonadism in males
   Improve libido & secondary sexual characteristics but cannot correct infertility

b. Delayed puberty

ADVERSE EFFECTS

1. Liver Injury (Specially with ORAL ALKYLATED FORMS)
   - Liver dysfunction
   - Cholestatic jaundice
   - hepatocellular adenoma/carcinoma
   - **Peliosis hepatitis (Haemorrhagic liver cysts)**
2. Prostate cancer
3. Acne, Gynaecomastia and Male pattern boldness

TOXIC EFFECTS
(WITH SUPRAPHYSIOLOGICAL DOSES)

1. Azoospermia & diminished fertility
2. ↓ testicular size
3. ↑ LDL and ↓ HDL
4. Gynaecomastia

Treatment - Benign Prostatic Hyperplasia (BPH)

- Pharmacologic treatment is suitable for patients who have,
  - moderate-to severe symptoms
  - ±
  - Bothersome symptoms

Pharmacological Treatment - BPH

1. α-adrenergic–receptor blockers
2. 5α-reductase inhibitors
3. antimuscarinic agents
4. Phosphodiesterase-5 inhibitors

α-ADRENERGIC–RECEPTOR BLOCKERS

- Block sympathetic adrenergic-receptor–mediated (α_{1A})contraction of the prostatic smooth muscle cells and bladder neck
- α_{1A} – selective :Tamsulosin and Silodosin
- α_{1A} – non selective: Prazosin, Doxazosin

ADVERSE EFFECTS

- Drowsiness, asthenia
- Postural hypotension
- Nasal congestion, headache, blurred vision
- Intra-operative floppy iris syndrome (most strongly associated with tamsulosin)

5α-REDUCTASE INHIBITORS

- Block the conversion of testosterone to its active metabolite, dihydrotestosterone

  shrink the prostate and reduce further prostatic growth
- E.g. Finasteride , Dutasteride

ADVERSE EFFECTS

- Decreased libido, erectile dysfunction,

decreased ejaculation

- Gynecomastia
- ↑ risk of high-grade prostate cancer

(reduction in overall risk of prostate cancer)

MUSCARINIC RECEPTOR ANTAGONISTS

- Inhibit muscarinic receptors in the detrusor muscle

  decrease the overactive-bladder component of bladder outflow tract obstruction symptoms
- E.g. Solifenacin, Oxybutynin, Tolterodine

PHOSPHODIESTERASE-5 INHIBITORS

- Increase the concentration and prolong the activity of intracellular cGMP

  reduce smooth muscle tone of the detrusor, prostate,and urethra
- E.g. Tadalafil

HORMONAL THERAPY FOR PROSTATIC CANCER

- Androgen Deprivation Therapy(ADT)
  e.g. GnRH agonists or antagonists
- Other Hormonal Treatments
  - Anti-androgens
  - Estrogens
  - Inhibitors of steroidogenesis

GnRH AGONISTS

- Bind to GnRH receptors on pituitary gonadotropin-producing cells,
  - Initially- release of both LH and FSH and a subsequent increase in testosterone production
    Can cause acute stimulation of prostate cancer growth (tumour 'flare')
  - Later(~1 week of therapy)- GnRH receptors are down regulated on the gonadotropin-producing cells, reducing FSH,LH and ↓testosterone production to castrate levels within 3-4 weeks of the first treatment

TUMOUR 'FLARE'

- "flare" of symptoms from metastatic deposits e.g. spinal cord compression, ureteric obstruction or increased bone pain
- counteracted with concurrent administration of 2-4 weeks of oral anti-androgen therapy

GnRH AGONISTS

- E.g. Leuprolide ,Goserelin

GnRH ANTAGONISTS

- E.g. Degarelix

ANTI-ANDROGENS

- Bind to androgen receptors and competitively inhibit the binding of testosterone and dihydrotestosterone
- Limited efficacy when used alone because the increased LH secretion stimulates higher serum testosterone concentrations

ANTI-ANDROGENS

A. Steroidal – e.g. Cyproterone ,
B. Nonsteroidal- e.g. Flutamide, Bicalutamide

Cyproterone:

a. Inhibit spermatogenesis and abnormal sperm forms produced
b. Hepatotoxicity