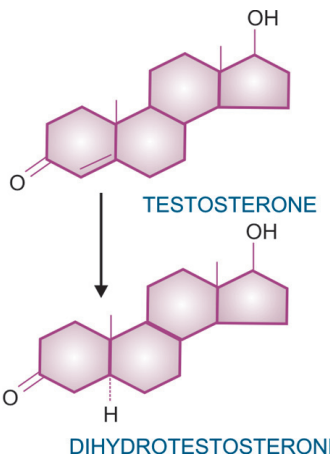
Chapter 21 Androgens and Drugs for Erectile Dysfunction

ANDROGENS (Male Sex Hormones)

These are substances which cause development of secondary sex characters in the castrated male. That testes are responsible for the male characters is known since prehistoric times. Its endocrine function was established by Berthold in 1849. *Testosterone* was isolated as the testicular hormone, its structure was worked out and it was synthetically prepared by the year 1935.

Natural androgens Testes of adult male produce 5–12 mg of *testosterone* daily, a part of which is converted in extraglandular tissues to the more active *dihydrotestosterone* (DHT); by the enzyme steroid 5 α-reductase; cholesterol is the starting material and the same pathway depicted in Fig. 20.1 is utilized. Adrenal cortex produces small quantities of *dehydroepiandrosterone* and *androstenedione* which are called 'weak androgens' (potency 1/20 to 1/30), but are infact inactive as such and derive their weak activity from partial conversion to testosterone in peripheral tissues. Adrenals themselves do not produce significant quantity of testosterone. In women ovary produces small quantity of testosterone; this together with that derived indirectly from adrenals amounts to 0.25–0.5 mg/day.



DIHYDROTESTOSTERONE

Androsterone It is a metabolite of testosterone which is excreted in urine. It has 1/10 the activity of testosterone.

Synthetic androgens *Methyltestosterone* and *fluoxymesterone* are 17-alkyl substituted derivatives of testosterone which are orally active because of resistance to first pass metabolism, but have submaximal androgenic efficacy and potential to cause cholestatic jaundice. Other orally active compounds are *testosterone undecanoate* which is administered as oily solution to be absorbed through lymphatics bypassing the liver, and *mesterolone*. A number of lipid-soluble esters of testosterone have been produced, suitable for injection in oily vehicle, from which they are absorbed slowly and exert prolonged action after deesterification in the body.

Regulation of secretion

Testosterone is secreted by the interstitial (Leydig) cells of the testes under the influence of pulsatile secretion of LH from pituitary. FSH is mainly responsible for promotion of spermatogenesis in tubular (Sertoli) cells. The mediator of feedback relationship with pituitary is uncertain. While relatively high concentration of testosterone inhibits LH secretion and in time causes atrophy of interstitial cells, it has only weak inhibitory action on FSH secretion. Estrogens are more potent inhibitors of Gn secretion even in males, and it is believed that the small amount of estradiol produced by testes as well as that resulting from conversion of testosterone to estradiol in liver and fat plays a role in feedback inhibition. *Inhibin*,

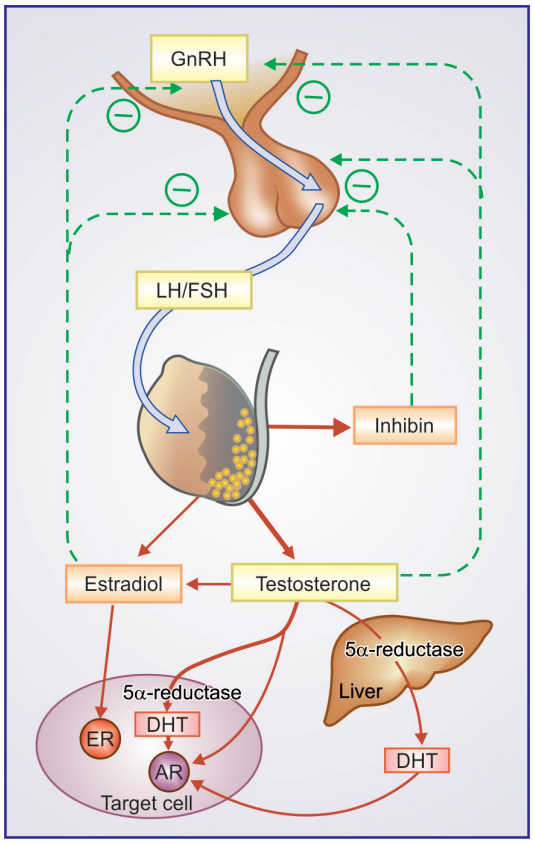


Fig. 21.1: Regulation and production of sex steroids in the male.
In liver and many target cells 5α-reductase enzyme converts testosterone to the more potent androgen dihydrotestosterone (DHT) which combines more avidly with the androgen receptor (AR). The aromatase enzyme in testes, liver and adipose tissue converts some testosterone into estradiol which exerts certain actions in male target cells by combining with estrogen receptor (ER) and is probably important for feedback inhibition of gonadotropins (LH/FSH) as well as that of gonadotropin releasing hormone (GnRH) from hypothalamus.

(a protein) produced by Sertoli cells, has strong FSH inhibitory action and may be mediating the feedback inhibition. Testosterone and estradiol act on hypothalamus to reduce GnRH as well as act directly on pituitary. The plasma level of testosterone in adult males ranges from 0.3 to 1 µg/dl. In women, small amounts of testosterone are produced by corpus luteum and adrenal cortex; blood levels remain low (20–60 ng/dl).

ACTIONS

1. Sex organs and secondary sex characters (Androgenic) Testosterone is responsible for all the changes that occur in a boy at puberty:
Growth of genitals—penis, scrotum, seminal vesicles, prostate.
Growth of hair—pubic, axillary, beard, moustache, body hair and male pattern of its distribution.
Thickening of skin which becomes greasy due to proliferation and increased activity of sebaceous glands—especially on the face. The duct often gets blocked and infection occurs resulting in acne. Subcutaneous fat is lost and veins look prominent.
Larynx grows and voice deepens.
Behavioral effects are—increased physical vigour, aggressiveness, penile erections. Male libido appears to be activated by testosterone directly, and probably to a greater extent by estradiol produced from testosterone.
Testosterone is also important for the intrauterine development of the male phenotype. Relatively large amounts of testosterone are produced by the foetal testes during the first half of intrauterine life.

2. Testes Moderately large doses cause testicular atrophy by inhibiting Gn secretion from pituitary. Still larger doses have a direct sustaining effect and atrophy is less marked. Testosterone is needed for normal spermatogenesis and maturation of spermatozoa. High concentration of testosterone is attained locally in the spermatogenic tubules by diffusion from the neighbouring Leydig cells and stimulates spermatogenesis.

3. Skeleton and skeletal muscles (Anabolic) Testosterone is responsible for the pubertal spurt of growth in boys and to a smaller extent in girls. There is rapid bone growth, both in thickness as well as in length. After puberty, the epiphyses fuse and linear growth comes to a halt. Estradiol produced from testosterone, and not testosterone itself, is responsible for fusion of epiphyses in boys as well as in girls. Moreover,

estradiol largely mediates the effect of testosterone on bone mineralization. Testosterone also promotes muscle building, especially if aided by exercise. There is accretion of nitrogen, minerals (Na, K, Ca, P, S) and water—body weight increases rapidly, more protoplasm is built. Appetite is improved and a sense of well being prevails. Testosterone given to patients prone to salt and water retention may develop edema.

4. Erythropoiesis Testosterone accelerates erythropoiesis by increasing erythropoietin production and probably direct action on haeme synthesis. Men have higher hematocrit than women.

Mechanism of action

Testosterone can largely be regarded as the circulating prohormone. In most target cells, the 4–5 double bond is reduced producing *dihydrotestosterone*—which binds more avidly with the cytoplasmic androgen receptor (AR), and this complex is more active than testosterone-receptor complex in combining with DNA. No subtypes of AR are known; both genital and nongenital (muscle, bone) cells express the same AR. After combining with androgen response elements of the target genes, DNA transcription is enhanced/repressed with the help of coactivators or corepressors, which may be tissue specific. The effects are expressed through modification of protein synthesis.

The 5α-reductase enzyme exists in two isoforms: 5α-reductase-1 and 5α-reductase-2. The genital skin of both sexes and urogenital tract of male contains 5α- reductase-2 which is more sensitive to inhibition by finasteride. Genetic deficiency of this isoenzyme causes male pseudohermaphroditism because of inability of male genitalia to produce the active hormone dihydrotestosterone from circulating testosterone. 5α-reductase-1 has a wider distribution in the body including nongenital skin and liver; and is inhibited by finasteride to a lesser extent.

Testosterone itself appears to be the active hormone at certain sites, such as—

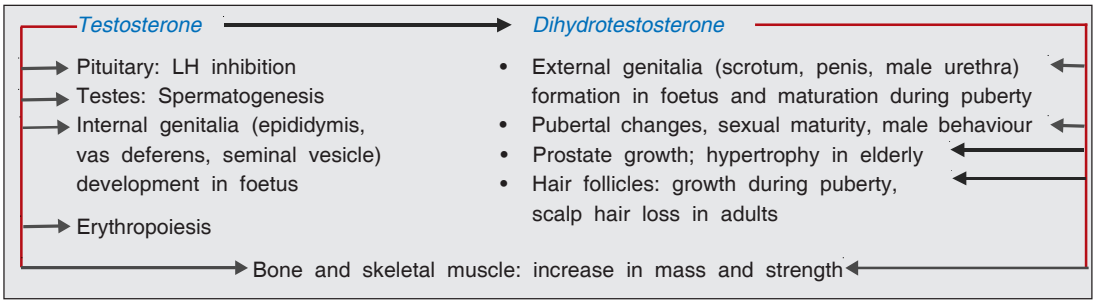
- foetal genital rudiments
- hypothalamus/pituitary site involved in feed back regulation
- erythropoietic cells
- spermatogenic cells in testes.

PHARMACOKINETICS

Testosterone is inactive orally due to high first pass metabolism in liver. The duration of action after i.m. injection is also very short. Therefore, slowly absorbed esters of testosterone are used by this route—are hydrolysed to the active free form. Testosterone in circulation is 98% bound to sex hormone binding globulin (SHBG) and to albumin. The SHBG bound testosterone is unavailable for action due to tight binding.

The major metabolic products of testosterone are androsterone and etiocholanolone which are excreted in urine, mostly as conjugates with glucuronic acid and sulfate. Small quantities of estradiol are also produced from testosterone by aromatization of A ring in extraglandular tissues (liver, fat, hypothalamus). Plasma t½ of testosterone is 10–20 min.

Principal androgen for different target tissue actions



Methyltestosterone and fluoxymesterone are metabolized slowly and have a longer duration of action, but are weaker androgens. Estrogens are not produced from fluoxymesterone and dihydrotestosterone.

Preparations and Dose

1. Testosterone (free): 25 mg i.m. daily to twice weekly; AQUAVIRON 25 mg in 1 ml inj.
2. Testosterone propionate: 25–50 mg i.m. daily to twice weekly: TESTOVIRON, PARENDREN, TESTANON 25, 50 mg/ml inj.
3. TESTOVIRON DEPOT 100: testo. propionate 25 mg + testo. enanthate 100 mg in 1 ml amp; 1 ml i.m. weekly.
4. TESTOVIRON DEPOT 250: testo. propionate 250 mg + testo. enanthate 250 mg in 1 ml amp; i.m. every 2–4 weeks.
5. SUSTANON '100': testo. propionate 20 mg + testo. phenyl propionate 40 mg + testo. isocaproate 40 mg in 1 ml amp; 1 ml i.m. every 2–3 weeks.
6. SUSTANON '250': testo. propionate 30 mg + testo. phenylpropionate 60 mg + testo. isocaproate 60 mg + testo. decanoate 100 mg in 1 ml amp; 1 ml i.m. every 3–4 weeks.
7. NUVIR, ANDRIOL; Testosterone undecanoate 40 mg cap, 1–3 cap daily for male hypogonadism, osteoporosis.
8. Mesterolone: Causes less feedback inhibition of Gn secretion and spermatogenesis, and has been promoted for treatment of male infertility PROVIRONUM, RESTORE, MESTILON 25 mg tab; 1–3 tab daily for androgen deficiency, oligozoospermia and male infertility.

Transdermal androgen Recently delivery of androgen across skin has been achieved by developing suitable solvents and absorption facilitators. By cutaneous delivery, testosterone/dihydrotestosterone circumvent hepatic first pass metabolism; uniform blood levels are produced round the clock. A gel formulation has been marketed for once daily application which has become the preferred method of androgen replacement for hypogonadism and impotence. ANDRACTIM: Dihydrotestosterone 25 mg/g gel (100 g tube); 5–10 g gel to be applied over nonscrotal skin once daily.

Fixed dose combinations of testosterone with yohimbine, strychnine and vitamins are banned in India.

SIDE EFFECTS

1. Virilization, excess body hair and menstrual irregularities in women. Many effects, e.g. voice change may be permanent after prolonged therapy.
2. Acne: in males and females.
3. Frequent, sustained and often painful erections in males in the beginning of therapy; subside spontaneously after sometime.
4. Oligozoospermia can occur with moderate doses given for a few weeks to men with normal testosterone levels. Prolonged use may produce testicular atrophy.
5. Precocious puberty, premature sexual behaviour, and stunting of stature due to early closure of epiphysis—if testosterone is given continuously to young boys for increasing stature.
6. Salt retention and edema: especially when large doses are used in patients with heart or kidney disease. It is rare with the doses used for hypogonadism.
7. Cholestatic jaundice: occurs with methyltestosterone and other 17-alkyl substituted derivatives (fluoxymesterone and some anabolic steroids like oxymetholone, stanozolol) in a dose dependent manner, but not with parenterally used esters of testosterone. For this reason, the latter are preferred. However, jaundice is reversible on discontinuation.
8. Hepatic carcinoma: incidence is higher in patients who have received long-term methyltestosterone or other oral androgens.
9. Gynaecomastia: may occur, especially in children and in patients with liver disease. This is due to peripheral conversion of testosterone to estrogens. Dihydrotestosterone does not cause gynaecomastia because it is not converted to estradiol.
10. Lowering of HDL and rise in LDL levels, especially with 17α-alkylated analogues.

Contraindications Androgens are contraindicated in carcinoma of prostate and male breast, liver and kidney disease and during pregnancy (masculinization of female foetus). They should not be given to men aged >65 years, and to those with coronary artery disease or CHF. Androgen therapy can worsen sleep apnoea, migraine and epilepsy.

USES

1. *Testicular failure* It may be primary—in children, resulting in delayed puberty. Treatment

with parenteral testosterone esters or transdermal testosterone/dihydrotestosterone in courses of 4–6 months at a time is highly satisfactory. Secondary testicular failure occurring later in life manifests mainly as loss of libido, muscle mass and energy, feminization, mild anaemia and impotence. These are corrected gradually over months by androgen treatment. However, impotence due to psychological and other factors, and not testosterone deficiency, does not respond.

2. *Hypopituitarism* Hypogonadism is one of the features of hypopituitarism. Androgens are added at the time of puberty to other hormonal replacement.

3. *AIDS related muscle wasting* Testosterone therapy has been shown to improve weakness and muscle wasting in AIDS patients with low testosterone levels.

4. *Hereditary angioneurotic edema* This is a genetic disorder. The attacks can be prevented by 17α-alkylated androgens (methyltestosterone, stanozolol, danazol) but not by testosterone. These drugs act by increasing synthesis of complement (C1) esterase inhibitor.

5. *Ageing* Because testosterone levels decline in old age, it has been administered to elderly males to improve bone mineralization and muscle mass. However, safety of such therapy in terms of metabolic, cardiovascular and prostatic complications is not known.

Occasionally small amount of androgen is added to postmenopausal hormone replacement.

6. *Idiopathic male infertility* Since high intratesticular level of testosterone is essential for spermatogenesis, it is presumed that exogenous androgens will stimulate spermatogenesis or improve sperm maturation in epididymis. On the other hand, androgens can adversely affect spermatogenesis by suppressing Gn secretion. Since mesterolone causes less feedback inhibition of Gn (probably due to restricted entry into brain) it is believed that moderate doses will predominantly stimulate testis directly.

A recent metaanalysis of 11 clinical trials has found that oral androgens (mesterolone and testosterone undecanoate) had no effect on sperm count or sperm motility as well as on subsequent pregnancy rate when given to oligo-astheno-spermic subfertile men. As such, use of these androgens for improving male fertility is unjustified.

ANABOLIC STEROIDS

These are synthetic androgens with supposedly higher anabolic and lower androgenic activity. Drugs are *Nandrolone, Oxymetholone, Stanozolol* and *Methandienone.*

The anabolic : androgenic activity ratio is determined by injecting the drug in castrated rats and measuring the increase in weight of levator ani muscles to that of ventral prostate. The anabolic : androgenic ratio of testosterone is considered as 1; The anabolic selectivity of these steroids is modest with ratios between 1 to 3 in the rat model, and probably still lower in man. The anabolic effects are similar to that of testosterone and are mediated through the same receptor as the androgenic effects. For all practical purposes, they are androgens.

Preparations and dose

1. Methandienone: 2–5 mg OD–BD oral; children 0.04 mg/kg/day, 25 mg i.m. weekly; ANABOLEX 2, 5 mg tab, 2 mg/ml drops, 25 mg/ml inj.
2. Nandrolone phenyl propionate: 10–50 mg; children 10 mg; i.m. once or twice weekly; DURABOLIN 10, 25 mg/ml inj.
3. Nandrolone decanoate: 25–100 mg i.m. every 3 weeks, DECADURABOLIN, 25, 100 mg/ml inj.
4. Oxymetholone: 5–10 mg, children 0.1 mg/kg, OD; ADROYD 5 mg tab.
5. Stanozolol: 2–6 mg/day, MENABOL, NEURABOL, TANZOL 2 mg tab.

Combination of anabolic steroids with any other drug is banned in India.

Side effects Anabolic steroids were developed with the idea of avoiding the virilizing side effects of androgens while retaining the anabolic effects. But the same adverse effect profile applies to these compounds.

The 17-alkyl substituted compounds oxymetholone, stanozolol, can produce jaundice and worsen lipid profile.

Contraindications are same as for testosterone.

Uses

1. *Catabolic states* Acute illness, severe trauma, major surgery, etc. are attended by

negative N balance. Anabolic steroids can reduce N_2 loss over short periods, but long-term benefits are questionable. They may cause a transient response in the elderly, under-nourished or debilitated individuals, but controlled studies have failed to demonstrate a difference in the total weight gained. However, short-term use may be made during convalescence for the sense of wellbeing and improvement in appetite caused by such treatment.

2. *Osteoporosis* In elderly males and that occurring due to prolonged immobilization may respond to anabolic steroids, but bisphosphonates are more effective and are the preferred drugs.

3. *Suboptimal growth in boys* Use is controversial; somatropin is a better option. Brief spurts in linear growth can be induced by anabolic steroids, but this probably does not make a difference in the final stature, except in hypogonadism. Use for more than 6 months is not recommended—premature closure of epiphyses and shortening of ultimate stature may result.

4. *Hypoplastic, haemolytic and malignancy associated anaemia* Majority of properly selected patients respond to anabolic steroids/androgens by an increase in RBC count and Hb%. However, erythropoietin therapy is more effective.

5. *To enhance physical ability in athletes* When administered during the period of training androgens/anabolic steroids can increase the strength of exercised muscles. However, effects are mostly short-lived and the magnitude of improvement in performance is uncertain except in women. This is considered illegal and anabolic steroids are included in the list of 'dope test' performed on athletes before competitive games.

IMPEDED ANDROGENS/ ANTIANDROGENS

Superactive GnRH agonists are the most potent inhibitors of gonadal function. Administered over a few days, they markedly inhibit LH and FSH release, resulting in loss of androgen secretion (*see* Ch. 17).

Ketoconazole at high doses inhibits steroidogenic CYP 450 enzymes: testosterone as well as adrenal steroid production is interfered. Plasma protein binding of testosterone is also reduced. However, toxicity of high doses precludes its use to suppress androgens.

Cimetidine and *spironolactone* have weak antiandrogenic action which manifests as side effects. *Progesterone* has weak androgen receptor blocking action.

Drugs that have been clinically used to modify androgen action are:

Danazol It is an orally active ethisterone derivative having weak androgenic, anabolic and progestational activities. Though labelled as an impeded/attenuated androgen, because it binds to the AR and induces some androgen-specific mRNA production, the most prominent action is suppression of Gn secretion from pituitary in both men and women → inhibition of testicular/ovarian function. In addition, it suppresses gonadal function directly by inhibiting steroidogenic enzymes. In women endometrial atrophy occurs over few a weeks and amenorrhoea may supervene. Danazol is metabolized with a t½ of 12–18 hours.

Dose: 200–600 mg/day; DANAZOL, LADOGAL, DANOGEN, GONABLOK 50, 100, 200 mg cap.

Uses are:

1. *Endometriosis* Danazol causes improvement in ~75% cases by inhibiting ovarian function. Relief of dysmenorrhoea is prompt. Pain, dyspareunia and excessive bleeding regress slowly. Estrogen-progestin combination contraceptive is the first line drug. Non-responsive cases are treated by a high dose progestin alone. Danazol is infrequently used now because of androgenic side effects and risk of liver damage.

2. *Menorrhagia* Danazol reduces menstrual blood loss. Usually complete amenorrhoea does not occur with 200 mg/day. It is a second line drug to an oral progestin.

3. *Fibrocystic breast disease* (chronic cystic mastitis): 3–6 months danazol treatment causes improvement with decrease in pain, nodularity and engorgement in ~ 75% cases.

4. *Hereditary angioneurotic edema* Danazol is a 17α alkylated steroid: has prophylactic effect in this condition by inducing complement (C1) esterase inhibitor (*see* above).

Side effects are frequent and dose related. Complete amenorrhoea occurs with higher doses. Androgenic side effects are acne, hirsutism, decreased breast size, deepening of voice, edema and weight gain. Loss of libido in men, hot flashes in women and night sweats, muscle cramps, g.i. upset, elivation of hepatic enzymes are the other problems.

Cyproterone acetate This relatively weak AR antagonist is chemically related to progesterone. In contrast to flutamide which increases LH release by blocking feedback inhibition, cyproterone inhibits LH release by its progestational activity. Lowering of serum testosterone (consequent to LH inhibition) supplements the direct antiandrogenic action of cyproterone.

Given to boys in relatively higher doses, it prevents pubertal changes, while in adult men libido and androgenic anabolism are suppressed. Its clinical indications are—precocious puberty in boys, inappropriate sexual behaviour in men, acne and hirsutism in women (usually in combination with an estrogen). Its efficacy in metastatic prostate carcinoma is inferior to other forms of androgen deprivation. Hepatotoxicity limits its use.

Dose: 2 mg OD; GINETTE-35, DINAC-35; cyproterone acetate 2 mg + ethinyl estradiol 35 µg tab.

Flutamide A nonsteroidal AR antagonist with no other hormonal activity. Its active metabolite 2-hydroxyflutamide competitively blocks androgen action on accessory sex organs as well as on pituitary. Thus, it increases LH secretion by blocking feedback inhibition. Plasma testosterone levels increase in males which partially overcome the direct antiandrogenic action. This limits utility of monotherapy with antiandrogens in carcinoma prostate. They are now used only in conjunction with a GnRH agonist (to suppress LH and testosterone secretion) or after castration to block the residual action of adrenal androgens as *combined androgen blockade (CAB)* therapy of metastatic carcinoma prostate (also *see* p. 872). It is preferably started 3 days before the GnRH agonist to block the initial flare up that may occur due to excess release of LH and testosterone in the beginning (before GnRH receptors are desensitized). However, long-term benefit of CAB over GnRH agonist alone is not established. Along with oral contraceptives it has been tried in female hirsutism, but its hepatotoxic potential may not justify such use. Though gynaecomastia and breast tenderness occur frequently, libido and potency are largely preserved during flutamide treatment. Reports of liver damage have restricted its use.

Dose: 250 mg TDS

PROSTAMID, FLUTIDE, CYTOMID 250 mg tab.

Bicalutamide This more potent and longer acting ($t_{1/2}$ 6 days) congener of flutamide is suitable for once daily administration in metastatic carcinoma of prostate as a component of CAB therapy. When used along with a GnRH agonist or castration, 50 mg OD affords marked relief in bone pain and other symptoms due to the metastasis. Side effects are hot flashes, chills, edema and loose stools, but it is better tolerated and less hepatotoxic than flutamide. Elevation of hepatic transaminase above twice normal is a signal for stopping the drug.

BIPROSTA, CALUTIDE, TABI 50 mg tab.

5 α-REDUCTASE INHIBITOR

Finasteride A competitive inhibitor of the enzyme 5 α-reductase which converts testosterone into more active DHT responsible for androgen action in many tissues including the prostate gland and hair follicles. It is relatively selective for 5 α-reductase type 2 isoenzyme which predominates in male urogenital tract. Circulating and prostatic DHT concentration are lowered, but plasma LH and testosterone levels remain unchanged because testosterone itself mediates feedback pituitary LH inhibition.

Treatment with finasteride has resulted in decreased prostate size and increased peak urinary flow rate in ~50% patients with symptomatic benign hypertrophy of prostate (BHP). The beneficial effects are typically delayed needing ~6 months for maximum symptomatic relief. Patients with large prostate (volume > 40 ml) obtain greater relief than those with smaller gland. Upto 20% reduction in prostate size may be obtained.

Withdrawal of the drug results in regrowth of prostate, but with continued therapy benefit is maintained for 3 years or more. The relief of obstructive symptoms, however, is less marked compared to surgery and adrenergic α_1 blockers (*see* p. 143). It primarily reduces the static component of obstruction, while α_1 blockers overcome the dynamic component. Concurrent treatment with both produces greater symptomatic relief.

Finasteride has also been found effective in male pattern baldness, though hair follicles have primarily type 1 enzyme. In such subjects it promotes hair growth and prevents further hair loss. Observable response takes 3 or more months therapy and benefit is reversed within 1 year of

treatment cessation. However, 20–30% cases do not improve.

Finasteride is effective orally, extensively metabolized in liver—metabolites are excreted in urine and faeces; plasma t½ 4–8 hours (elderly 6–15 hours). It is well tolerated by most patients; side effects are decreased libido, impotence and decreased volume of ejaculate (each in 3–4% patients). Gynaecomastia, skin rashes, swelling of lips are rare.

Dose for BHP 5 mg OD, review after 6 months;
for male pattern baldness 1 mg/day.
FINCAR, FINAST, FINARA 5 mg tab; FINPECIA, ASTIFINE 1 mg tab.

Dutasteride This newer congener of finasteride inhibits both type 1 and type 2 5α-reductase and reduces DHT levels. It is metabolized by CYP3A4 and is very long-acting (t½ is ~ 9 weeks). It is approved for use in BHP and can benefit male pattern baldness. In clinical trias, both finasteride and dutasteride have been found to reduce the risk of developing carcinoma prostate by upto 25%. Interactions with CYP3A4 inducers and inhibitors are possible.

Dose: 0.5 mg OD; DUPROST, DURIZE 0.5 mg tab.

DRUGS FOR ERECTILE DYSFUNCTION

Erectile dysfunction (ED) refers to the inability of men to attain and maintain an erect penis with sufficient rigidity to allow sexual intercourse. It occurs mainly past middle-age and is common after the age of 65 years. A variety of vascular, neurogenic, hormonal, pharmacologic or psychogenic causes may underlie the disorder.

Sexual arousal increases blood flow to the penis and relaxes the cavernosal sinusoids so that they fill up with blood, making the penis rigid, elongated and erect. Nitric oxide (NO) released from parasympathetic nonadrenergic noncholinergic (NANC) nerves and vascular endothelium is the major transmitter causing relaxation of smooth muscle in corpus cavernosum and the blood vessels supplying it; ACh and PGs also play a role. A variety of mechanical/prosthetic devices and surgery have been used for ED, but drug therapy has made a big impact recently.

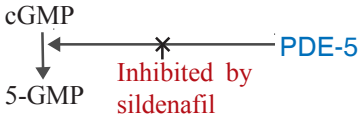
1. Androgens

Hypogonadism is an infrequent cause of ED. Parenteral testosterone esters or transdermal testosterone therapy is effective only when androgen deficiency is proven to be responsible for the loss of libido and ED.

2. Phosphodiesterase-5 (PDE-5) inhibitors

This class of drugs have become the first line therapy for ED.

Nitric oxide causes smooth muscle relaxation by generating cGMP intracellularly which then promotes dephosphorylation of myosin light chain kinase (MLCK) so that myosin fails to interact with actin (*see* Fig. 39.3). Inhibition of PDE-5, the cGMP degrading isoenzyme in cavernosal and vascular smooth muscle, results in accumulation of cGMP and marked potentiation of NO action. *Sildenafil, Tadalafil* and *vardenafil* are selective PDE-5 inhibitors found effective in a majority of patients with ED.



Sildenafil It is an orally active drug, marketed in the USA in 1998 and 2 years later in India, for treatment of ED. It became an instant hit, and evoked worldwide response. Sildenafil acts by selectively inhibiting PDE-5 and enhancing NO action in corpus cavernosum. Penile tumescence during sexual arousal is improved, but it has no such effect in the absence of sexual activity. It does not cause priapism in most recipients.

Oral bioavailability of sildenafil is ~40%, peak blood levels are attained in 1–2 hr; it is metabolized largely by CYP3A4 and an active metabolite is produced; t½ in men <65 years averages 4 hours. It is recommended in a dose of 50 mg (for men > 65 years 25 mg), if not effective then 100 mg 1 hour before intercourse. Duration and degree of penile erection is increased in 74–82% men with ED including diabetic neuropathy cases. Over

20 controlled trials have confirmed its efficacy. However, sildenafil is ineffective in men who have lost libido or when ED is due to cord injury or damaged nervi eregantis.

Adverse effects Side effects are mainly due to PDE-5 inhibition related vasodilatation—headache, nasal congestion, dizziness, facial flushing and fall in BP, loose motions. Relaxation of lower esophageal sphincter may cause gastric reflux and dyspepsia. Sildenafil, in addition, weakly inhibits the isoenzyme PDE-6 which is involved in photoreceptor transduction in the retina. As such, impairment of colour vision, especially blue-green discrimination, occurs in some recipients. Few cases of sudden loss of vision due to nonarteritic ischaemic optic neuropathy (NAION) among users of PDE-5 inhibitors have been reported.

Sildenafil markedly potentiates the vasodilator action of nitrates; precipitous fall in BP; MI can occur. After >6 million prescriptions dispensed in USA, the FDA received reports of 130 deaths related to sildenafil use by the year 2002. Most deaths occurred in patients with known risk factors, drug interactions or contraindications, and were timed either during or within 4–5 hours of sex. Sildenafil is contraindicated in patients of coronary heart disease and those taking nitrates. Though sildenafil remains effective for <8 hours, it is advised that nitrates be avoided for 24 hours. Caution is advised in presence of liver or kidney disease, peptic ulcer, bleeding disorders. Inhibitors of CYP3A4 like erythromycin, ketoconazole, verapamil, cimetidine potentiate its action. Caution is required also in patients of leukaemia, sickle cell anaemia or myeloma which predispose to priapism.

Sildenafil is erroneously perceived as an aphrodisiac. Men even without ED are going for it to enhance sexual satisfaction/pleasure.

PENEGRA, CAVERTA, EDEGRA 25, 50, 100 mg tabs.

Pulmonary arterial hypertension (PAH) Since NO is an important regulator of pulmonary vascular resistance, PDE-5 inhibitiors lower pulmonary arterial pressure. Sildenafil is more selective for pulmonary circulation than vardenafil, and has been shown to improve arterial oxygenation in pulmonary hypertension. It significantly increases exercise capacity. Sildenafil 20 mg TDS has now become the drug of choice for PAH.

Tadalafil It is a more potent and longer acting congener of sildenafil; t½ 18 hours and duration of action 24–36 hours. Peak plasma levels are attained between 30–120 min; time to onset of action may be longer. Side effects, risks, contraindications and drug interactions are similar to sildenafil. In addition, back pain is reported, which has been ascribed to some degree of PDE II inhibition by tadalafil. Because of its longer lasting action, nitrates are contraindicated for upto 3 days after tadalafil. Due to its lower affinity for PDE-6, visual disturbances occur less frequently.

Dose: 10 mg at least 30 min before intercourse (max. 20 mg)

MEGALIS, TADARICH, TADALIS 10, 20 mg tabs, MANFORCE 10 mg tab.

Vardenafil Another congener of sildenafil with similar time-course of action; peak levels in 30–120 min and t½ 4–5 hours. Side effects, contraindications and interactions are also the same. It prolongs Q-T interval; should be avoided in hyperkalaemia and in patients with long Q-T or those receiving class IA and class III antiarrhythmics.

Dose: 10 mg (elderly 5 mg), max 20 mg.

3. Papaverine/Phentolamine induced penile erection (PIPE) therapy

Injection of papaverine (3–20 mg) with or without phentolamine (0.5–1 mg) in the corpus cavernosum produces penile tumescence to permit intercourse. However, the procedure requires skill and training. Priapism occurs in 2–15% cases, which if not promptly treated leads to permanent damage. This is reversed by aspirating blood from the corpus cavernosum or by injecting phenylephrine locally. Repeated injections can cause penile fibrosis. Other complications are—local haematoma, infection, paresthesia and penile deviation. In view of the availability of PDE-5 inhibitors, it is rarely used now; only in cases not responding to sildenafil and alprostadil.

4. Prostaglandin E_1

Alprostadil (PGE_1) injected directly into the corpus cavernosum using a fine needle produces erection lasting 1–2 hours to permit intercourse. Alprostadil injections are less painful than papaverine, but local tenderness may occur. Penile fibrosis and priapism are rare. It is now the most commonly used drug in patients not responding to PDE-5 inhibitors, such as neurogenic and psychogenic ED.

A transurethral pellet termed 'medicated urethral system for erection' (MUSE) has been developed which avoids intracavernosal injection, but is less effective and may cause urethral burning.

☞ PROBLEM DIRECTED STUDY

21.1 A 65-year-old man presented with severe pain in the left shoulder region. The pain has progressively increased over the last 4 weeks, is not relieved by analgesics or NSAIDs and is worsened by pressure or movement. He also has increasing micturition difficulty for the last 6 months. Shoulder X-ray showed osteolytic lesion in the head of humerus. Rectal examination was consistent with prostate cancer which was confirmed by needle biopsy and raised serum PSA level (30 ng/ml). He refused orchidectomy and was prescribed injection triptorelin 3.75 mg i.m. to be repeated after one week and then every 4 weeks. After 1 week of 1st injection, he reported increased bone pain and greater bladder voiding difficulty. The serum PSA level was 34 ng/ml.

(a) What is the cause of the increase in bone pain and urinary obstructive symptoms? Is the choice of the drug incorrect?

(b) Could this flaring of symptoms be avoided; if so how?

(c) Can any other drug be given to relieve the bone pain?

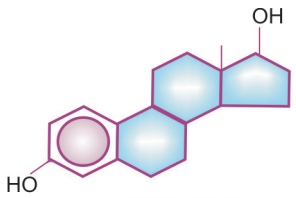
(see Appendix-1 for solution)

Chapter 22 Estrogens, Progestins and Contraceptives

ESTROGENS (Female Sex Hormones)

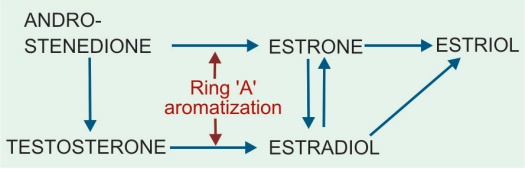
These are substances which can induce estrus in spayed (ovariectomized) animals.

It was established in the year 1900 that ovaries control female reproductive function through a hormonal mechanism. Allen and Doisy (1923) found that an alcoholic extract of ovaries was capable of producing estrus and devised a simple bioassay method. The active principle estradiol was obtained in pure form in 1929 and soon its chemical structure was worked out.



ESTRADIOL

Natural estrogens *Estradiol* is the major estrogen secreted by the ovary. It is synthesized in the graafian follicle, corpus luteum and placenta from cholesterol. Steps depicted on the right hand side in Fig. 20.1 are carried out. Further steps are shown below.

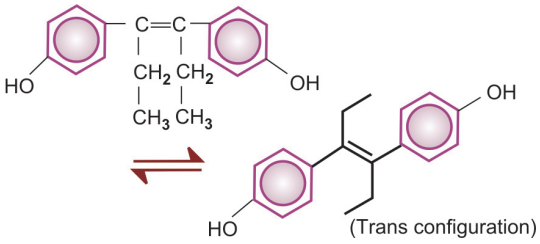


Estradiol is rapidly oxidized in liver to *estrone* which is hydroxylated to form *estriol*. All three are active and circulate in blood, but estradiol is the most potent estrogen. Small quantity (2–20 µg/day) of estradiol is derived in human males also from aromatization of testosterone in the testes and extraglandular tissues. In mare, large quantity of *equilin* is produced which has 1/5 estrogenic potency of estradiol.

Synthetic estrogens Natural estrogens are inactive orally and have a short duration of action due to rapid metabolism in liver. To overcome this, synthetic compounds have been produced:

Steroidal	Ethinylestradiol, Mestranol, Tibolone.
Nonsteroidal	Diethylstilbestrol (stilbestrol) Hexestrol, Dienestrol

The nonsteroidal compounds assume a trans configuration as depicted below and sterically resemble natural estrogens.



DIETHYLSTILBESTROL

Regulation of secretion The daily secretion of estrogens in menstruating women varies from 10–100 µg depending on the phase of the cycle. Its secretion starts from the graafian follicle under the influence of FSH and the blood level rises gradually during the follicular phase. Due to the modest preovulatory FSH surge, estrogens further rise transiently. After ovulation, corpus luteum continues to secrete estrogens till about two days before menstruation. Estrogens exercise feedback inhibition of FSH (also of LH at higher

concentrations) by direct action on pituitary as well as through hypothalamus (*see* p. 240).

During pregnancy, placenta secretes large quantities of estrogens, (mainly estrone and estriol) reaching a peak of upto 30 mg/day at term. Their level declines sharply after delivery. In the postmenopausal women, daily production of estrogen has been estimated as 2–10 µg—derived primarily by extraglandular aromatization of adrenal androgens.

ACTIONS

1. Sex organs The estrogens bring about pubertal changes in the female including growth of uterus, fallopian tubes and vagina. Vaginal epithelium gets thickened, stratified and cornified. They are responsible for the proliferation of endometrium in the preovulatory phase, and it is only in concert with estrogens that progesterone brings about secretory changes.

In the absence of progesterone (anovulatory cycles) withdrawal of estrogens alone produces menstruation. If modest doses of estrogen are given continuously without added progesterone —menstruation is delayed but breakthrough bleeding occurs at irregular intervals. However, the normal event which triggers menstruation is progesterone withdrawal. The progesterone withdrawal bleeding cannot be suppressed even by high doses of estrogens.

Estrogens augment rhythmic contractions of the fallopian tubes and uterus, and induce a watery alkaline secretion from the cervix. This is favourable to sperm penetration. They also sensitize the uterus to oxytocin. Deficiency of estrogens is responsible for atrophic changes in the female reproductive tract that occur after menopause.

2. Secondary sex characters Estrogens produced at puberty cause growth of breasts—proliferation of ducts and stroma, accumulation of fat. The pubic and axillary hair appear, feminine body contours and behaviour are influenced.

Acne is common in girls at puberty as it is in boys—probably due to small amount of androgens produced simultaneously. Administration of estrogens to suppress pituitary-gonadal axis causes regression of acne.

3. Metabolic effects Estrogens are anabolic, similar to but weaker than testosterone. Therefore, small amount of androgen may be contributing to the pubertal growth spurt even in girls, as estrogens do in boys. Continued action of estrogen promotes fusion of epiphyses both in girls and boys.

Estrogen is important in maintaining bone mass primarily by retarding bone resorption. Osteoclast pit formation is inhibited and there is increased expression of bone matrix proteins such as osteonectin, osteocalcin, collagen and alkaline phosphatase. It promotes positive calcium balance, partly by inducing renal hydroxylase enzyme which generates the active form of Vit D_3.

Both osteoblasts and osteoclasts express estrogen receptors (ERs). The major action of estrogens is to reduce maturation and activity of osteoclasts by modifying regulatory cytokine signals from osteoblasts (*see* Ch. 24 for bone remodeling mechanisms). Estrogens enhance elaboration of OPG from osteoblasts which binds RANKL and prevents activation of osteoclast-precursors from fusing and maturing into osteoclasts. The direct action on osteoclasts is to accelerate their apoptosis.

Pharmacological doses of estrogens can cause mild salt and water retention—edema occurs in predisposed patients, but it can be treated with diuretics. BP may rise after prolonged use. Combination contraceptives containing higher doses of estrogens and progestins impair glucose tolerance. Normal blood sugar is not affected but diabetes may be precipitated or its control vitiated. However, amounts used for HRT and low dose contraception do not affect carbohydrate metabolism.

Estrogens decrease plasma LDL cholesterol while HDL and triglyceride levels are raised. The raised HDL : LDL ratio is probably responsible for rarity of atherosclerosis in premenopausal women. However, blood coagulability is increased due to induction of synthesis of clotting factors (factors II, VII, IX and X). Fibrinolytic activity in plasma also tends to increase due to lowering of plasminogen-activator inhibitor-1 (PAI-1).

Estrogens induce nitric oxide synthase and PGI_2 production in vascular endothelium. The increased availability of NO and PGI_2 could promote vasodilatation. They increase lithogenicity of bile by increasing cholesterol secretion and reducing bile salt secretion. Plasma levels of sex hormone binding globulin (SHBG), thyroxine binding globulin (TBG) and cortisol binding globulin (CBG) are elevated—but without any change in hormonal status.

Mechanism of action

Estrogens bind to specific nuclear receptors in target cells and produce effects by regulating protein synthesis. Estrogen receptors (ERs) have been demonstrated in female sex organs, breast, pituitary, liver, bone, blood vessels, heart, CNS and in certain hormone responsive breast carcinoma cells. The ER is analogous to other steroid receptors: agonist binding to the ligand binding domain brings about receptor dimerization and interaction with 'estrogen response elements' (EREs) of target genes. Gene transcription is promoted through certain *coactivator proteins.* On binding an estrogen antagonist the receptor assumes a different conformation and interacts with other *corepressor proteins* inhibiting gene transcription.

Two distinct ERs designated ERα and ERβ have been identified, cloned and structurally characterized. Most tissues express both subtypes, but ERα predominates in uterus, vagina, breast, bone, hypothalamus and blood vessels, while ERβ predominates in prostate gland of males and ovaries in females. Estradiol binds to both ERα and ERβ with equal affinity, but certain ligands have differing affinities. More importantly ERα and ERβ may have a different pattern of interaction with coactivators and corepressors.

Few nongenomic rapid actions of estrogens in certain tissues mediated through the same ERs but located on the cell membrane have also been observed.

PHARMACOKINETICS

Estrogens are well absorbed orally and transdermally, but natural estrogens are inactive by the oral route due to rapid metabolism in liver. Estradiol esters injected i.m. are slowly absorbed and exert prolonged action. Natural estrogens in circulation are largely plasma protein bound—to SHBG as well as to albumin.

Estradiol is converted to estrone and *vice versa* in liver. Estriol is derived from estrone. All three are conjugated with glucuronic acid and sulfate—excreted in urine and bile. Considerable enterohepatic circulation occurs due to deconjugation in intestines and reabsorption—ultimate disposal occurs mostly in urine.

Ethinylestradiol is metabolized very slowly (t½ 12–24 hours). It is orally active and more potent.

Preparations and dose

All estrogen preparations have similar action. Their equivalent *parenteral* doses are—

Estradiol 0.1 mg = Ethinylestradiol 0.1 mg = Mestranol 0.15 mg = Conjugated estrogens 10 mg = Estriol succinate 16 mg = Diethylstilbestrol 10 mg.

The *oral* potencies differ from the above due to differing extents of first pass metabolism. Estradiol is inactive orally, conjugated estrogens and estriol succinate undergo partial presystemic metabolism, while in case of ethinylestradiol, mestranol and diethylstilbestrol the oral and parenteral doses are practically the same.

The preferred route of administration of estrogens is oral. Intramuscular injection is resorted to only when large doses have to be given, especially for carcinoma prostate.

1. Estradiol benzoate/cypionate/enanthate/valarate: 2.5–10 mg i.m.; OVOCYCLIN-P 5 mg inj, PROGYNON DEPOT 10 mg/ml inj.
2. Conjugated estrogens: 0.625–1.25 mg/day oral; PREMARIN 0.625 mg, 1.25 mg tab, 25 mg inj (for dysfunctional uterine bleeding).
3. Ethinylestradiol: for menopausal syndrome 0.02–0.2 mg/day oral; LYNORAL 0.01, 0.05, 1.0 mg tab, PROGYNON-C 0.02 mg tab.
4. Mestranol: acts by getting converted to ethinylestradiol by demethylation in the liver: 0.1–0.2 mg/day oral; in OVULEN 0.1 mg tab, with ethynodiol diacetate 1 mg.
5. Estriol succinate: 4–8 mg/day initially, maintenance dose in menopause 1–2 mg/day oral: EVALON 1, 2 mg tab, 1 mg/g cream for vaginal application in atrophic vaginitis 1–3 times daily.
6. Fosfestrol tetrasodium: initially 600–1200 mg slow i.v. inj for 5 days, maintenance 120–240 mg/day oral or 300 mg 1–3 times a week i.v. HONVAN 120 mg tab, 60 mg/ml inj 5 ml amp.
7. Dienestrol: 0.01% topically in vagina: DIENESTROL 0.01% vaginal cream.

Transdermal estradiol A transdermal patch (Estradiol-TTS) is available in 3 sizes, *viz.* 5, 10 and 20 cm^2 delivering 0.025 mg, 0.05 mg and 0.1 mg respectively in 24 hr for 3–4 days. The usual dose in menopause is 0.05 mg/day which produces plasma estradiol levels seen in premenopausal women in the early or mid follicular phase. Cyclic therapy (3 weeks on, 1 week off) with estradiol-TTS is advised with an oral progestin added for the last 10–12 days. Beneficial effects of estradiol-TTS on menopausal symptoms, bone density, vaginal epithelium and plasma Gn levels are comparable to those of oral therapy, but improvement is serum lipid profile is less marked.

Systemic side effects of estradiol-TTS are the same as with oral estrogens, but are milder. Oral therapy delivers high dose of the hormone to the liver and increases synthesis of several proteins. Estradiol-TTS avoids high hepatic delivery: consequently plasma levels of TBG, CBG, angiotensinogen and clotting factors are not elevated—risk of thromboembolic phenomena may not be increased.

ESTRADERM-MX: Estradiol 25, 50 or 100 µg per 24 hr transdermal patches; apply to nonhairy skin below waist, replace every 3–4 days using a different site; add an oral progestin for last 10–12 days every month.

Recently a combined estradiol 50 µg + norethisterone acetate 0.25 mg patch has become available in some countries (ESTRAGEST-TTS). Two weeks of estraderm-TTS followed by 2 weeks estragest-TTS with patches changed twice weekly is used for total transdermal HRT.

A gel formulation of estradiol for application over skin is also available. OESTRAGEL, E_2 GEL 3 mg/5 g in 80 g tube, SANDRENA 1 mg/g gel; apply over the arms and spread to cover a large area once daily for HRT.

ADVERSE EFFECTS

Most of the adverse effects of estrogens are described with HRT and with oral contraceptives (*see* p. 325).

In addition, dose dependent adverse effects noted when use is made for other indications are—

1. Suppression of libido, gynaecomastia and feminization when given to males.
2. Fusion of epiphyses and reduction of adult stature when given to children.
3. In postmenopausal women, estrogens can increase the risk of irregular bleeding and endometrial carcinoma (5–15 fold). A progestin given concurrently blocks the risk.
4. Estrogens can accelerate the growth of existing breast cancer, but low-dose estrogen only HRT does not appear to increase the risk of developing new breast cancer (*see* p. 311).
5. Long-term estrogen therapy doubles the incidence of gallstones. Benign hepatomas are more common in women taking estrogens in their teens and twenties.
6. Migraine, epilepsy and endometriosis may be worsened by estrogens.
7. Stilbestrol given to pregnant women, especially during first trimester (as test of pregnancy or otherwise)—increased the incidence of vaginal and cervical carcinoma in the female offspring in childhood or early adulthood. Other genital abnormalities are possible in the female as well as male offspring. Estrogens are contraindicated during pregnancy.

USES

Currently, the two most common uses of estrogens are as contraceptives and for hormone replacement therapy in postmenopausal women, but there are some other indications as well.

1. Hormone replacement therapy (HRT)

Due to cessation of ovarian function at menopause women suffer a number of physical, psychological and emotional consequences.

Medical problems related to menopause are:

- *Vasomotor disturbances* Hot flushes, chilly sensation, inappropriate sweating, faintness, paresthesias, aches and pains.
- *Urogenital atrophy* Change in vaginal cytology and pH, vaginal dryness, vulval shrinkage, dyspareunia, vaginitis, itching, urinary urgency, predisposition to urinary tract infection.
- *Osteoporosis* Loss of osteoid as well as calcium → thinning and weakening of bone → minimal trauma fractures especially of femur, hip, radius, vertebrae.
- *Dermatological changes* Thinning, drying and loss of elasticity of skin, wrinkles, thin and listless hairs.
- *Psychological/Cognitive disturbances* Irritability, depressed mood, loss of libido and self confidence, anxiety and dementia.
- *Increased risk of cardiovascular diseases* Coronary artery disease, myocardial infarction, stroke.

The vasomotor symptoms tend to subside over a few years, but the other changes progress continuously.

Estrogen ±progestin HRT or 'menopausal hormone therapy' (MHT) is highly efficacious in suppressing the perimenopausal syndrome of vasomotor instability, psychological disturbances as well as in preventing atrophic changes and osteoporosis. However, several recent findings have emphasized a number of risks and limitations of long-term HRT, so that the whole outlook has changed.

The *dose* of estrogen used in HRT is substantially lower than that for contraception. Typically conjugated estrogens are used at 0.625 mg/day dose (equivalent to ethinylestradiol 10 µg) either cyclically (3 weeks treatment 1 week gap) or continuously, but there is a trend now to use lower doses (0.3–0.45 mg/day). A progestin (medroxy progesterone acetate/norethisterone 2.5 mg daily) is added for the last 10–12 days each month. Though the progestin may attenuate the metabolic and cardiovascular benefits of estrogen, it is needed to block the increased risk of dysfunctional uterine bleeding and endometrial carcinoma due to continuous estrogenic stimulation of endometrium. Estrogen alone is used in hysterectomised women and when a progestin is not tolerated or is contraindicated. Transdermal estradiol (with oral or transdermal progestin) appears to have certain advantages (*see* above) and is preferred by some.

The benefits and risks of HRT are considered below:

a. Menopausal symptoms and atrophic changes The vasomotor symptoms respond promptly and almost completely. They are the primary indication for using HRT which also improves general physical, mental and sexual well being. HRT should be discontinued once the vasomotor symptoms abate. Estrogens also arrest genital and dermal atrophic changes; vulval and urinary problems resolve. Vaginal application of estrogen is effective in relieving local symptoms and should be preferred when this is the only aim of HRT.

b. Osteoporosis and fractures HRT restores Ca^{2+} balance; further bone loss is prevented and the excess fracture risk is nullified. When used for this purpose, HRT should be initiated before significant bone loss has occurred, because reversal of osteoporosis is none or slight. Calcium + vit D supplements and exercise aid the beneficial effect of HRT. However, accelerated bone loss starts again on cessation of HRT. The 'Women's health, osteoporosis, progestin-estrogen' trial (2002) has shown that even lower doses of conjugated estrogens (0.3, 0.45 mg/day) increased bone mineral density in postmenopausal women, though 0.625 mg/day was more effective.

Not withstanding the above, appreciation of the other risks of HRT (*see* below) has dislodged estrogen from its prime position in the treatment of osteoporosis. Bisphosphonates are more effective and the drugs of choice. If prevention and treatment of osteoporosis is the goal, HRT is not the best option, and is not recommended beyond 5 years of use.

c. Cardiovascular events Since hypertension and cardiovascular disease are rare in premenopausal women, and estrogens improve HDL : LDL ratio, retard atherogenesis, reduce arterial impedance, increase NO and PGI_2 production and prevent hyperinsulinaemia, it was believed that estrogen therapy in postmenopausal women will have a protective cardiovascular influence. This was supported by early reports relying mainly on retrospective/epidemiological studies and those using surrogate markers to indicate that HRT in otherwise healthy women reduced risk of coronary artery disease (CAD), myocardial infarction (MI) and stroke. This lead to the extensive use of HRT; a segment of doctors contended that menopausal women should take HRT for the rest of their lives.

In the past decade many large scale placebo controlled randomized interventional trials and cohort studies have yielded opposite results. The 'Heart and estrogen/progestin replacement study' (HERS and HERS II) conducted in older women with preexisting cardiovascular disease found that HRT triples the risk of venous thromboembolism, increases risk of MI in the 1st year and affords no secondary prophylaxis of CAD in the long-term. The larger 'women's health initiative' (WHI) study conducted in over 16000 younger women without CAD found 24% increase in CAD, 40% increase in stroke and doubling of venous thromboembolism with the use of combined HRT. The study was terminated prematurely in 2002. The increased risk of MI was attributed to the progestin component, since women who took estrogen alone had no increase in the incidence of MI. Reexamination of the data has revealed ~30% reduction in incidence of MI among women who took HRT within 10 years of menopause. As such, a few years of HRT just after menopause may be protective. The committee on safety of medicines (CSM) of UK has estimated that ~20 out of 1000 women aged 60–69 years and not using HRT develop venous thromboembolism over 5 years; 4 extra cases occur in those taking estrogen alone, while 9 extra cases occur in those taking combined HRT. Thus, progestin use adds to the risk.

d. Cognitive function and dementia: Contrary to earlier belief, the 'women's health initiative memory study' (WHIMS) conducted among older women (65–79 years) has failed to detect any protection against cognitive decline by either estrogen alone or combined HRT. There was in fact a slight global deterioration. Surprisingly, the incidence of dementia (Alzheimer's) was doubled.

e. Cancer: That estrogens enhance the growth of *breast cancer* has been well recognized. However, it was contended

that small replacement doses of estrogens will not induce new cancer. This appears to be supported by the estrogen alone arm of WHI study in hysterectomized women, as the occurrence of breast cancer was actually lower (but insignificantly). However, in the combined HRT group, a significantly higher incidence of cancer breast occurred, indicating that medroxyprogesterone was the culprit. The prospective observational cohort 'Million women study' (MWS) in the UK found a marginally higher incidence of breast cancer with estrogen alone, but a clearly higher one with estrogen + progestin. Some other studies have also implicated the progestin, and the CSM of UK has drawn similar conclusions. Thus, the protective effect of progestin on endometrial cancer appears to be counter balanced by the procarcinogenic effect on the breast.

Estrogen is well known to induce endometrial hyperplasia and its continuous use unopposed by progestin results in irregular uterine bleeding. In the long-term it predisposes to *endometrial carcinoma*. The MWS has supported this contention. The standard practice is to give combined HRT to women with an intact uterus. However, a Cochrane Database Review has concluded that lower dose unopposed estrogen does not increase endometrial carcinoma risk; may be used in women with intact uterus when a progestin is contraindicated.

A small protective effect of combined HRT on *colorectal carcinoma* has been detected by the WHI study, but this needs to be confirmed.

f. Gallstone, migraine: Estrogens slightly increase the risk of developing gallstones, while progestins may trigger migraine.

Tibolone It is a 19-norsteroid developed specifically to be used for HRT. It is converted into 3 metabolites which exert estrogenic, progestational and weak androgenic actions in specific tissues. In a dose of 2.5 mg daily, it suppresses menopausal symptoms and lowers the raised Gn levels. No endometrial stimulation has been noted. Urogenital atrophy, psychological symptoms, libido and osteoporosis are improved similar to other forms of HRT. Contraindications are the same as for conventional HRT, but long term benefits and risks are not defined.

Weight gain, increased facial hair and occasional vaginal spotting may be noted.

LIVIAL 2.5 mg tab, one tab daily without interruption; institute therapy only after the women has been menopausal for atleast 12 months.

2. *Senile vaginitis* Estrogens change vaginal cytology to the premenopausal pattern and are effective in preventing as well as treating atrophic vaginitis that occurs in elderly women. Oral therapy can be given but more commonly a topical preparation is used; an antibacterial may be combined. Estrogens help in overcoming infection and relieve symptoms of *Kraurosis vulvae*.

3. *Delayed puberty in girls* It may be due to ovarian agenesis (Turner's syndrome) or hypopituitarism. In both, pubertal changes are brought about by estrogen treatment, except the rapid gain in height for which growth hormone and/or a small dose of androgen may be added. Usually cyclic treatment is given; some prefer to start with a lower dose and gradually attain the full replacement dose.

Current conclusions regarding HRT

1. The main indication of HRT is vasomotor and other symptoms in the perimenopausal period. It should be used at the smallest effective dose and for the shortest duration.
2. Young women with premature menopause clearly deserve HRT.
3. Hysterectomized women should receive estrogen alone, while those with intact uterus be given estrogen + progestin.
4. Perimenopausal women should be given cyclic HRT rather than continuous HRT.
5. HRT is not the best option to prevent osteoporosis and fractures.
6. HRT affords protection against coronary artery disease only in early postmenopausal women. Combined HRT at conventional dose may even increase the risk of venous thromboembolism, MI and stroke in elderly women.
7. HRT does not protect against cognitive decline; may increase the risk of dementia.
8. Combined HRT increases the risk of breast cancer, gallstones and migraine.
9. Transdermal HRT may have certain advantages over oral HRT.
10. The need for HRT should be assessed in individual women, and not prescribed routinely.

4. *Dysmenorrhoea* While PG synthesis inhibitors are the first line drugs, cyclic estrogen therapy (with added progestin to ensure withdrawal bleeding) benefits by inhibiting ovulation (anovular cycles are painless) and decreasing prostaglandin synthesis in endometrium; but this should be reserved for severe cases.

5. *Acne* It occurs at puberty due to increased androgen secretion in both boys and girls. Estrogens benefit by suppressing ovarian production of androgen by inhibiting Gn release from pituitary. Cyclic treatment (with added progestin) is quite effective. Use of estrogen in boys is out of question. Even in girls, topical therapy with antimicrobials, tretinoin and other drugs is preferred (*see* Ch. 64).

6. *Dysfunctional uterine bleeding* A progestin given cyclically is the rational and effective therapy. Estrogens have adjuvant value.

7. *Carcinoma prostate* Estrogens are palliative; produce relief in primary as well as metastatic carcinoma prostate by suppressing androgen production (through pituitary). GnRH agonists with or without androgen antagonist are preferred.

ANTIESTROGENS AND SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

Two nonsteroidal compounds *clomiphene citrate* and *tamoxifen citrate* previously grouped as estrogen antagonists have been in use since 1970s, but their differing antagonistic and agonistic actions depending on species, target organ and hormonal background could not be explained. The recent discovery of two estrogen receptors (ERα and ERβ) and that ligand binding could change their configuration in multiple ways allowing interaction with different coactivators and corepressors in a tissue specific manner has paved the way for development of compounds with unique profile of agonistic and antagonistic actions in different tissues. These drugs have been designated '*selective estrogen receptor modulators' (SERMs)*, and two new compounds *Raloxifene* and *Toremifene* are in clinical use. It has been demonstrated that the conformation of ER after binding tamoxifen or raloxifene is different from that after binding estradiol.

Antiestrogens

Clomiphene citrate It binds to both ERα and ERβ and acts as a pure estrogen antagonist in all human tissues, but the racemate displays weak agonistic action in rats. It induces Gn secretion in women by blocking estrogenic feedback inhibition of pituitary. The amount of LH/FSH released at each secretory pulse is increased. In response, the ovaries enlarge and ovulation occurs if the ovaries are responsive to Gn. Antagonism of peripheral actions of estrogen results in hot flushes. Endometrium and cervical mucus may be modified.

The chief use of clomiphene is for infertility due to failure of ovulation: 50 mg once daily for 5 days starting from 5th day of cycle. Treatment is given monthly. Conception occurs in many women who previously were amenorrhoeic or had anovular cycles. If 1–2 months treatment does not result in conception—the daily dose may be doubled for 2–3 cycles. No more than 6 treatment cycles should be tried. The antiestrogenic effect of clomiphene on developing follicle, endometrium or cervical mucus can be counterproductive. Luteal phase dysfunction has also been blamed for therapeutic failures. Addition of menotropins or chorionic gonadotropin on the last 2 days of the course improves the success rate.

Clomiphene is well absorbed orally, gets deposited in adipose tissue and has long t½ of ~6 days. It is largely metabolized and excreted in bile.

Adverse effects Polycystic ovaries, multiple pregnancy, hot flushes, gastric upset, vertigo, allergic dermatitis. Risk of ovarian tumour may be increased.

Other uses *To aid in vitro fertilization* Clomiphene given with Gns causes synchronous maturation of several ova—improves their harvesting for *in vitro* fertilization.

Oligozoospermia: In men also clomiphene increases Gn secretion → promotes spermatogenesis and testosterone secretion. For male infertility—25 mg daily given for 24 days in a month with 6 days rest for upto 6 months has been recommended. However, success rates are low.

CLOMID, FERTOMID. CLOFERT, CLOME 25, 50, 100 mg tab.

Fulvestrant It is the first member of a distinct class of ER ligands called 'selective estrogen receptor down-regulators' (SERDs) or 'pure estrogen antagonists' that has been introduced for the treatment of metastatic ER positive breast cancer in postmenopausal women which has stopped responding to tamoxifen. In contrast to tamoxifen, it inhibits ER dimerization so that ER interaction with DNA is prevented and receptor degradation is enhanced. The ER is thus down regulated resulting in more complete suppression of ER responsive gene function. This feature along with its higher affinity for the ER probably accounts for its efficacy in tamoxifen resistant cases.

Fulvestrant is administered as (250 mg) monthly i.m. injections in the buttock. It is slowly absorbed and has an elimination t½ of more than a month.

Selective estrogen receptor modulators (SERMs)

These are drugs which exert estrogenic as well as antiestrogenic actions in a tissue selective manner.

Tamoxifen citrate Though chemically related to clomiphene, it has complex actions; acts as potent estrogen antagonist in breast carcinoma cells, blood vessels and at some peripheral sites, but as partial agonist in uterus, bone, liver and pituitary. Inhibition of human breast cancer cells and hot flushes reflect antiestrogenic action, while the weak estrogen agonistic action manifests as stimulation of endometrial proliferation, lowering of Gn and prolactin levels in postmenopausal women as well as improvement in their bone density.

A decrease in total and LDL cholesterol without any change in HDL and triglyceride level reflects estrogenic action. Similar to estrogen HRT, it increases the risk of deep vein thrombosis by 2–3 times.

Till recently tamoxifen has been the standard hormonal treatment of breast cancer in both pre- and post-menopausal women, but aromatase inhibitors have now gained prominence. In early cases tamoxifen is given as postmastectomy adjuvant therapy, while in advanced cases, it is a constituent of palliative treatment. Response rates are high in ER-positive breast carcinomas, but some ER-negative tumours also respond suggesting additional nonhormonal mechanism of action. Tamoxifen is the only drug approved for primary as well as metastatic breast carcinoma in premenopausal women. It is also effective in surgically treated cancer of male breast.

Based on large epidemiological studies which have shown 45% reduction in the incidence of ER-positive breast cancer, tamoxifen has been approved for primary prophylaxis of breast cancer in high-risk women. Recurrence rate in ipsilateral as well as contralateral breasts is reduced by tamoxifen, but benefits of prophylactic therapy beyond 5 years are not proven; outcomes may even be worse. Adjuvant therapy of breast carcinoma with tamoxifen when used in postmenopausal women is now generally replaced after 2 years by an aromatase inhibitor, while in premenopausal women, tamoxifen itself is continued till 5 years postmastectomy.

Improvement in bone mass due to anti-resorptive effect, and in lipid profile are the other benefits of tamoxifen therapy. However, endometrial thickening occurs and risk of endometrial carcinoma is increased 2–3 fold due to estrogenic action.

Tamoxifen is effective orally; has a biphasic plasma t½ (10 hours and 7 days) and a long duration of action. Some metabolites of tamoxifen are more potent antiestrogens. The drug is excreted primarily in bile.

Dose 20 mg/day in 1 or 2 doses, max. 40 mg/day; TAMOXIFEN, MAMOFEN, TAMODEX 10, 20 mg tabs.

Male infertility: May be used as alternative to clomiphene.

Side effects Hot flushes, vomiting, vaginal bleeding, vaginal discharge, menstrual irregularities are the side effects. Increased risk of venous thromboembolism is due to estrogenic action on clotting mechanism.

Dermatitis, anorexia, depression, mild leucopenia and ocular changes are infrequent.

Tamoxifen is much less toxic than other anticancer drugs.

Toremifene It is a newer congener of tamoxifen with similar actions, but is a weaker ER agonist. Uses and adverse effects are also similar.

Raloxifene This SERM has a different pattern of action than tamoxifen. It is an estrogen partial agonist in bone and cardiovascular system, but an antagonist in endometrium and breast. It has high affinity for both ERα and ERβ, and has a distinct DNA target the *'raloxifene response element'* (RRE).

Several long-term multicentric studies have shown that raloxifene prevents bone loss in postmenopausal women; bone mineral density (BMD) may even increase by 0.9–3.4% over years in different bones, particularly the lumbar vertebrae. However, accelerated bone loss occurs when raloxifene is stopped. The risk of vertebral fracture is reduced to half, but not that of long bones. Reloxifene is less efficacious than bisphosphonates in preventing fractures.

In postmenopausal women raloxifene reduces LDL cholesterol, probably by upregulating hepatic LDL receptors. In contrast to estrogen HRT there is no increase in HDL and triglyceride levels. Follow up studies have shown that raloxifene reduces the risk of breast cancer by 65%, though the protection was confined to ER-positive breast cancer.

Raloxifene does not stimulate endometrial proliferation and there is no increase in the risk of endometrial carcinoma. No relief of menopausal vasomotor symptoms occurs; rather hot flushes may be induced in some women.

Raloxifene is absorbed orally but has low bioavailability due to extensive first pass glucuronidation. The t½ is 28 hours and major route of excretion is faeces.

Side effects Hot flushes, leg cramps are generally mild; vaginal bleeding is occasional. The only serious concern is 3-fold increase in risk of deep vein thrombosis and pulmonary embolism. However, similar risk attends estrogen HRT.

Use Raloxifene is a second line drug for prevention and treatment of osteoporosis in postmenopausal women; Ca^{2+} and vit D supplements enhance the benefit. According to British guidelines, raloxifene is not recommended for primary prophylaxis of osteoporotic fractures in postmenopausal women, but is an alternative option for secondary prevention and treatment of vertebral fractures, *i.e.* in those who have already suffered a fracture. It has no use in men.

Dose: 60 mg/day;

BONMAX, RALOTAB, ESSERM 60 mg tab.

AROMATASE INHIBITORS

Aromatization of 'A' ring of testosterone and androstenedione is the final and key step in the production of estrogens (estradiol/estrone) in the body. In addition to the circulating hormone, locally produced estrogens appear to play an important role in the development of breast cancer. Though some aromatase inhibitors (AIs) were produced in the past, three recent 'third generation' AIs *Letrozole, Anastrozole* and *Exemestane* have demonstrated clinical superiority and are widely used now in the treatment of breast cancer.

Properties of AIs are compared with that of tamoxifen in Table 22.1.

Letrozole It is an orally active nonsteroidal (type 2) compound that reversibly inhibits aromatization all over the body, including that within the breast cancer cells, resulting in nearly total estrogen deprivation. Proliferation of estrogen dependent breast carcinoma cells is suppressed to a greater extent than with tamoxifen. Letrozole is rapidly absorbed with 100% oral bioavailability, large volume of distribution, slow metabolism and a t½ of ~40 hours. Randomized clinical trials have established its utility in:

(a) *Early breast cancer:* Letrozole is a first line drug for adjuvant therapy after mastectomy in ER+ive postmenopausal women. Extended adjuvant therapy with letrozole beyond the standard 5 year tamoxifen treatment continues to afford protection, whereas continuation of tamoxifen is not useful. Replacement of tamoxifen by an AI is now recommended after 2 years (sequential therapy). Survival is prolonged in patients who have positive axillary lymph nodes.

(b) *Advanced breast cancer:* Current guidelines recommend letrozole as first line therapy because of longer time to disease progression and higher response rate obtained with it compared to tamoxifen. It is also effective as second line treatment when tamoxifen has failed.

TABLE 22.1 Comparative properties of tamoxifen (SERM) and letrozole/anastrozole (AIs)

Tamoxifen	*Letrozole/Anastrozole*
1. Estrogen antagonist in breast and blood vessels, but agonist in uterus, bone, liver and pituitary.	1. Inhibits production of estrogens in all tissues. Nearly total estrogen deprivation.
2. Can be used for breast Ca. in premenopausal women as well.	2. Not to be used in premenopausal women.
3. Less effective in delaying recurrence when used as adjuvant therapy after surgery.	3. More effective in delaying recurrence of early stage breast Ca. (adjuvant therapy)
4. Prophylactic use for breast Ca. recurrence limited to 5 years.	4. Continues to exert prophylactic effect beyond 5 years.
5. Less delay in disease progression and lower survival advantage in advanced/metastatic breast Ca. than AIs.	5. Greater delay in disease progression and greater survival advantage in palliative treatment of advanced/metastatic breast Ca.
6. Not effective in failure cases.	6. Effective in tamoxifen failure cases of advanced breast Ca.
7. Causes endometrial hyperplasia, predisposes to endometrial carcinoma	7. No endometrial hyperplasia/cancer predisposition.
8. No bone losss, no increase in fractures or arthritic symptoms	8. Accelerates bone loss, predisposes to fractures, arthritic symptoms.
9. Increases risk of venous thromboembolism	9. No increase in thromboembolic risk
10. Improves lipid profile; small lowering of LDL Ch.	10. No effect on lipid profile.

SERM—Selective estrogen receptor modulate; AIs—aromatase inhibitors; Ca.—Carcinoma; LDL Ch—Low density lipoprotein cholesterol

Adverse effects Hot flushes, nausea, diarrhoea, dyspepsia and thinning of hair are the side effects. Joint pain is common and bone loss may be accelerated. However, there is no endometrial hyperplasia or increased risk of endometrial carcinoma. Risk of venous thromboembolism is also not increased, and there is no deterioration of lipid profile.

Dose: 2.5 mg OD oral.

LETOVAL, LETROZ, FEMARA, ONCOLET 2.5 mg tab.

Though contraindicated in premenopausal women, letrozole was clandestinely promoted and tested as an ovulation inducing fertility drug. Use of letrozole for inducing ovulation in infertile women has been banned in India since Oct. 2011.

Anastrozole Another nonsteroidal and reversible (Type 2) AI, more potent than letrozole and suitable for single daily dosing. It accumulates in the body to produce peak effect after 7–10 days. Anastrozole is useful as adjuvant therapy in early ER+ive breast cancer as well as for palliation of advanced cases in postmenopausal women. In early cases, tumor recurrence time was found to be longer than with tamoxifen. Risk of new tumor appearing in the contralateral breast was also lower with anastrozole. A longer time to disease progression compared to tamoxifen has been obtained in advanced ER+ive breast cancer. Many tamoxifen resistant cases responded with increased survival. Like letrozole, it is also a first line drug for early as well as advanced breast carcinoma in postmenopausal women. Side effects are hot flushes, vaginal dryness, vaginal bleeding, nausea, diarrhoea, thinning of hair. Arthralgia and acceleration of osteoporosis are prominent. However, it does not predispose to endometrial carcinoma or to venous thromboembolism.

Dose: 1 mg OD.

ALTRAZ, ARMOTRAZ, ANABREZ 1 mg tab.

Exemestane: This steroidal and irreversible (Type 1) inhibitor of aromatase acts like a suicide substrate by covalent binding to the enzyme. As a result >90% suppression of estradiol production is obtained. However, it has weak androgenic activity similar to androstenedione. Exemestane has been found beneficial in early breast cancer by reducing the risk of disease progression when it was substituted for tamoxifen as adjuvant therapy. In advanced breast cancer, longer survival, increased time to disease progression and fewer treatment failures have been obtained with exemestane. It is administered orally and is well tolerated. Adverse effects are similar to other AIs.

PROGESTINS

These are substances which convert the estrogen primed proliferative endometrium to secretory and maintain pregnancy in animals spayed after conception (*Progestin* = favouring pregnancy).

At the turn of the last century it became apparent that ovaries secrete two hormones, and that corpus luteum was essential for maintenance of pregnancy. Progesterone was isolated in 1929, but its full therapeutic potential has been exploited only after the 1950s when a large number of orally active synthetic progestins were developed.

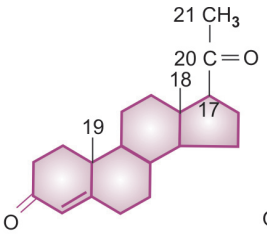
Natural progestin Progesterone, a 21 carbon steroid, is the natural progestin and is derived from cholesterol (*see* Fig. 20.1). It is secreted by the corpus luteum (10–20 mg/day) in the later half of menstrual cycle under the influence of LH. Its production declines a few days before the next menstrual flow. If the ovum gets fertilized and implants—the blastocyst immediately starts producing chorionic gonadotropin which is absorbed into maternal circulation and sustains the corpus luteum in early pregnancy. Placenta starts secreting lots of estrogens and progesterone from 2nd trimester till term. Men produce 1–5 mg progesterone per day from adrenals and testes; its role if any, in males is not known.

Synthetic progestins A number of synthetic progestins with high oral activity have been produced. These are either progesterone derivatives (21 C) or 19-nortestosterone derivatives, also called *'estranes'* (18 C).

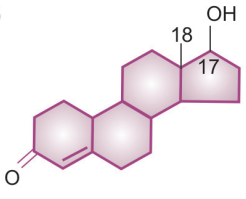
The progesterone derivatives are almost pure progestins, have weaker antiovulatory action and are used primarily as adjuvants to estrogens for HRT in postmenopausal women, threatened abortion, endometriosis, etc. for selective progestational effect. The older 19-nortestosterone derivatives developed in the 1950-60s have additional weak estrogenic, androgenic, anabolic and potent antiovulatory action: are used primarily in combined contraceptive pills. Estranes with a 13-ethyl substitution are called '*gonanes*', e.g. *norgestrel*. Gonanes are more potent (especially the levoisomers, e.g. *levonorgestrel*) and have reduced androgenic activity.

In the 1980-90s a number of other gonane compounds were introduced, of which *desogestrel* has been marketed in India. Desogestrel and *norgestimate* are prodrugs. In addition to being very potent progestins they have strong antiovulatory action (*gestodene* inhibits ovulation at as low as 40 µg/day dose), and little or no androgenic property. Therefore, they do not antagonise the beneficial action of estrogens on lipid profile and are preferable in women with hyperandrogenemia. High antiovulatory potency allows reduction of ethinylestradiol dose when these are combined in oral contraceptives.

The newer 19-norprogesterone derivative *nomegestrol* has weak antiandrogenic property, is less antiovulatory, but has strong antiestrogenic effect on endometrium. Adverse effects on lipid profile and glucose tolerance appear to be lacking.



PROGESTERONE



19-NOR TESTOSTERONE

PROGESTERONE DERIVATIVES

Medroxyprogesterone acetate
Megestrol acetate
Dydrogesterone
Hydroxyprogesterone caproate

Newer compound
Nomegestrol acetate

19-NORTESTOSTERONE DERIVATIVES

Older compounds	*Newer compounds*
Norethindrone (Norethisterone)	*(Gonanes)*
Lynestrenol (Ethinylestrenol)	Desogestrel
Allylestrenol	Norgestimate
Levonorgestrel *(Gonane)*	Gestodene

ACTIONS

The main function of progesterone is preparation of the uterus for nidation and maintenance of pregnancy. The latter is due to prevention of endometrial shedding, decreased uterine motility and inhibition of immunological rejection of the foetus: progesterone depresses T-cell function and cell-mediated immunity (CMI).

1. *Uterus* Progesterone brings about secretory changes in the estrogen primed endometrium: hyperemia, tortuocity of glands and increased secretion occurs while epithelial proliferation is halted. It is lack of progestational support which causes mucosal shedding during menstruation.

Continued action of progesterone (when pregnancy occurs) brings about decidual changes in endometrium—stroma enlarges and becomes spongy, glands atrophy, and sensitivity of myometrium to oxytocin is decreased.

2. *Cervix* Progesterone converts the watery cervical secretion induced by estrogens to viscid, scanty and cellular secretion which is hostile to sperm penetration.

3. *Vagina* Progesterone induces pregnancy like changes in the vaginal mucosa: leukocyte infiltration of cornified epithelium occurs.

4. *Breast* Progesterone causes proliferation of acini in the mammary glands. Cyclic epithelial proliferation and turnover occurs during luteal phase, but continuous exposure to progesterone during pregnancy halts mitotic activity and stabilizes mammary cells. Acting in concert with estrogens, it prepares breast for lactation. Withdrawal of these hormones after delivery causes release of prolactin from pituitary and milk secretion starts.

5. *CNS* High circulating concentration of progesterone (during pregnancy) appears to have a sedative effect. It can also affect mood.

6. *Body temperature* A slight (0.5°C) rise in body temperature by resetting the hypothalamic thermostat and increasing heat production is induced. This is responsible for the higher body temperature seen during the luteal phase.

7. *Respiration* Progestins in relatively higher doses stimulate respiration, as occurs during pregnancy.

8. *Metabolism* Prolonged use of oral contraceptives impairs glucose tolerance in some women. This has been ascribed to the progestational component. Progestins, especially those with androgenic activity (19-nortestosterone derivatives) tend to raise LDL and lower HDL cholesterol levels. This may reduce the beneficial effect of estrogen used concurrently for HRT or in contraceptives. Micronized oral progesterone formulation (referred to as *'natural progesterone')* has been shown not to counteract the beneficial effect of estrogen on LDL and HDL cholesterol.

9. *Pituitary* Progesterone is a weak inhibitor of Gn secretion from pituitary. It exerts negative feedback primarily at the level of hypothalamic pulse generator—reducing the frequency of GnRH pulses. However, the amount of LH at each pulse may increase. Administration of progestin during follicular phase suppresses the preovulatory LH surge and prevents ovulation. It synergises with estrogen for this action. The gonanes markedly suppress GnRH and are potent antiovulatory drugs.

Mechanism of action

Unlike other steroid receptors, the progesterone receptor (PR) has a limited distribution in the body: confined mostly to the female genital tract, breast, CNS and pituitary. The PR is normally present in the nucleus of target cells. Analogous to ER, upon hormone binding the PR undergoes dimerization, attaches to progesterone response element (PRE) of target genes and regulates transcription through coactivators. The antiprogestins also bind to PR, but the conformation assumed is different from agonist bound receptor and opposite effects are produced by interaction with corepressors.

The PR exists in a short (PR-A) and a longer (PR-B) isoforms. The two have differing activities, but because the ligand binding domain of both is identical, all agonists and antagonists display similar binding properties for them. Tissue selective modulation of PR has not yet been possible, as has

been in the case of ER. Progesterone also acts on cell membrane receptors in certain tissues and produces rapid effects, like Ca^{2+} release from spermatozoa and oocyte maturation, but their physiological significance is not clear.

Estrogens have been shown to increase PR density, whereas progesterone represses ER and enhances local degradation of estradiol.

PHARMACOKINETICS

Progesterone, unless specially formulated, is inactive orally because of high first-pass metabolism in liver. It is mostly injected i.m. in oily solution. Even after an i.m. dose it is rapidly cleared from plasma, has a short t½ (5–7 min). Nearly complete degradation occurs in the liver—major product is pregnanediol which is excreted in urine as glucuronide and sulfate conjugates. However, effects of progesterone last longer than the hormone itself.

A micronized formulation of progesterone has been developed for oral administration. Microfine particles of the drug are suspended in oil and dispensed in gelatin capsules. Absorption occurs through lymphatics bypassing liver. Though bioavailability is low, effective concentrations are attained in the body.

Most of the synthetic progestins are orally active and are metabolized slowly; have plasma t½ ranging from 8–24 hours.

Preparations and dose

1. Progesterone: 10–100 mg i.m. (as oily solution) OD; PROGEST, PROLUTON, GESTONE 50 mg/ml inj., 1 and 2 ml amp; 100–400 mg OD oral: NATUROGEST, DURAGEST, OGEST 100, 200, 400 mg caps containing micronized oily suspension.
2. Hydroxyprogesterone caproate: 250–500 mg i.m. at 2–14 days intervals; PROLUTON DEPOT, MAINTANE INJ, PROCAPRIN 250 mg/ml in 1 and 2 ml amp.
3. Medroxyprogesterone acetate: 5–20 mg OD–BD oral, 50–150 mg i.m. at 1–3 month interval; FARLUTAL 2.5, 5, 10 mg tab., PROVERA, MEPRATE, MODUS 2.5, 10 mg tab, DEPOT-PROVERA 150 mg in 1 ml inj. (as contraceptive). Has weak androgenic and antiestrogenic property.
4. Dydrogesterone: 5–10 mg OD/TDS oral; DUPHASTON 5 mg tab. It has poor antiovulatory action: may be preferred when contraceptive effect is not required.
5. Norethindrone (Norethisterone): 5–10 mg OD–BD oral; PRIMOLUT-N, STYPTIN, REGESTRONE, NORGEST 5 mg tab; REGESTRONE HRT, NORETA HRT 1 mg tab (for HRT); NORISTERAT 200 mg/ml inj (as enanthate) for contraception 1 ml i.m every 2 months; has androgenic, anabolic and antiestrogenic activity.
6. Lynestrenol (Ethinylestrenol): 5–10 mg OD oral; ORGAMETRIL 5 mg tab. Has additional androgenic, anabolic and estrogenic activity.
7. Allylestrenol: 10–40 mg/day; GESTANIN, FETUGARD, MAINTANE 5 mg tab. Has been especially used for threatened/habitual abortion, PROFAR 25 mg tab.
8. Levonorgestrel: 0.1–0.5 mg/day; DUOLUTON-L, OVRAL 0.25 mg+ ethinylestradiol 0.05 mg tab. Has androgenic, anabolic and antiestrogenic property.
9. Desogestrel 150 µg + ethinylestradiol 30 µg (NOVELON) tab, 1 tab OD 3 week on 1 week off cyclic therapy.

(Other preparations are given with oral contraceptives).

ADVERSE EFFECTS

- Breast engorgement, headache, rise in body temperature, edema, esophageal reflux, acne and mood swings may occur with higher doses.
- Irregular bleeding or amenorrhoea can occur if a progestin is given continuously.
- The 19-nortestosterone derivatives lower plasma HDL levels—may promote atherogenesis, but progesterone and its derivatives have no such effect.
- Long-term use of progestin in HRT may increase the risk of breast cancer.
- Blood sugar may rise and diabetes may be precipitated by long-term use of potent agents like levonorgestrel.
- Intramuscular injection of progesterone is painful.
- Given in early pregnancy, progestins can cause masculinization of female foetus and other congenital abnormalities.

Use of a progestin for diagnosis of pregnancy is contraindicated.

USES

1. *As contraceptive* Most common use (*see* later).

2. *Hormone replacement therapy (HRT)*

In nonhysterectomised postmenopausal women estrogen therapy is supplemented with a progestin for 10–12 days each month to counteract the risk of inducing endometrial carcinoma.

A progesterone derivative lacking androgenic activity is preferred.

3. *Dysfunctional uterine bleeding* It is often associated with anovular cycles. Continued estrogenic action on endometrium (causing hyperplasia) without progesterone induction and withdrawal resulting in incomplete sloughing leads to irregular, often profuse bleeding. A progestin in relatively large doses (medroxyprogesterone acetate/norethindrone 10–20 mg/day or equivalent) promptly stops bleeding and keeps it in abeyance as long as given. Subsequently cyclic treatment at lower doses regularizes and normalizes menstrual flow. A progestin with inherent estrogenic action is preferred; often supplemental dose of estrogen is combined, or a combination oral contraceptive pill is given cyclically for 3–6 months.

4. *Endometriosis* This condition results from presence of endometrium at ectopic sites. Manifestations are dysmenorrhoea, painful pelvic swellings and infertility. Continuous administration of progestin induces an anovulatory, hypoestrogenic state by suppressing Gn release. The direct action on endometrium prevents bleeding in the ectopic sites by suppressing menstruation. Treatment for a few months causes atrophy and regression of the ectopic masses. Therapy can be withdrawn in many cases after 6 months without reactivation. Fertility returns in some patients. Progestin treatment of endometriosis is cheap and generally well tolerated, but not all cases respond and recurrences are frequent. Initial progestin therapy is often replaced by cyclic tratment with an estrogen-progestin contraceptive pill given for 3–6 months. GnRH agonist and danazol are alternatives used in nonresponsive cases. Aromatase inhibitors are being tried in resistant cases.

5. *Premenstrual syndrome/tension* Some women develop headache, irritability, fluid retention, distention and breast tenderness a few days preceding menstruation. When depression predominates, it has been labelled 'premenstrual dysphoric disorder'. Fluoxetine and other SSRIs given daily on symptom days dampen irritability and mood changes in majority of women. If severe, premenstrual syndrome requires suppression of ovulation by combined estrogen-progesterone treatment given cyclically. Relatively higher dose of progestin is generally used. Progestins are added to estrogen when it is used for severe dysmenorrhoea.

6. *Threatened/habitual abortion* In most such patients there is no progesterone deficiency; administration of excess hormone is of no benefit. Progestin therapy may be considered in those patients who have established deficiency. However, progestins are briskly promoted and almost routinely prescribed in India. There is some recent evidence of its efficacy in preventing premature delivery in high risk pregnancy. If such use is made—a pure progestin without estrogenic or androgenic activity should be employed.

7. *Endometrial carcinoma* Progestins are palliative in about 50% cases of advanced/ metastatic endometrial carcinoma. High doses are needed.

ANTIPROGESTIN

Mifepristone It is a 19-norsteroid with potent antiprogestational and significant antiglucocorticoid, antiandrogenic activity.

Given during the follicular phase, its antiprogestin action results in attenuation of the midcycle Gn surge from pituitary → slowing of follicular development and delay/failure of ovulation. If given during the luteal phase, it prevents secretory changes by blocking progesterone action on the endometrium. Later in the cycle, it blocks progesterone support to the endometrium, unrestrains PG release from it—this stimulates uterine contractions. Mifepristone also sensitizes the myometrium to PGs and induces menstruation. If implantation has occurred, it blocks decidualization, so that conceptus is dislodged, HCG production falls, secondary luteolysis occurs–endogenous progesterone secretion decreases and cervix is softened. All these effects lead to abortion.

Mifepristone is a partial agonist and competitive antagonist at both A and B forms of PR. In the absence of progesterone (during anovulatory cycles or after menopause) it exerts weak progestational activity—induces predecidual changes. Therefore, it is now regarded as 'progesterone receptor modulator' rather than 'pure antagonist.' The weak agonistic action is not manifest in the presence of progesterone.

The antiglucocorticoid action of usual doses is also not manifest in normal individuals because blockade of the negative feedback at hypothalamic-pituitary level elicits ACTH release → plasma cortisol rises and overcomes the direct antiglucocorticoid action. Amelioration of Cushing's symptoms has been obtained with large doses (*see* p. 295).

Pharmacokinetics Mifepristone is active orally, but bioavailability is only 25%. It is largely metabolized in liver by CYP 3A4 and excreted in bile; some enterohepatic circulation occurs; t½ 20–36 hr.

Interaction with CYP 3A4 inhibitors (erythromycin, ketoconazole) and inducers (rifampin, anticonvulsants) has been reported.

Uses

1. *Termination of pregnancy* of up to 7 weeks: 600 mg as single oral dose causes complete abortion in 60–85% cases. To improve the success rate, current recommendation is to follow it up 48 hours later by a single 400 mg oral dose of misoprostol. This achieves >90% success rate and is the accepted nonsurgical method of early first trimester abortion. In place of oral misoprostol, a 1 mg gemeprost pessary can be inserted intravaginally. Mifepristone administered within 10 days of a missed period results in an apparent late heavy period (with dislodged blastocyst) in upto 90% cases.

This procedure is generally safe, but prolonged bleeding and failed abortion are the problems in some cases. Anorexia, nausea, tiredness, abdominal discomfort, uterine cramps, loose motions are the other side effects.

2. *Cervical ripening* 24–30 hours before attempting surgical abortion or induction of labour, mifepristone 600 mg results in softening of cervix; the procedure is facilitated.

3. *Postcoital contraceptive* Mifepristone 600 mg given within 72 hr of intercourse interferes with implantation and is a highly effective method of emergency contraception. The subsequent menstrual cycle, however, is disturbed.

4. *Once-a-month contraceptive* A single 200 mg dose of mifepristone given 2 days after midcycle each month prevents conception on most occasions. Administering mifepristone in late luteal phase to dislodge the embryo (if present) and to ensure menstruation irrespective of conception, has also been tried. These alternative methods of contraception, though attractive, may prolong/disrupt the next menstrual cycle, and thus cannot be used continuously. There is little experience and little justification to use these methods on regular basis.

5. *Induction of labour* By blocking the relaxant action of progesterone on uterus of late pregnancy, mifepristone can promote labour. It may be tried in cases with intrauterine foetal death and to deliver abnormal foetuses.

6. *Cushing's syndrome* Mifepristone has palliative effect due to glucocorticoid receptor blocking property. May be used for inoperable cases.

Other proposed uses are—in endometriosis, uterine fibroid, certain breast cancers and in meningioma.

MIFEGEST, MIFEPRIN 200 mg tab.

T-PILL + MISO: Mifepristone 200 mg (3 tabs) + Misoprostol 200 µg (2 tabs); for medical termination of pregnancy of upto 49 days: take 3 tablets of T-PILL on day 1, followed on day 3 by 2 tablets of MISO.

Ulipristal It is a recently approved 'selective progesterone receptor modulator' (SPRM) for use as emergency contraceptive. It inhibits ovulation by suppressing LH surge as well as by direct effect on follicular rupture. In addition, its action on endometrium can interfere with implantation. In clinical trials the efficacy of ulipristal (30 mg) as emergency contraceptive has been rated equal to that of levonorgestrel (1.5 mg) when taken within 72 hours of unprotected intercourse, and to extend for 2 more days. Thus, it may have an advantage, if the woman misses to take the drug within 3 days.

Headache, nausea, vomiting, abdominal pain and menstrual delay are the side effects, as they

are with levonorgestrel. Few cases of ovarian cysts are reported.

The antiglucocorticoid activity of ulipristal is weaker than that of mifepristone.

Onapristone (a pure progesterone antagonist) and *Gestinone* (more efficacious in endometriosis) are the other antiprogestins.

HORMONAL CONTRACEPTIVES

These are hormonal preparations used for reversible suppression of fertility. Because of our alarming population trends, antifertility drugs are the need of the day. In developing countries particularly, the mortality rate has declined and birth rate has increased due to urbanization. In the earlier part of 20th century, methods of contraception used (condoms, diaphragms, spermicidal creams, foam tablets, etc.) were intimately related to sexual intercourse, therefore, despised by most couples. These also have higher failure rate. Rock and Pincus (1955) announced the successful use of an oral progestin for contraception, separating fertility control from coitus.

It was soon discovered that addition of a small quantity of an estrogen enhanced their efficacy; combined pills have become the most popular method of contraception, particularly because the hormone content of the pills has been reduced, minimizing the potential harm and affording other health benefits.

FEMALE CONTRACEPTION

Over 100 million women worldwide are currently using hormonal contraceptives. With these drugs, fertility can be suppressed at will, for as long as desired, with almost 100% confidence and complete return of fertility on discontinuation. The efficacy, convenience, low cost and overall safety of oral contraceptives (OCs) has allowed women to decide whether and when they want to become pregnant and to plan their activities. A variety of oral and parenteral preparations are now available offering individual choices.

TYPES OF METHODS

Oral

1. *Combined pill* It contains an estrogen and a progestin in fixed dose for all the days of a treatment cycle (monophasic). With accumulated experience, it has been possible to reduce the amount of estrogen and progestin in the 'second generation' OC pills without compromising efficacy, but reducing side effects and complications. 'Third generation'pills containing newer progestins like desogestrel with improved profile of action have been introduced in the 1990s. Ethinylestradiol 30 µg daily is considered threshold but can be reduced to 20 µg/day if a progestin with potent antiovulatory action is included. The progestin is a 19-nortestosterone because these have potent antiovulatory action. Used alone the ovulation inhibitory dose (per day) of the currently used progestins is estimated to be—levonorgestrel 60 µg, desogestrel 60 µg, norgestimate 200 µg, gestodene 40 µg, but the amount in the pill is 2–3 times higher to attain 100% certainty. While both estrogens and progestins synergise to inhibit ovulation, the progestin ensures prompt bleeding at the end of a cycle and blocks the risk of developing endometrial carcinoma due to the estrogen. One tablet is taken daily for 21 days, starting on the 5th day of menstruation. The next course is started after a gap of 7 days in which bleeding occurs. Thus, a cycle of 28 days is maintained. Calendar packs of pills are available (Table 22.2). This is the most popular and most efficacious method.

2. *Phased pill* Triphasic regimens have been introduced to permit reduction in total steroid dose without compromising efficacy by mimicking the normal hormonal pattern in a menstrual cycle. The estrogen dose is kept constant (or varied slightly between 30–40 µg), while the amount of progestin is low in the first phase and progressively higher in the second and third phases.

Phasic pills are particularly recommended for women over 35 years of age and for those with no withdrawal bleeding or breakthrough bleeding while on monophasic pill, or when other risk factors are present.

TABLE 22.2 **Oral contraceptive preparations**

PROGESTIN		ESTROGEN		TRADE NAME
COMBINED PILLS				
1. Norgestrel	0.3 mg	Ethinylestradiol	30 µg	MALA–D (21 tabs + 7 ferrous sulfate 60 mg tabs.)
2. Norgestrel	0.5 mg	Ethinylestradiol	50 µg	OVRAL-G 20 tabs.
3. Levonorgestrel	0.25 mg	Ethinylestradiol	50 µg	OVRAL, DUOLUTON-L 21 tabs.
4. Levonorgestrel	0.15 mg	Ethinylestradiol	30 µg	OVRAL-L, OVIPAUZ 21 tabs.
5. Levonorgestrel	0.1 mg	Ethinylestradiol	20 µg	LOETTE, OVILOW, COMBEE 21 tabs
6. Desogestrel	0.15 mg	Ethinylestradiol	30 µg	NOVELON 21 tabs.
7. Desogestrel	0.15 mg	Ethinylestradiol	20 µg	FEMILON 21 tabs.
PHASED PILL				
1. Levonorgestrel	50–75 –125 µg	Ethinylestradiol	30–40 –30 µg	TRIQUILAR (6 + 5 + 10 tablets)
2. Norethindrone	0.5–0.75 –1.0 mg	Ethinylestradiol	35–35 –35 µg	ORTHONOVUM 7/7/7 (7+7+7 tabs)
POSTCOITAL PILL				
1. Levonorgestrel	0.25 mg	Ethinylestradiol	50 µg	OVRAL, DUOLUTON-L (2+2 tabs)
2. Levonorgestrel	0.75 mg	-Nil-	—	NORLEVO, ECEE2 (1+1 tab)
	1.5 mg	-Nil-	—	iPILL, NOFEAR-72, OH GOD (1 tab)
MINI PILLS				
1. Norethindrone	0.35 mg	-Nil-	—	MICRONOR*, NOR-QD*
2. Norgestrel	75 µg	-Nil-	—	OVRETTE*

*Not marketed in India.

3. *Progestin-only pill (Minipill)* It has been devised to eliminate the estrogen, because many of the long-term risks have been ascribed to this component. A low-dose progestin-only pill is an alternative for women in whom an estrogen is contraindicated. It is taken daily continuously without any gap. The menstrual cycle tends to become irregular and ovulation occurs in 20–30% women, but other mechanisms contribute to the contraceptive action. The efficacy is lower (96–98%) compared to 98–99.9% with combined pill. Pregnancy should be suspected if amenorrhoea of more than 2 months occurs. This method is less popular.

4. *Emergency (postcoital) pill* These are for use in a woman not taking any contraceptive who had a sexual intercourse risking unwanted pregnancy. The most commonly used and standard regimen is—

- Levonorgestrel 0.75 mg two doses 12 hours apart, or 1.5 mg single dose taken as soon as possible, but before 72 hours of unprotected intercourse.

Trials conducted globally by a WHO task force on postovulatory methods of fertility control have found this regimen to be 2–3 times more effective and better tolerated than the earlier 'Yuzpe method' which used levonorgestrel 0.5 mg + ethinylestradiol 0.1 mg, two doses at 12 hour interval within 72 hours of exposure. Incidence of nausea and vomiting is ~6% in the progestin only regimen compared to 20–50% with the estrogen+progestin regimen. Headache and other side effects are also milder. However, the next period may be delayed or disrupted with either regimen.

Recently (2010) a SPRM ulipristal has been approved for emergency contraception.

- Ulipristal 30 mg single dose as soon as possible, but within 120 hours of intercourse.

  It is an equally effective (failure rate 1–3% compared to levonorgestrel 2–4%) and equally well tolerated alternative method now available with an extended window of protective action (*see* p. 320).

  Another antiprogestin that has been used, particularly in Europe and China, with high success rate and few side effects is—
- Mifepristone 600 mg single dose taken within 72 hours of intercourse.

Emergency postcoital contraception should be reserved for unexpected or accidental exposure (rape, condom rupture) only, because all emergency regimens have higher failure rate and side effects than regular low-dose combined pill.

Injectable

These have been developed to obviate the need for daily ingestion of pills. They are given i.m. as oily solution; are highly effective; over 50 million women have used them so far. Their major limitations are:

(a) Animal data has indicated carcinogenic potential, but there is no proof from human studies despite >30 years of experience. No increase in overall risk of cervical, ovarian or hepatic cancer has been noted by a WHO sponsored study. Breast cancer risk may be slightly increased in younger women (< 35 yr). The logistics of administration and supervision for mass use are considered inadequate in developing countries and use–effectiveness in field conditions is low. In India approval has been granted for use only under close supervision, but not on mass scale under the National Programme.

(b) Menstrual irregularities, excessive bleeding or amenorrhoea are very common; incidence of amenorrhoea increases with increasing duration of use. Return of fertility may take 6–30 months after discontinuation; permanent sterility may occur in some women. Weight gain and headache occur in >5% subjects. Bone mineral density may decrease after 2–3 years of use (especially with DMPA) due to low estrogen levels caused by Gn suppression. This may also produce menopause-like symptoms (hot flushes, vaginal dryness, reduced libido).

Only the *long-acting progestin only* injections are in use now. They are injected once in 2–3 months depending on the steroid and its dose. Two compounds have been marketed:

(a) Depot medroxyprogesterone acetate (DMPA) 150 mg at 3-month intervals. After i.m. injection peak blood levels are reached in 3 weeks and decline with a t½ of ~ 50 days.

DEPOT-PROVERA 150 mg in 1 ml vial for deep i.m. injection during first 5 days of menstrual cycle. Repeat every 3 months.

(b) Norethindrone (Norethisterone) enanthate (NEE) 200 mg at 2-month intervals.

NORISTERAT 200 mg in 1 ml vial for deep i.m. injection during first 5 days of menstrual cycle. Repeat every 2 months.

The most important drawback is complete disruption of menstrual bleeding pattern or total amenorrhoea (more common with DMPA). It is not suitable for adolescent girls and lactating mothers. Use of DMPA is generally restricted to women who are unlikely to use other contraceptives effectively. NEE is shorter acting and failure rates have been higher than with DMPA. All fixed dose combination injectable preparations of synthetic estrogens and progestins are not allowed in India and discontinued in most countries.

Implants These are drug delivery systems implanted under the skin, from which the steroid is released slowly over a period of 1–5 years. They consist of either—

(a) Biodegradable polymeric matrices—do not need to be removed on expiry.

(b) Non-biodegradable rubber membranes—have to be removed on expiry.

NORPLANT: A set of 6 capsules each containing 36 mg levonorgestrel (total 216 mg) for subcutaneous implantation is available in some countries, but has been discontinued in the USA. Works for up to 5 years.

A progesterone impregnated intrauterine insert (PROGESTASERT) has been introduced in some countries. It contains 52 mg of levonorgestrel which primarily acts locally on endometrium. The device remians effective for 5 years, but efficacy is rated lower.

MECHANISM OF ACTION

Hormonal contraceptives interfere with fertility in many ways; the relative importance depends

on the type of method. This is summarized in Table 22.3.

1. Inhibition of Gn release from pituitary by reinforcement of normal feedback inhibition. The progestin reduces frequency of LH secretory pulses (an optimum pulse frequency is required for tiggering ovulation) while the estrogen primarily reduces FSH secretion. Both synergise to inhibit midcycle LH surge. When the combined pill is taken both FSH and LH are reduced and the midcycle surge is abolished. As a result, follicles fail to develop and fail to rupture—*ovulation does not occur*.

The minipill and progestin only injectable regimen also attenuate LH surge but less consistently—ovulation may occur irregularly in ~ 1/3 cycles. Postcoital pill when taken before ovulation can dampen LH surge and inhibit ovulation in some cases. However, pregnancy is still prevented by direct actions on the genital tract.

2. Thick *cervical mucus* secretion *hostile to sperm penetration* is evoked by progestin action. As such, this mechanism can operate with all methods except postcoital pill.

3. Even if ovulation and fertilization occur, the blastocyst may fail to implant because *endometrium* is either hyperproliferative or hypersecretory or atrophic and in any case *out of phase* with fertilization—not suitable for nidation. This action appears to be the most important in case of minipills and postcoital pill.

4. *Uterine and tubal contractions* may be modified to disfavour fertilization. This action is uncertain but probably contributes to the efficacy of minipills and postcoital pill.

5. The postcoital pill may *dislodge* a just implanted blastocyst or may interfere with fertilization/implantation.

Practical considerations

1. Discontinuation of all OCs results in full return of fertility within 1–2 months. There may even be a rebound increase in fertility—chances of multiple pregnancy are more if conception occurs within 2–3 cycles. With injectable preparations, return of fertility is delayed. The cycles take several months to normalize or may not do so at all. They are to be used only if the risk of permanent infertility is acceptable.

2. If a woman on combined pills misses to take a tablet, she should be advised to take two tablets the next day and continue as usual. If more than 2 tablets are missed, then the course should be interrupted, an alternative method of contraception used and next course started on the 5th day of bleeding.

TABLE 22.3 Effects of different forms of hormonal contraception

	Oral pills			*Injections*
	Combined E + P	*Minipill only P*	*Postcoital only P*	*Progestin only*
1. FSH inhibition	++	–	–	+
2. LH inhibition	+++	+	+	+++
3. Antiovulatory effect	+++	+	+,–	++
4. Hostile cervical mucus	+++	+++	–	+++
5. Endometrium	Hyper-secretory	Out of phase	Unfavourable	Atrophic
6. Failure rate (pregnancy/100 women years)	0.1–0.3	2–3	2–4%	< 0.5
7. Contraceptive efficacy	++++	+++	++	++++

E—Estrogen; P—Progestin

3. If pregnancy occurs during use of hormonal contraceptives—it should be terminated by suction-aspiration, because the risk of malformations, genital carcinoma in female offspring and undescended testes in male offspring is increased.
4. While for most women a pill containing 30 µg ethinylestradiol is sufficient, the obese may require a pill containing 50 µg, and only 20 µg may be appropriate/sufficient for those with cardiovascular risk factor, as well as for those above 40 yr age.
5. If breakthrough bleeding occurs—switch over to a pill containing higher estrogen dose.
6. In women with contraindications for estrogen (*see* below), a progestin only contraceptive may be used.

ADVERSE EFFECTS

Since contraceptives are used in otherwise healthy and young women, adverse effects, especially long-term consequences assume great significance. The adverse effects are dose dependent; most of the past data with high-dose preparations cannot be directly extrapolated to the present-day low-dose preparations which carry relatively minor risk. The following applies primarily to combined oral pill which has been most extensively used.

A. Nonserious side effects These are frequent, especially in the first 1–3 cycles, and then disappear gradually.

1. Nausea and vomiting: similar to morning sickness of pregnancy.
2. Headache is generally mild; migraine may be precipitated or worsened.
3. Breakthrough bleeding or spotting: especially with progestin only preparations. Rarely bleeding fails to occur during the gap period. Prolonged amenorrhoea or cycle disruption occurs in few women taking injectables or minipill.
4. Breast discomfort.

B. Side effects that appear later

1. Weight gain, acne and increased body hair may be noted due to androgenic action of older 19-nortestosterone progestins. The newer ones like desogestrel are relatively free of this effect.
2. Chloasma: pigmentation of cheeks, nose and forehead, similar to that occurring in pregnancy.
3. Pruritus vulvae is infrequent.
4. Carbohydrate intolerance and precipitation of diabetes in few subjects taking high dose preparations; but this is unlikely with the present pills. Many large studies have found no link between OC use and development of diabetes.
5. Mood swings, abdominal distention are occasional; especially reported with progesterone only contraceptives.

C. Serious complications

1. *Leg vein thrombosis and pulmonary embolism:* The older preparations increased the incidence of venous thromboembolism, but this is found to be only marginal with the newer reduced steroid content pills. Those who develop such complication, generally do it in the 1st year of use. However, even low-dose pills pose significant risk in women >35 years of age, diabetics, hypertensives and in those who smoke. The excess risk normalizes shortly after stopping the OC.
2. *Coronary and cerebral thrombosis* resulting in *myocardial infarction or stroke:* A 2 to 6-fold increase in risk was estimated earlier, but recent studies have found no increased incidence with the low dose pills in the absence of other risk factors.

The estrogen component of OC has been mainly held responsible for venous thromboembolism, while both estrogen and progestin have been blamed for the arterial phenomena. The mechanisms involved may be:

- Increase in blood clotting factors (coagulability is enhanced).
- Decreased antithrombin III.
- Decreased plasminogen activator in endothelium.
- Increased platelet aggregation.

3. *Rise in BP*: occurred in 5–10% women taking the earlier pills. This again is less frequent and smaller in magnitude with the low-dose pills of today. If the BP rises, best is to stop OCs—BP normalizes in the next 3–6 months. Both the estrogen and progestin components are

responsible for this effect, probably by increasing plasma angiotensinogen level and renin activity which induces salt and water retention.

4. Estrogen tends to raise plasma HDL/LDL ratio (beneficial), but the progestin nullifies this benefit. Lipid profile is not significantly altered by low dose OCs, except that triglyceride level may rise marginally which poses no excess risk.

5. *Genital carcinoma:* an increased incidence of vaginal, cervical, and breast cancers was feared on the basis of animal data, but extensive epidemiological data over the past 30 years has repeatedly shown that oral as well as injected contraceptives do not increase the occurrence of these cancers in the general population. However, risk is increased in predisposed individuals. Growth of already existing hormone dependent tumour may be hastened.

Epidemiological data has recorded minor increase in breast cancer incidence among current OC users, but not among past users. Since breast cancer is rare in young women, this finding is considered inconsequential.

A protective effect against endometrial carcinoma has been shown for the progestin component. Prolonged suppression of gonadotropic stimulation of ovary may account for the lower incidence of ovarian malignancy noted in contraceptive users.

6. *Benign hepatomas:* which may rupture or turn malignant; incidence of this rare tumour appears to be slightly higher in OC users.

7. *Gallstones:* Estrogens increase biliary cholesterol excretion; incidence of gallstones is slightly higher in women who are taking OCs, or after long-term use.

Contraindications

The combined oral contraceptive pill is absolutely contraindicated in:

1. Thromboembolic, coronary and cerebrovascular disease or a history of it.
2. Moderate-to-severe hypertension; hyperlipidaemia.
3. Active liver disease, hepatoma or h/o jaundice during past pregnancy.
4. Suspected/overt malignancy of genitals/breast.
5. Prophyria.
6. Impending major surgery—to avoid excess risk of postoperative thromboembolism.

Relative contraindications (requiring avoidance/cautious use under supervision)

1. Diabetes: control may be vitiated.
2. Obesity
3. Smoking
4. Undiagnosed vaginal bleeding
5. Uterine leiomyoma: may enlarge with estrogenic preparations; progestin only pills can be used.
6. Mentally ill
7. Age above 35 years
8. Mild hypertension
9. Migraine
10. Gallbladder disease

Interactions Contraceptive failure may occur if the following drugs are used concurrently:

(a) *Enzyme inducers:* phenytoin, phenobarbitone, primidone, carbamazepine, rifampin, ritonavir. Metabolism of estrogenic as well as progestational component is increased.

(b) *Suppression of intestinal microflora:* tetracyclines, ampicillin, etc. Deconjugation of estrogens excreted in bile fails to occur → their enterohepatic circulation is interrupted → blood levels fall.

With both types of interacting drugs, it is wise to switch over to a preparation containing 50 µg of ethinylestradiol or to use alternative method of contraception. Rifampin is usually taken for a long time and is such a potent enzyme inducer that alternative contraception should be advised.

Other health benefits Apart from benefits due to prevention of unwanted pregnancy and the risks during delivery, use of oral contraceptives affords certain other beneficial effects as a bonus:

- Lower risk of developing endometrial and ovarian carcinoma; probably colorectal cancer as well.

- Reduced menstrual blood loss and associated anaemia; cycles if irregular become regular; premenstrual tension, dysmenorrhoea and menorrhagia are ameliorated.
- Endometriosis and pelvic inflammatory disease are improved.
- Reduced incidence as well as symptomatic relief of fibrocystic breast disease and ovarian cysts.

Ormeloxifene (Centchroman) It is a non-steroidal SERM developed at CDRI India as an oral contraceptive. It has predominant estrogen antagonistic action in uterus and breast with little action on vaginal epithelium and cervical mucus. Endometrial proliferation is suppressed by down regulation of endometrial ER. Contraceptive action is probably due to utero-embyonic asynchrony and failure of implantation. Pituitary, ovarian and other endocrine functions remain practically unaffected. Menstrual cycle is not disrupted, but in some women it may be lengthened irregularly. Excessive bleeding attending anovulatory cycles (that generally occurs near menopause) is diminished; ormeloxifene is approved for use in dysfunctional uterine bleeding.

The plasma t½ of ormeloxifene is long (~1 week). It prevents conception as long as taken with return of fertility few months after stoppage. Failure rate is considered acceptable, but it has failed to gain popularity for widespread use. Side effects are nausea, headache, fluid retention, weight gain, rise in BP and prolongation of menstrual cycles.

Dose: For contraception—30 mg twice a week for 12 weeks followed by once a week.

For dysfunctional uterine bleeding—60 mg twice a week for 12 weeks, then once a week for 12 weeks.

CENTRON 30 mg tab, SAHELI 60 mg tab.

MALE CONTRACEPTIVE

The only way to suppress male fertility by drugs is to inhibit spermatogenesis. Though considerable effort has been made in this direction and effective drugs have been found, no satisfactory/acceptable solution is yet tangible. Reasons are—

1. Complete suppression of spermatogenesis is relatively difficult without affecting other tissues: millions of spermatozoa are released at each ejaculation *vs* a single ovum per month in women.

2. Spermatogenesis takes 64 days. A drug which even completely inhibited spermatogenesis will take a long latent period to produce infertility. Accordingly, return of fertility will be slow.

3. Gonadotropin suppression inhibits testosterone secretion as well, resulting in loss of libido and impotence: unacceptable to all men and to most spouses.

4. Risk of adverse effects.

5. Most importantly—men don't get pregnant: few would be ready to bear the contingency of regular medication so that their sexual partners do not become pregnant.

Drugs and approaches tried are—

1. *Antiandrogens* Depress spermatogenesis, but raise Gns; cause unacceptable loss of libido.

2. *Estrogens and progestins* Act by suppressing Gns—cause unacceptable feminization.

3. *Androgens* They inhibit Gns but have poor efficacy. Even combination with progestin is not reliable.

4. *Superactive Gn RH analogues* They inhibit Gn release by continuous action; inhibit testosterone secretion as well; produce impotence, loss of libido.

5. *Cytotoxic drugs* Cadmium, nitrofurans and indoles suppress spermatogenesis, but are toxic.

6. *Gossypol* It is a nonsteroidal compound, obtained from cotton seed; has been studied in China. It is effective orally—causes suppression of spermatogenesis and reduces sperm motility—infertility develops after a couple of months. Fertility is restored several months after discontinuation. However, about 10% men remain oligozoospermic. During treatment serum LH and testosterone levels do not change: libido and potency are not affected. The mechanism of action is uncertain; probably involves direct toxicity on seminiferous epithelium.

Most important adverse effect is hypokalaemia (due to renal loss of K^+) with its attendant muscular weakness (even paralysis). Other side effects are—edema, diarrhoea, breathlessness and neuritis.

☞ PROBLEM DIRECTED STUDY

22.1 A 55-year-old postmenopausal woman developed a cancerous lump in the left breast for which radical mastectomy was performed. The tumour was ER positive and only one of the excised axillary lymph nodes had metastasis. She was put on adjuvant therapy with tamoxifen 20 mg per day. On her checkup visit one year later, she was found to be asymptomatic with no sign of local recurrence or lymph node enlargement, but ultrasound examination of the uterus revealed thickening of endometrium.

(a) What could be the cause and implication of the increase in endometrial thickness?

(b) Should the same adjuvant therapy continue, or should it be stopped altogether, or be replaced by another drug? Give reasons.

22.2 A 28-year-old mother with a 9 month baby wants to space out her next child and consults you for taking oral contraceptive.

(a) What questions will you ask, what physical examination will you perform and what investigations will you order before advising her whether she should take oral contraceptive or not, as well as for selecting the contraceptive preparation most suitable for her?

(see Appendix-1 for solutions)

Chapter 23 Oxytocin and Other Drugs Acting on Uterus

Drugs acting on uterus can primarily affect the endometrium or the myometrium. The most important drugs affecting endometrium are estrogens, progestins and their antagonists. Myometrium receives both sympathetic and parasympathetic innervation: autonomic drugs can affect its motility. However, directly acting drugs are more important and have more selective action. The responsiveness of myometrium to drugs is markedly affected by the hormonal and gestational status.

UTERINE STIMULANTS (Oxytocics, Abortifacients)

These drugs increase uterine motility, especially at term.

1. *Posterior pituitary hormone* Oxytocin, Desamino oxytocin
2. *Ergot alkaloids* Ergometrine (Ergonovine), Methylergometrine
3. *Prostaglandins* PGE_2, $PGF_{2\alpha}$, 15-methyl $PGF_{2\alpha}$, Misoprostol
4. *Miscellaneous* Ethacridine, Quinine.

OXYTOCIN

Oxytocin is a nonapeptide secreted by the posterior pituitary along with vasopressin (ADH). Pituitary extract was first used in labour in 1909. Controversy as to whether the antidiuretic and uterine stimulating activities were due to one substance or two separate substances was finally resolved by du Vigneaud in 1953 when he separated *Oxytocin* and *Vasopressin*, determined their chemical structure and synthesized them. Both are nonapeptides which differ at positions 3 and 8.

Both oxytocin and ADH are synthesized within the nerve cell bodies in supraoptic and paraventricular nuclei of hypothalamus; are transported down the axon and stored in the nerve endings within the neurohypophysis. They are stored in separate neurones as complexes with their specific binding proteins (neurophysins) to form granules. Both are released by stimuli appropriate for oxytocin, i.e. coitus, parturition, suckling; or for ADH, i.e. hypertonic saline infusion, water deprivation, haemorrhage, etc., or nonspecific, i.e. pain and apprehension. However, the proportion of oxytocin to ADH can vary depending upon the nature of the stimulus.

ACTIONS

1. Uterus Oxytocin increases the force and frequency of uterine contractions. With low doses, full relaxation occurs inbetween contractions; basal tone increases only with high doses. Increased contractility is due to hightened electrical activity of the myometrial cell membrane—burst discharges are initiated and accentuated. Estrogens sensitize the uterus to oxytocin; increase oxytocin receptors. Nonpregnant uterus and that during early pregnancy is rather resistant to oxytocin; sensitivity increases progressively in the third trimester; there is a sharp increase near term and quick fall during puerperium. Progestins decrease the sensitivity, but this effect is not marked *in vivo*.

At term the increased contractility is restricted to the fundus and body; lower segment is not contracted; may even be relaxed.

Mechanism of action Action of oxytocin on myometrium is independent of innervation. There are specific G-protein coupled oxytocin receptors which mediate the response mainly by depolarization of muscle fibres and influx of Ca^{2+} ions

as well as through phosphoinositide hydrolysis and IP_3 mediated intracellular release of Ca^{2+} ions. The number of oxytocin receptors increases markedly during later part of pregnancy. Oxytocin increases PG synthesis and release by the endometrium which may contribute to the contractile response. Distinct subtypes of oxytocin receptors have been shown on the myometrium and the endometrium.

2. Breast Oxytocin contracts the myoepithelium of mammary alveoli and forces milk into the bigger milk sinusoids—'milk ejection reflex' (milk letdown in cattle) is initiated by suckling so that it may be easily sucked by the infant. Oxytocin has been used in milch cattle to facilitate milking.

3. CVS Conventional doses used in obstetrics have no effect on BP, but higher doses cause vasodilatation → brief fall in BP, reflex tachycardia and flushing. This action is most marked in chicken and is used for bioassay of oxytocin. The umbilical vessels are markedly constricted; oxytocin may help in their closure at birth.

4. Kidney Oxytocin in high doses exerts ADH-like action—urine output is decreased: pulmonary edema can occur if large amounts of i.v. fluids and oxytocin are infused together. Conventional doses are without any effect.

Physiological role

1. *Labour* Oxytocin is released during labour and the uterus is highly sensitive to it at this time. However, it does not appear to be obligatory for initiating parturition—delivery occurs even in hypophysectomized animals and humans, though labour may be prolonged in its absence. A facilitatory role is more plausible. PGs and PAF are complementary to oxytocin.

2. *Milk ejection reflex* Suckling induces oxytocin release from pituitary which contracts the myoepithelial cells. These cells in breast are more sensitive than myometrium to oxytocin. Milk ejection reflex is absent in the hypophysectomized animal.

3. *Neurotransmission* Oxytocin appears to function as a peptide neurotransmitter of oxytocinergic neurones in the hypothalamus and brainstem to regulate autonomic outflow.

PHARMACOKINETICS

Being a peptide, oxytocin is inactive orally and is generally administered by i.m. or i.v. routes, rarely by intranasal spray. It is rapidly degraded in liver and kidney; plasma t½ 6–12 min, and is still shortened at term. Pregnant uterus and placenta elaborate a specific aminopeptidase called *oxytocinase*—which can be detected in maternal plasma.

Unitage and preparations 1 IU of oxytocin = 2 µg of pure hormone. Commercially available oxytocin is produced synthetically.

OXYTOCIN, SYNTOCINON 2 IU/2 ml and 5 IU/ml inj., PITOCIN 5 IU/0.5 ml inj.

USE

1. *Induction of labour* Labour needs to be induced in case of postmaturity or prematurely in toxaemia of pregnancy, diabetic mother, erythroblastosis, ruptured membranes or placental insufficiency. For this purpose oxytocin is given by slow i.v. infusion: 5 IU is diluted in 500 ml of glucose or saline solution (10 milli IU/ml)—infusion is started at a low rate and progressively accelerated according to response (0.2–2.0 ml/min). Before starting infusion, confirm that:

- presentation is correct
- foetal lungs are adequately mature
- there is no cephalopelvic disproportion
- no placenta previa
- no foetal distress and
- no uterine scar (due to previous surgery).

Uterine contractions are then closely monitored: the drug is discontinued when they are strong enough. Usually a total of 2–4 IU is needed.

2. *Uterine inertia* When uterine contractions are feeble and labour is not progressing

satisfactorily—oxytocin can be infused i.v. (as described above) to augment contractions. It should not be used to hasten normally progressing labour. Before deciding to use an oxytocic for strengthening uterine contractions, all the conditions as setout above (for induction of labour) must be fulfilled. Too strong contraction can be catestrophic: use should only be made in selected cases and by experienced people.

Oxytocin is the drug of choice and is preferred over ergometrine/PGs for the above two purposes:
(a) Because of its short t½ and slow i.v. infusion, intensity of action can be controlled and action can be quickly terminated.
(b) Low concentrations allow normal relaxation inbetween contractions—foetal oxygenation does not suffer.
(c) Lower segment is not contracted: foetal descent is not compromised.
(d) Uterine contractions are consistently augmented.

3. *Postpartum haemorrhage, Caesarean section* Oxytocin 5 IU may be injected i.m. or by i.v. infusion for an immediate response, especially in hypertensive women in whom ergometrine is contraindicated. It acts by forcefully contracting the uterine muscle which compresses the blood vessels passing through its mesh work to arrest haemorrhage from the inner surface exposed by placental separation.

4. *Breast engorgement* It may occur due to inefficient milk ejection reflex. Oxytocin is effective only in such cases; an intranasal spray may be given few minutes before suckling. It does not increase milk production.

5. *Oxytocin challenge test* It is performed to determine uteroplacental adequacy in high risk pregnancies. Oxytocin is infused i.v. at very low concentrations till uterine contractions are elicited every 3–4 mins. A marked increase in foetal heart rate indicates uteroplacental inadequacy. The test is risky and is rarely performed.

Adverse effects

(i) Injudicious use of oxytocin during labour can produce too strong uterine contractions forcing the presenting part through incompletely dilated birth canal, causing maternal and foetal soft tissue injury, rupture of uterus, foetal asphyxia and death.
(ii) Water intoxication: This occurs due to ADH like action of large doses given along with i.v. fluids, especially in toxaemia of pregnancy and renal insufficiency. It is a serious (may be fatal) complication.

Desamino-oxytocin It has been developed as a buccal formulation; action is similar to injected oxytocin, but less consistent. Its indications are:
Induction of labour: 50 IU buccal tablet repeated every 30 min, max 10 tabs.
Uterine inertia: 25 IU every 30 min.
Promotion of uterine involution 25–50 IU 5 times daily for 7 days.
Breast engorgement 25–50 IU just before breast feeding.
BUCTOCIN 50 IU tab

Carbetocin It is a long-acting analogue of oxytocin that has been introduced recently for prevention of uterine atony after caesarean section and to control PPH.

ERGOMETRINE, METHYLERGOMETRINE

The pharmacology of ergot alkaloids is described in Ch. 12. Only the amine ergot alkaloid ergometrine (ergonovine) and its derivative methylergometrine are used in obstetrics. Both have similar pharmacological property.

1. *Uterus* They increase force, frequency and duration of uterine contractions. At low doses, contractions are phasic with normal relaxation in between, but only moderate increase in dose raises the basal tone, contracture occurs with high doses. Gravid uterus is more sensitive, especially at term and in early puerperium. Their stimulant action involves the lower segment also. The uterotonic action is believed to result from partial agonistic action on 5-HT_2 and α adrenergic receptors.

2. *CVS* Ergometrine and methylergometrine are much weaker vasoconstrictors than ergotamine and have low propensity to cause endothelial damage. Though they can raise BP, this is not significant at doses used in obstetrics.

3. *CNS* No overt effects occur at usual doses. However, high doses produce complex actions—partial agonistic/antagonistic interaction with

adrenergic, serotonergic and dopaminergic receptors in the brain have been shown.

4. *GIT* High doses can increase peristalsis.

Methylergometrine is 1½ times more potent than ergometrine on the uterus, but other actions are less marked. It has thus replaced ergometrine at many obstetric units.

Pharmacokinetics In contrast to the amino acid ergot alkaloids, ergometrine and methylergometrine are rapidly and nearly completely absorbed from the oral route. The onset of uterine action is: Oral—15 min; i.m.—5 min; i.v.—almost immediate.

They are partly metabolized in liver and excreted in urine. Plasma t½ is 1–2 hours. Effects of a single dose last 3–4 hours.

Adverse effects Ergometrine and methylergometrine are less toxic than ergotamine. When correctly used in obstetrics—hardly any complications arise. Nausea, vomiting and rise in BP occur occasionally. They can decrease milk secretion if higher doses are used for many days postpartum; this is due to inhibition of prolactin release (dopaminergic action).

Ergometrine should be avoided in—

(i) patients with vascular disease, hypertension, toxaemia.

(ii) presence of sepsis—may cause gangrene.

(iii) liver and kidney disease.

They are contraindicated during pregnancy and before 3rd stage of labour.

Use

1. The primary indication for ergometrine/methylergometrine is to control and prevent postpartum haemorrhage (PPH): 0.2–0.3 mg i.m. at delivery of anterior shoulder reduces blood loss attending delivery and prevents PPH. However, routine use in all cases is not justified—only in those expected to bleed more, e.g. grand multipara, uterine inertia. Multiple pregnancy should be excluded before injecting.

If PPH is occurring—0.5 mg i.v. is recommended. A combination of 0.5 mg ergometrine with oxytocin 5 IU i.m./i.v. may be used in severe bleeding.

These drugs produce sustained tonic uterine contraction: perforating uterine arteries are compressed by the myometrial meshwork—bleeding stops.

2. After caesarean section/instrumental delivery—to prevent uterine atony.

3. To ensure normal involution: A firm and active uterus involutes rapidly. To ensure this: 0.125 mg of ergometrine or methylergometrine has been given TDS orally for 7 days. However, routine use in all cases is not justified because normal involution is not hastened. Multipara and others in whom slow involution is apprehended, these drugs may be given prophylactically.

4. Diagnosis of variant angina: A small dose of ergometrine injected i.v. during coronary angiography causes prompt constriction of reactive segments of coronary artery that are responsible for variant angina.

ERGOMETRINE 0.25, 0.5 mg tab, 0.5 mg/ml inj.

Methylergometrine: METHERGIN, METHERONE, ERGOMET 0.125 mg tab, 0.2 mg/ml inj.

PROSTAGLANDINS

PGE_2, $PGF_{2\alpha}$ and 15-methyl $PGF_{2\alpha}$ are potent uterine stimulants, especially in the later part of pregnancy and cause ripening of cervix. Their actions and use in obstetrics is described in Ch. 13. Since misoprostol (a PG analogue used for peptic ulcer) produces less side effects, it is being used for obstetric indications as well.

Ethacridine Available as 50 mg/50 ml solution (EMCREDIL, VECREDIL) for extra-amniotic infusion: 150 ml (containing 150 mg) is injected slowly for medical termination of pregnancy in the 2nd trimester. This is an alternative method used occasionally.

UTERINE RELAXANTS (Tocolytics)

These are drugs which decrease uterine motility. They have been used to delay or postpone labour, arrest threatened abortion and in dysmenorrhoea. Prevention of premature labour in those at higher risk due to past history has been attempted by administration of high dose *progesterone* in the

later half of pregnancy, with some success. Suppression of premature labour may be needed to allow the foetus to mature, to allow time for initiating glucocorticoid therapy for foetal lung maturation or to transfer the mother in labour to a centre with proper facilities. However, no clearly satisfactory drug is available since none of them has been shown to improve foetal outcome. An attempt to delay premature labour is likely to succeed only if cervical dilatation is < 4 cm and 'taking up' of lower segment is minimal. Measures to delay labour should not be undertaken if membranes have ruptured, antepartum haemorrhage is occurring, in severe toxaemia of pregnancy, intrauterine infection or foetal death.

1. Adrenergic agonists (*see* Ch. 9) *Ritodrine*, the β_2 selective agonist having more prominent uterine relaxant action is approved to suppress premature labour and to delay delivery in case of some exigency or acute foetal distress. For dependable action it is started as 50 µg/min i.v. infusion, the rate is increased every 10 min till uterine contractions cease or maternal HR rises to 120/min. Contractions are kept suppressed by continuing i.v. infusion or by 10 mg i.m. 4–6 hourly followed by 10 mg oral 4–6 hourly. However, treatment beyond 48 hours is not recommended, since risk to mother increases and benefit is uncertain. Delivery can be postponed in about 70% cases by few hours to few weeks. However, cardiovascular (hypotension, tachycardia, arrhythmia, pulmonary edema) and metabolic (hyperglycaemia, hyperinsulinaemia, hypokalaemia) complications and anxiety, restlessness, headache occur frequently. Use of ritodrine to arrest labour has been found to increase maternal morbidity. Foetal pulmonary edema can develop; volume of i.v. infusion should be kept to a minimum to avoid fluid overload. The neonate may develop hypoglycaemia and ileus. It should not be used if mother is diabetic, having heart disease, or receiving β blockers or steroids.

Ritodrine has been discontinued in the USA, but is still available in UK and India.

YUTOPAR, RITROD 10 mg/ml inj (5 ml amp), 10 mg tab. RITODINE 10 mg tab, 10 mg in 1 ml inj.

Salbutamol and terbutaline can be used as alternatives to ritodrine. *Isoxsuprine* oral/i.m. has been used to stop threatened abortion, but efficacy is uncertain.

2. Calcium channel blockers Because influx of Ca^{2+} ions plays an important role in uterine contractions, Ca^{2+} channel blockers (*see* Ch. 39) reduce the tone of myometrium and oppose contractions. These drugs, especially nifedipine, which has prominent smooth muscle relaxant action, can postpone labour if used early enough. Efficacy comparable to β_2 adrenergic agonists has been demonstrated and side effects are fewer. Oral *nifedipine* 10 mg repeated once or twice after 20–30 min, followed by 10 mg 6 hourly has been used. Tachycardia and hypotension are prominent at doses which suppress uterine contractions. Reduced placental perfusion causing foetal hypoxia is apprehended. However, fewer babies delivered after nifedipine needed intensive care.

3. Oxytocin antagonist *Atosiban* is a peptide analogue of oxytocin that acts as antagonist at the oxytocin receptors. In clinical trials, it has been found to suppress premature uterine contractions and postpone preterm delivery with fewer cardiovascular and metabolic complications than β_2 adrenergic agonists. In Europe and UK it is available for inhibition of labour between 24–33 weeks of gestation, and may offer better benefit: risk ratio than other tocolytics. However, it is not yet approved in USA and India.

4. Magnesium sulfate Infused i.v. it is a first line drug for prevention and treatment of seizures in preeclampsia and eclampsia. It also acts as a tocolytic by competing with Ca^{2+} ions for entry into myometrium through both voltage sensitive as well as ligand gated Ca^{2+} channels. However, its use to delay premature labour is risky, may increase perinatal mortality and is not recommended now.

5. Miscellaneous drugs Ethyl alcohol, nitrates, progesterone, general anaesthetics and indomethacin (PG synthesis inhibitors) are the other drugs, which can depress uterine contractions. However, their effect is not dependable and they are not used clinically as tocolytics.

Halothane is an efficacious uterine relaxant that has been used as the anaesthetic when external or internal version is attempted.

☞ PROBLEM DIRECTED STUDY

23.1 A full term primigravida aged 26 years is brought to the hospital with the complaint of having labour pains for the past 24 hours without making much progress. Two hours ago she had passed meconium stained liquor. The lady is in distress, mildly dehydrated and looks exhausted. The presentation is vertex and head is engaged, but cervix is incompletely dilated and uterine contractions are relatively weak. Foetal tachycardia is noted with irregularity during contractions.

(a) What course of action is appropriate?

(b) Can she be administered a uterine stimulant to strengthen the contractions? If yes, which drug should be given and how? If no, then why?

(see Appendix-1 for solution)

Chapter 24 Drugs Affecting Calcium Balance

CALCIUM

After C, O, H and N, calcium is the most abundant body constituent, making up about 2% of body weight, or 1–1.5 kg in an adult. Over 99% of this is stored in bones, the rest being distributed in plasma and all tissues and cells. Calcium serves important physiological roles.

Physiological roles

1. Calcium controls excitability of nerves and muscles and regulates permeability of cell membranes. It also maintains integrity of cell membranes and regulates cell adhesion.
2. Ca^{2+} ions are essential for excitation-contraction coupling in all types of muscle and excitation-secretion coupling in exocrine and endocrine glands, release of transmitters from nerve ending and other release reactions.
3. Ca^{2+} is an intracellular messenger for hormones, autacoids and transmitters.
4. Ca^{2+} controles impulse generation in heart; determines level of automaticity and A-V conduction.
5. Ca^{2+} is essential for coagulation of blood.
6. Calcium serves structural function in bone and teeth.

Plasma calcium level It is precisely regulated by 3 hormones almost exclusively devoted to this function, viz. *parathormone* (PTH), *calcitonin* and *calcitriol* (active form of vit D). These regulators control its intestinal absorption, exchange with bone and renal excretion as summarized in Fig. 24.1. In addition, several other hormones, metabolites and drugs influence calcium homeostasis (*see* box).

Influences affecting bone turnover

↑ *Resorption*	↓ *Resorption*
Corticosteroids	Androgens/Estrogens
Parathormone	Calcitonin
Thyroxine (excess)	Growth hormone
Hypervitaminosis D	Bisphosphonates
Prostaglandin E_2	Fluoride
Interleukin 1 & 6	Gallium nitrate
Alcoholism	Mithramycin
Loop diuretics	Thiazide diuretics

Normal plasma calcium is 9–11 mg/dl. Of this about 40% is bound to plasma proteins—chiefly to albumin; 10% is complexed with citrate, phosphate and carbonate in an undissociable form; the remaining (about 50%) is ionized and physiologically important. For example, in hypoalbuminemia, total plasma calcium may be low but the concentration of Ca^{2+} ion is usually normal. Acidosis favours and alkalosis disfavours ionization of calcium. As such, hyperventilation (by raising plasma pH) precipitates tetany and laryngospasm in calcium deficiency by reducing ionization.

Calcium turnover Major fraction of calcium in the bone is stored as crystalline hydroxyapatite deposited on the organic bone matrix *osteoid,* while a small labile pool is in dynamic equilibrium with plasma. Even the fully laid down parts of the bone undergo constant *remodeling* by way of two closely coupled but directionally opposite processes of resorption and new bone formation (Fig. 24.2). Millions of tiny remodeling units are working on the surface of bone trabeculae and Haversian canals to dig micropits by osteoclastic activity and then repair by osteoblastic activity in which first collagen and other proteins (osteoid) are deposited followed by mineralization; the full cycle taking 4–6 months. Diet, exercise, several hormones and drugs regulate the number and efficiency of bone remodeling units at any given time. Remodeling deficits accumulate over lifetime to account for age related bone loss, the pace of which can be retarded or accelerated by modulating the above listed influences. Estrogen lack after menopause mainly causes loss of trabecular bone, particularly affecting vertebrae, wrist bones and femoral neck. Minimal trauma/compression fractures are most common at these sites.

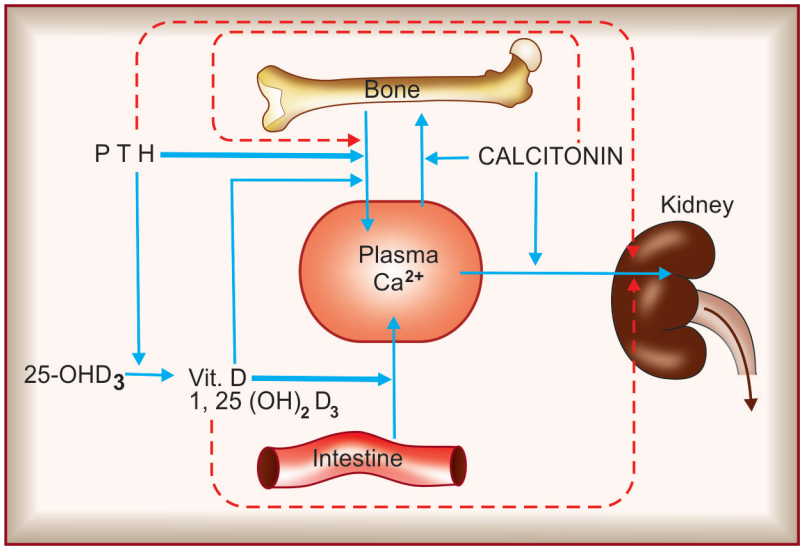


Fig. 24.1: Regulation of plasma level of calcium.
⟶ stimulation, - - - - - → Inhibition; Bold arrow indicates—major action.
PTH—Parathormone; 25-OHD_3—Calcifediol; 1,25 $(OH)_2D_3$—Calcitriol.

Absorption and excretion Calcium is absorbed by facilitated diffusion from the entire small intestine as well as from duodenum by a carrier-mediated active transport under the influence of vit D. Phytates, phosphates, oxalates and tetracyclines complex with Ca^{2+} in an insoluble form in the intestines and interfere with its absorption. Glucocorticoids and phenytoin also reduce calcium absorption.

Ionized calcium is totally filtered at the glomerulus and most of it is reabsorbed in the tubules. Vit D and PTH increase, while calcitonin decreases tubular reabsorption of Ca^{2+}. About 300 mg of endogenous calcium is excreted daily: half in urine and half in faeces. To maintain calcium balance, the same amount has to be absorbed in the small intestine from the diet. Because normally only 1/3rd of ingested calcium is absorbed, the dietary allowance for calcium is 0.8–1.5 g per day. However, fractional calcium absorption is greater in presence of calcium deficiency and low dietary calcium.

Thiazide diuretics impede calcium excretion by facilitating tubular reabsorption.

Preparations

1. *Calcium carbonate* (40% Ca): It is an insoluble, tasteless and nonirritating salt. Reacts with gastric HCl to form chloride, and can be used as antacid. It is the most common salt present in calcium supplements, but gastric acid is required for converting it into the absorbable form. Calcium availability from it is poor in patients taking proton pump inhibitors (PPIs), H_2 blockers, and in elderly.
2. *Calcium citrate* (as tetrahydrate, 21% Ca^{2+}): Slightly soluble in water, but dissolves well in presence of HCl. It is nonirritating and is used in supplements; absorption in patients taking PPIs/H_2 blockers and elderly is satisfactory.
3. *Calcium gluconate* (9% Ca): is available as 0.5 g and 1 g tablets and 10% injection (5 ml amp.). It is nonirritating to g.i.t. and the vascular endothelium. A sense of warmth is produced on i.v. injection: extravasation should be guarded. It is the preferred injectable salt.
4. *Calcium lactate:* (13% Ca) is given orally, nonirritating and well tolerated.
5. *Calcium dibasic phosphate* (23% Ca): is insoluble, reacts with HCl to form soluble chloride in the stomach. It is bland; used orally as antacid and to supplement calcium. Availability of calcium from it is reduced by PPIs and H_2 blockers.
6. *Calcium chloride* (27% Ca): It is freely soluble in water, but highly irritating to gastric mucosa and tissues; therefore not used.

Side effects Calcium supplements are usually well tolerated; only g.i. side effects like

constipation, bloating and excess gas (especially with cal. carbonate) have been reported.

Some combined formulations

CALCINOL-RB: Cal. carb 0.375 g, Cal. Phos 75 mg + vit D3 250 IU tab.
MILICAL: Cal. citrate 1 g + vit D_3 200 IU tab.
CALCIBONE: Cal. citrate 1 g + vit D_3 200 IU tab and susp.
CALSHINE: Cal. citrate 0.5 g + vit D_3 500 IU tab.
CALCIUM-SANDOZ: Cal. gluco-bionate 137.5 mg/ml inj. 10 ml amp., also tabs containing cal. carbonate 650 mg.
KALZANA: Cal. dibasic phos 430 mg + Vit C and D3 200 IU tab, also syrup: Cal. gluconate 300 mg, Cal. lactobionate 1.1 g, Cal. phos. 75 mg per 5 ml, containing Vit A, C, niacinamide and D3 200 IU.
OSTOCALCIUM: Cal. phos 380 mg + Vit D3 400 IU tab, also syrup: Cal. phos 240 mg per 5 ml containing Vit D3 200 IU and B12.
SHELCAL: Cal. carb. 625 mg (eq 250 mg elemental cal), Vit D_3 125 IU tab and per 5 ml syr.
MACALVIT: Cal. carb. 1.25 g, cholecalciferol 250 IU tab; Cal. gluconate 1.18 g, Cal. lactobionate 260 mg + Vit D_3 100 IU per 5 ml syr.
CALCIMAX: Cal. carb. (150 mg cal), dibasic cal. phos. (23.3 mg cal) with magnesium, zinc and vit D3 200 IU tab.; also syrup cal. carb. (150 mg cal) with magnesium, zinc and vit D3 200 IU per 5 ml syrup.

Use

1. *Tetany* For immediate treatment of severe cases 10–20 ml of Cal. gluconate (elemental calcium 90–180 mg) is injected i.v. over 10 min, followed by slow i.v. infusion. A total of 0.45-0.9 g calcium (50 to 100 ml of cal. gluconate solution) over 6 hours is needed for completely reversing the muscle spasms. Supportive treatment with i.v. fluids and oxygen inhalation may be required. Long-term oral treatment to provide 1–1.5 g of calcium daily is instituted along with vit. D. Milder cases need oral therapy only.
2. *As dietary supplement* especially in growing children, pregnant, lactating and menopausal women. The dietary allowance recommended by National Institute of Health (1994) is—
   - Children 1–10 yr : 0.8–1.2 g
   - Young adult 11–24 yr, pregnant and lactating women : 1.2–1.5 g
   - Men 25–65 yr, women 25–50 yr and 51–65 yr if taking HRT : 1.0 g
   - Women 51–65 yr not taking HRT, *every one > 65 yr* : *1.5 g*

Calcium supplement can reduce bone loss in predisposed women as well as men. It is often given to fracture patients, but if diet is adequate this does not accelerate healing.

3. *Osteoporosis* In the prevention and treatment of osteoporosis with alendronate/HRT/raloxifene, it is important to ensure that calcium deficiency does not occur. Calcium + vit D_3 have adjuvant role to these drugs in prevention and treatment of osteoporosis.

However, the efficacy of calcium ± vit D supplements alone in increasing bone mass or preventing fractures among menopausal women/elderly men is controversial. It does not appear to reduce fracture risk in otherwise healthy subjects taking adequate diet. In the recently concluded 7 year prospective WHI study involving >36000 postmenopausal women (51–79 years), the overall risk of fractures was the same in the calcium (1 g/day) + vit D (400 IU/day) group as in the placebo group, though the bone mineral density at the hip was 1% higher in the treated group. Certain subgroups of osteoporotic subjects may benefit from calcium supplements, but the benefit appears to be marginal and limited to cortical bone loss only. On the other hand, a metaanalysis has shown that subjects receiving calcium supplements had a 27% higher incidence of MI. Thus, calcium supplements should be given only to subjects taking diet low in calcium.

4. Empirically, Cal. gluconate i.v. has been used in dermatoses, paresthesias, weakness and other vague complaints. Any benefit is probably psychological due to warmth and other subjective effects produced by the injection.
5. As antacid (*see* Ch. 46).

PARATHYROID HORMONE (Parathormone)

Vassale and Generali (1900) were the first to perform selective parathyroidectomy (without removing thyroids) and found that it produced tetany and death. MacCallum and Voegtlin in 1909 established this to be due to decrease in plasma calcium levels; parathormone (PTH) was isolated in 1925.

PTH is a single chain 84 amino acid polypeptide, MW 9500. It is synthesized as prepro-PTH, the excess amino acids are split off in two steps and it is then stored in intracellular vesicles. Secretion of PTH is regulated by plasma Ca^{2+}

concentration through a calcium-sensing receptor (CaSR), that is a G-protein coupled receptor on the surface of parathyroid cells. There is no trophic hormone for it. Fall in plasma Ca^{2+} induces PTH release and rise inhibits secretion by decreasing cAMP in the parathyroid cells. Agents that increase cAMP cause PTH release, but direct activation of protein kinase C by fall in Ca^{2+} concentration is more important physiologically. Prolonged hypocalcaemia causes hypertrophy and hyperplasia of parathyroids, while sustained hypercalcaemia has the opposite effect. Changes in phosphate concentration in plasma affect PTH secretion indirectly by altering Ca^{2+} concentration. The active form of vit. D calcitriol inhibits expression of PTH gene in parathyroid cells reducing PTH production. PTH is rapidly degraded in liver and kidney; its plasma t½ is 2–5 min.

Actions

PTH increases plasma calcium levels by:

1. *Bone* PTH promptly increases resorption of calcium from bone. This is the most prominent action of PTH—exerted by increasing the number of bone remodeling units and activating osteoclasts when high concentrations are present continuously. Since bone resorption is followed by new bone deposition, this is also promoted by PTH: increased bone formation occurs when PTH is given intermittently and in low doses.

2. *Kidney* PTH increases calcium reabsorption in the distal tubule and provides moment to moment regulation of calcium excretion. It also promotes phosphate excretion which tends to supplement the hypercalcaemic effect. However, grossly increased plasma calcium level occurring in hyperparathyroidism overrides the direct action on tubules and calcium excretion in urine is actually increased. The converse occurs in hypoparathyroidism.

3. *Intestines* PTH has no direct effect on calcium absorption but increases it indirectly by enhancing the formation of calcitriol (active form of vit D) in the kidney by activating 1α-hydroxylase. Calcitriol then promotes intestinal absorption of calcium.

4. PTH decreases calcium levels in milk, saliva and ocular lens. This may be responsible for development of cataract in hypoparathyroidism.

Mechanism of action The PTH receptor is a G protein coupled receptor which on activation increases cAMP formation and intracellular Ca^{2+} in target cells. In bone, the target cell is the osteoblast because PTH receptors are not expressed on the surface of osteoclasts. Acting on the osteoblast, PTH induces a factor 'Receptor for activation of nuclear factor-κB-ligand' (RANKL) which diffuses and combines with RANK on osteoclast precursors and transforms them into osteoclasts as well as activates osteoclasts (Fig. 24.2). In addition, birth rate of bone remodeling units into which osteoclasts are recruited is enhanced. Formation of the remodeling pit is followed by osteoblastic deposition of new bone into it. PTH enhances proliferation and differentiation of preosteoblasts and deposition of osteoid as well. Bone resorption predominates when high concentrations of PTH are present continuously, but intermittent exposure to low concentrations has the opposite effect.

Hypoparathyroidism Manifestations are:
Low plasma calcium levels, tetany, convulsions, laryngospasm, paresthesias, cataract and psychiatric changes. Pseudohypoparathyroidism occurs due to reduced sensitivity of target cells to PTH caused by a mutant G protein that couples PTH receptor activation to cAMP generation in target cells.

Hyperparathyroidism It is mostly due to parathyroid tumour. It produces—
Hypercalcaemia, decalcification of bone—deformities and fractures (osteitis fibrosa generalisata), metastatic calcification, renal stones, muscle weakness, constipation and anorexia.

Treatment is surgical removal of the parathyroid tumour. When this is not possible—low calcium, high phosphate diet with plenty of fluids is advised.

Cinacalcet It activates the Ca^{2+} sensing receptor (CaSR) in the parathyroids and blocks PTH secretion. It is indicated in secondary hyperparathyroidism due to renal disease and in parathyroid tumour.

Use PTH is not used in hypoparathyroidism because plasma calcium can be elevated and kept in the normal range more

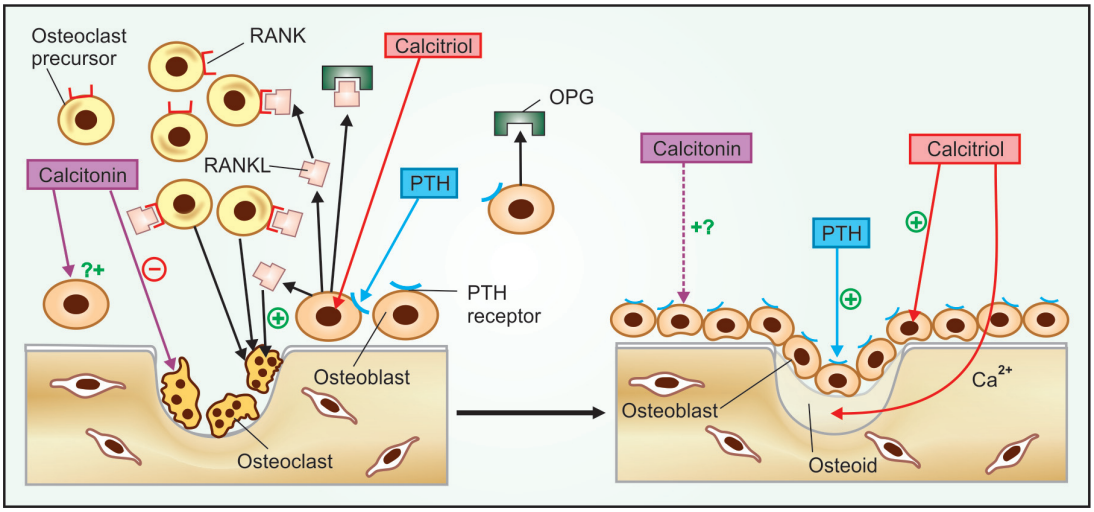


Fig. 24.2: Hormonal regulation of bone remodeling unit

The monocyte osteoclast precursor cells in the marrow near the bony surface are activated to proliferate and fuse to form multinucleated osteoclasts. The osteoclast-precursors express a 'receptor for activation of nuclear factor-κ B' (RANK) on their surface. The osteoblasts on activation release a protein RANK-ligand (RANKL). When RANKL is bound to RANK on the surface of osteoclast-precursors they are transformed into mature osteoclasts and develop bone lysing ruffled surface. A bone resorption pit is dug out by secretion of acid and proteolytic acid hydrolases.

Osteoblasts produce another protein osteoprotegerin (OPG) as well, which can bind RANKL and prevent it from combining with RANK to activate osteoclasts. Thus, osteoblasts by producing RANKL and OPG regulate bone resorption.

After formation of the remodeling pit, preosteoblasts from bone marrow stem cells proliferate, migrate to the base of the pit, transform into mature osteoblasts and laydown new osteoid, which is later mineralized.

Parathormone (PTH) acts on PTH-receptor located on the osteoblast membrane and induces RANKL production—indirectly activating osteoclast differentiation and function. Subsequently PTH promotes new bone formation as well.

Calcitriol also induces RANKL in osteoblasts to indirectly activate osteoclasts. Similarly, it promotes laying of osteoid as well as bone mineralization.

Calcitonin directly inhibits osteoclast function and probably enhances osteoblastic new bone formation.

conveniently by vit D therapy. PTH has to be given parenterally, while vit D can be given orally. Vit D is cheap. However, recombinant human PTH (1–84 amino acid) has been produced and is being clinically evaluated for use in hypoparathyroidism.

Teriparatide This recombinant preparation of 1–34 residues of amino terminal of human PTH has been recently introduced for the treatment of severe osteoporosis. It duplicates all the actions of long (1–84) PTH. Injected s.c. 20 µg once daily, it acts only for 2–3 hours, and has been found to increase bone mineral density in osteoporotic women. The effect was faster and more marked than that produced by estrogens and bisphosphonates (BPNs). Teriparatide is the only agent which stimulates bone formation, whereas the other two only check bone resorption. In clinical trials it was found to be equally or more effective than estrogens and BPNs in reducing risk of vertebral as well as non-vertebral fractures in osteoporotic women as well as men. After s.c. injection its plasma t½ is 1 hr; given once daily only intermittent action is produced and the bone forming action predominates over bone resorbing action. High cost and need for daily s.c. injections are the limitations. Its use may be justified in severely osteoporotic women, those who have already suffered osteoporotic fractures or have multiple risk factors for fracture. Treatment beyond 2 years is not recommended. Side effects include dizziness and leg cramps. Pagets disease and hypercalcaemia are the contraindications.

Diagnostic use To differentiate pseudo from true hypoparathyroidism: teriparatide is given i.v.: if plasma calcium level fails to rise, then it is pseudohypoparathyroidism.

CALCITONIN

Calcitonin is the hypocalcaemic hormone discovered by Copp in 1962. It is a 32 amino acid single chain polypeptide (MW 3600) produced

by parafollicular 'C' cells of thyroid gland. Parathyroids, thymus and cells of medullary carcinoma of thyroid also contain calcitonin.

Synthesis and secretion of calcitonin is regulated by plasma Ca^{2+} concentration itself: rise in plasma Ca^{2+} increases, while fall in plasma Ca^{2+} decreases calcitonin release. However, circulating level of calcitonin is low and its physiological role in regulating plasma Ca^{2+} appears to be minor. The plasma t½ of calcitonin is 10 min, but its action lasts for several hours.

Actions

The actions of calcitonin are generally opposite to that of PTH. It inhibits bone resorption by direct action on osteoclasts—decreasing their ruffled surface which forms contact with the resorptive pit. Whether it also promotes calcium deposition by osteoblasts is not certain. The hypocalcaemic action of calcitonin lasts ~8 hours.

Calcitonin inhibits proximal tubular reabsorption of calcium and phosphate by direct action on the kidney. However, hypocalcaemia overrides the direct action by decreasing the total calcium filtered at the glomerulus—urinary Ca^{2+} is actually reduced.

The actions of calcitonin are mediated through a G-protein coupled calcitonin receptor (CTR) and increase in cAMP formation, but its target cells are different from that of PTH.

Preparation and unitage Synthetic salmon calcitonin is used clinically, because it is more potent and longer acting due to slower metabolism. Human calcitonin has also been produced.

1 IU = 4 µg of the standard preparation.

CALSYNAR, ZYCALCIT: Synthetic salmon calcitonin 100 IU/ml amp. for i.m. or s.c. injection.

Nausea, flushing and tingling of fingers is frequent after calcitonin injection. Bad taste, flu-like symptoms, allergic reactions and joint pain are the other adverse effects.

Uses

1. *Hypercalcaemic states* Hyperparathyroidism, hypervitaminosis D, osteolytic bony metastasis and hypercalcaemia of malignancy; 4–8 IU/kg i.m. 6–12 hourly only for 2 days. It acts rapidly within 4 hours, the response peaks at 48 hours and then refractoriness develops. It also relieves bone pain.

For emergency treatment of hypercalcaemia 5–10 IU/kg may be diluted in 500 ml saline and infused i.v. over 6 hours. Calcitonin is a relatively weak hypocalcaemic drug. Therefore, used only to supplement BPNs initially, because BPNs take 24–48 hours to act.

2. *Postmenopausal osteoporosis* Though i.m. or s.c. calcitonin can be used, a nasal spray formulation delivering 200 IU per actuation is employed. MIACALCIN NASAL SPRAY, OSTOSPRAY 2200 IU metered dose vial, CALCINASE 200 IU per actuation nasal spray. One spray in alternate nostril daily has been shown to increase bone mineral density in menopausal women and to reduce vertebral, but not nonvertebral, fractures. It is less effective than BPNs/HRT. Calcitonin is indicated only when other drugs cannot be given and in women who are menopausal for at least 5 years with definite evidence of osteoporosis. Though nausea and flushing are less with nasal spray, rhinitis, epistaxis, nasal ulceration and headache are produced frequently.

3. *Paget's disease* 100 IU i.m./s.c. daily or on alternate days produces improvement for few months. Later, resistance usually develops due to production of antibodies. Bisphosphonates are preferred; calcitonin may be used as adjuvant or 2nd line drug.

4. *Diagnosis of medullary carcinoma of thyroid* Detection of high blood level of calcitonin is diagnostic of this tumour, which arises from the calcitonin producing parafollicular cells of thyroid.

VITAMIN D

Vitamin D is the collective name given to antirachitic substances synthesized in the body and found in foods activated by UV radiation.

D3 : cholecalciferol — synthesized in the skin under the influence of UV rays.

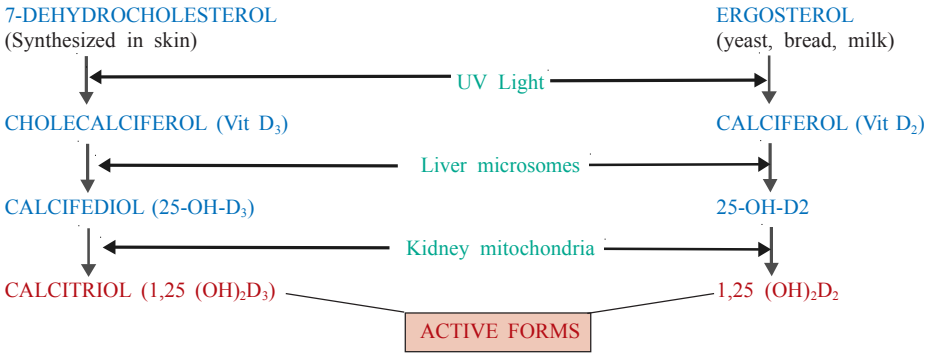
D2 : calciferol—present in irradiated food—yeasts, fungi, bread, milk.

D1 : mixture of antirachitic substances found in food—only of historic interest.

In 1919 it was established that rickets was due to deficiency of a dietary factor as well as lack of exposure to sunlight. McCollum (1922) showed that this fat soluble dietary factor was different from vit A and its structure was determined in 1935. The interrelation between calciferol and cholecalciferol and their activation in the body has been fully understood only in the 1970s.

Activation of vit D It takes place in the following manner—

Ergosterol differs from 7-dehydrocholesterol in having an extra double bond between C22–23 and a methyl group at C24. In man vit D_2 and D_3 are equally active and *calcitriol* (active form of D_3) is more important physiologically; 25-OH D_3 is released in blood from the liver and binds



loosely to a specific vit D binding globulin. The final 1α-hydroxylation in kidney is rate limiting and is controlled by many factors. This step is activated or induced by calcium/vit D deficiency as well as by PTH, estrogens and prolactin, while calcitriol inhibits it in a feedback manner.

Thus, vit D should be considered a hormone because:

(a) It is synthesized in the body (skin); under ideal conditions it is not required in the diet.
(b) It is transported by blood, activated and then acts on specific receptors in the target tissues.
(c) Feedback regulation of vit D activation occurs by plasma Ca^{2+} level and by the active form of vit D itself.

Actions

1. Calcitriol enhances absorption of calcium and phosphate from *intestine*. This is brought about by increasing the synthesis of calcium channels and a carrier protein for Ca^{2+} called 'calcium binding protein' (Ca BP) or *Calbindin*. The action of calcitriol is analogous to that of steroid hormones. It binds to a cytoplasmic vitamin D receptor (VDR) → translocate to the nucleus → increase synthesis of specific mRNA → regulation of protein synthesis. Another line of evidence suggests that activation of VDR promotes endocytotic capture of calcium, its transport across the duodenal mucosal cell and finally its active extrusion through the serosal membrane. At least part of vit D action is quick (within minutes) and, therefore, appears to be exerted by mechanisms not involving gene regulation.
2. Calcitriol enhances resorption of calcium and phosphate from *bone* by promoting recruitment and differentiation of osteoclast precursors in the bone remodeling units, but mature osteoclasts lack VDR. Like PTH, calcitriol induces RANKL in osteoblasts which may then activate the osteoclasts. Osteoblastic cells express VDR and respond to calcitriol by laying down osteoid, but it mainly appears to help bone mineralization indirectly by maintaining normal plasma calcium and phosphate concentration. Its action is independent of but facilitated by PTH.
3. Calcitriol enhances tubular reabsorption of calcium and phosphate in the *kidney,* but the action is less marked than that of PTH. However, in hypervitaminosis D, influence of hypercalcaemia overrides the direct action and more calcium is excreted in urine.
4. *Other actions* Actions of calcitriol on immunological cells, lymphokine production, proliferation and differentiation of epidermal and certain malignant cells, neuronal and skeletal muscle function have also been demonstrated.

Vit D deficiency Plasma calcium and phosphate tend to fall due to inadequate intestinal absorption. As a consequence, PTH is secreted → calcium is mobilized from bone in order to restore plasma Ca^{2+}. The bone fails to mineralize normally in the newly laid area, becomes soft → rickets in children and osteomalacia in adults. However, in contrast to *osteoporosis*, the organic matrix (osteoid) is normal in these conditions.

Hypervitaminosis D It may occur due to chronic ingestion of large doses (~50,000 IU/day) or due to increased sensitivity of tissues to vit D. Manifestations are due to elevated plasma calcium and its ectopic deposition. These are: hypercalcaemia, weakness, fatigue, vomiting, diarrhoea, sluggishness, polyuria, albuminuria, ectopic Ca^{2+} deposition (in soft tissues, blood vessels, parenchymal organs), renal stones or nephrocalcinosis, hypertension, growth retardation in children. Even coma has been reported.

Treatment: consists of withholding the vitamin, low calcium diet, plenty of fluids and corticosteroids. Recovery may be incomplete in many cases.

Pharmacokinetics

Vit D is well absorbed from the intestines in the presence of bile salts, mainly through lymphatics. Absorption of the D_3 form is somewhat better than that of D_2. Malabsorption and steatorrhoea interfere with its absorption.

In the circulation, it is bound to a specific α globulin and is stored in the body, mostly in adipose tissues, for many months. It is hydroxylated in the liver to active and inactive metabolites. The t½ of different forms varies from 1–18 days: 25-OHD_3, having the longest t½ , constitutes the primary circulating form. Calcitriol is cleared rapidly.

Metabolites of vit D are excreted mainly in bile.

Unitage and preparations

1 µg of cholecalciferol = 40 IU of vit D.

The daily requirement varies, depending on exposure to sunlight. It is estimated that if no vit D3 is synthesized in the body, a dietary allowance of 400 IU/day will prevent deficiency symptoms. However, higher amounts (upto 1000 IU/day) are also recommended. The forms in which vit D is supplied are—

1. *Calciferol (Ergocalciferol, vit D2)* As solution in oil, filled in gelatin capsules 25,000 and 50,000 IU caps.
2. *Cholecalciferol (vit D3)* As granules for oral ingestion and oily solution for i.m. injection.

ARACHITOL 300,000 IU (7.5 mg) and 600,000 IU (15 mg) per ml inj.

CALCIROL, CALCIBEST SACHET 60,000 IU in 1 g granules—suspended in milk/water and taken at 3–4 weeks intervals, and then every 2–6 months.

3. *Calcitriol* 0.25–1 µg orally daily or on alternate days; CALTROL, ROLSICAL, ROCALTROL 0.25 µg cap. CALCIBEST 1 µg in 1 ml aqueous inj; 0.5–1 µg i.v. on alternate days.

Hypercalcaemia is the main adverse effect; must be watched for and therapy promptly stopped if plasma Ca^{2+} rises.

4. *Alfacalcidol* It is 1 α-OHD_3—a prodrug that is rapidly hydroxylated in the liver to 1,25 $(OH)_2$ D_3 or calcitriol. Therefore, it does not require hydroxylation at position 1 which is the limiting step in the generation of active form of vit D, and which takes place in the kidney. As such, it is effective in renal bone disease, vit D dependent rickets, vit D resistant rickets, hypoparathyroidism, etc. i.e. indications for which calcitriol is needed. It is also being used in osteoporosis.

Alfacalcidol is orally active and clinically equally effective on long term basis to calcitriol. Its metabolic activation in liver does not pose a problem even in severe liver disease.

Dose: 1–2 µg/day, children < 20 kg 0.5 µg/day. Repeated serum calcium measurements are essential for regulation of maintenance dose. Hypercalcaemia should be watched for and therapy promptly interrupted for few days when it develops.

ONE ALPHA, ALPHA D_3, ALPHADOL 0.25 and 1 µg caps, ALFACAL 0.25, 0.5 µg caps.

5. *Dihydrotachysterol* A synthetic analogue of vit D_2 that is much less active in antirachitic tests, but directly mobilizes calcium from bone after 25-hydroxylation in liver, and does not require PTH dependent activation in the kidney. It is particularly useful in hypoparathyroidism and renal bone disease.

Dose: 0.25–0.5 mg/day.

Combination preparations of vit D are listed on p. 337 and in Table 67.2.

Use

1. *Prophylaxis* (400 IU/day) *and treatment* (3000–4000 IU/day) *of nutritional vit D deficiency* This is given to prevent and treat rickets in children and osteomalacia in adults. Alternatively 300,000–600,000 IU can be given orally or i.m. once in 2–6 months. Prophylactic treatment may be given in obstructive jaundice, steatorrhoea and other conditions which predispose to vit D deficiency.

2. *Metabolic rickets* These are a group of conditions in which tissues do not respond to normal doses of vit D.

(a) *Vit D resistant rickets:* X-linked hereditary disease in which vit D metabolism is normal but calcium and phosphate metabolism is deranged. Administration of phosphate with high dose of calcitriol or alfacalcidol is beneficial.

(b) *Vit D dependent rickets:* Another genetic disorder due to deficiency of renal hydroxylating mechanism which converts 25-OHD_3 into calcitriol. Administration of calcitriol or alfacalcidol is effective in normal doses.

(c) *Renal rickets:* Conversion of 25-OHD_3 into calcitriol does not occur due to chronic renal disease. Calcitriol/alfacalcidol or dihydrotachysterol are needed in usual doses.

3. *Senile or postmenopausal osteoporosis* Age-related decrease in calcium absorption from gut has been noted. Vit D_3 + calcium have been shown to improve calcium balance in osteoporotic females and elderly males. However, benefit in terms of improved bone mass or reduced fracture risk is controversial or marginal (*see* p. 337). But this does not apply to active therapy with calcitriol/alfacalcidol for patients with established osteoporosis, treated with BPNs, etc. because calcitriol suppresses parathyroids and reduces bone remodeling. Vit D deficiency results in secondary hyperparathyroidism which contributes to osteoporosis. Calcitriol therapy carries the risk of hypercalcaemia, calcium stones and metastatic calcification which should be watched for.

4. *Hypoparathyroidism* Dihydrotachysterol or calcitriol/alfacalcidol are more effective than vit, D_2 or D_3, because they act quickly and directly without requiring hydroxylation in kidney which needs PTH. Alternatively, conventional preparations of vit D_3 may be given in high doses (25000-100,000 IU/day).

5. *Fanconi syndrome* Vit D can raise the lowered phosphate levels that occur in this condition.

6. A nonhypercalcaemic analogue of vit D *Calcipotriol* (DAIVONEX 0.005% oint) is used locally in plaque type psoriasis, and has yielded good results (*see* Ch. 64). Systemically it has been tried in skin cancer and immunological disorders.

Interactions

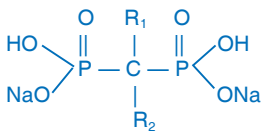
1. Cholestyramine and chronic use of liquid paraffine can reduce vit D absorption.
2. Phenytoin and phenobarbitone reduce the responsiveness of target tissues to calcitriol; their prolonged use (for epilepsy) can cause rickets/osteomalacia. It was believed earlier that these drugs enhance degradation of vit D. However, now it has been shown that plasma level of calcitriol is normal, but its effect on intestine and bone is diminished.

BISPHOSPHONATES

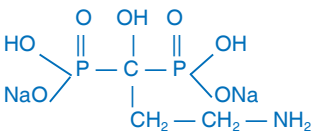
Bisphosphonates (BPNs) are analogues of pyrophosphate: carbon atom replacing oxygen in the P-O-P skeleton. They inhibit bone resorption and have recently attracted considerable attention because of their ability to prevent osteoporosis in addition to their usefulness in metabolic bone diseases and hypercalcaemia. They are the most effective antiresorptive drugs. Chronologically and according to potency, the BPNs can be grouped into 3 generations (*see* box). The first generation compounds have simpler side chains, are the least potent and seldom used now. The second and third generation compounds have an amino or nitrogenous ring substitution in the side chain, are more potent, have higher efficacy and additional mode of action.

Bisphosphonate	Relative potency
First generation BPNs	
Etidronate	1
*Tiludronate	10
Second generation BPNs	
Pamidronate	100
Alendronate	100–500
*Ibandronate	500–1000
Third generation BPNs	
Risedronate	1000
Zoledronate	5000

* Not marketed in India



Bisphosphonate



Pamidronate

The mechanism of action of BPNs is not fully understood, but two facets of action have been delineated:

(a) BPNs have strong affinity for calcium phosphate and have selective action in calcified tissue. The two main components of bone are protein matrix and the solid mineral phase (hydroxyapatite). On the surface of resorptive pits the mineral phase is solubilized in the clear acidic zone created at the ruffled border of osteoclasts, followed by resorption of protein matrix in this area by acid hydrolases secreted from osteoclasts. BPNs localise in the acidic zone under the osteoclasts due to their high affinity for Ca^{2+} ions. When Ca^{2+} ions are released from the bone surface due to high acidity, the BPNs are also released and are internalized into osteoclasts by endocytosis. This results in:

- Accelerated apoptosis of osteoclasts reducing their number.
- Disruption of cytoskeleton and ruffled border of osteoclasts.

In addition, BPNs appear to affect osteoclast precursors and inhibit their differentiation by suppressing IL-6.

(b) It has been shown now that BPNs, especially the second and third generation potent amino-derivatives like alendronate, zoledronate, have important metabolic effects in the mevalonate pathway for isoprenoid lipid synthesis. They inhibit prenylation of certain GTP-binding proteins involved in cytoskeletal organization, membrane ruffling and vesicle movement. The net result is inactivation of osteoclasts, impaired vesicle fusion and enhanced apoptosis. Interference with mevalonate pathway may also impart antitumor action on bony metastasis.

All oral BPNs are poorly absorbed, and produce gastric irritation, esophagitis as the major side effect. They are contraindicated in gastroesophageal reflux, peptic ulcer and renal impairment.

The BPNs are useful in conditions characterized by enhanced bone turnover.

1. *Osteoporosis* The second and third generation BPNs (e.g. alendronate, risedronate) are effective in preventing and treating post-menopausal osteoporosis in women as well as age related, idiopathic and steroid-induced osteoporosis in both men and women. Alendronate is equally or more effective than HRT or raloxifene in conserving bone mineral density and has reduced the risk of vertebral as well as hip fracture by 47–56%.

Estrogens prevent vertebral but not other fractures. BPNs are more effective than calcitonin and continue to afford protection for at least 5 years of continuous use. Thus, they are the first choice drugs now for osteoporosis. Since the t½ of alendronate in bone is ~ 10 years, treatment beyond 5 years is considered unnecessary.

2. *Paget's disease* This disease due to abnormal osteoclast function producing disordered bone remodeling and honeycomb-like bone architecture is benefited by BPNs. They arrest osteolytic lesions, reduce bone pain and improve secondary symptoms. Long-lasting remissions may be induced. Alendronate, risedronate, pamidronate and zoledronate are used now. They are more convenient, more effective and cheaper than calcitonin. Combined use of BPNs and calcitonin further increases efficacy. Treatment with BPNs should not exceed 6 months; but courses may be repeated after a gap.

3. *Hypercalcaemia of malignancy* Severe hypercalcaemia, a common complication of malignancy, is a medical emergency with altered consciousness. Pamidronate (60–90 mg i.v. over 2–4 hours) or zoledronate (4 mg i.v. over 15 min) are the most effective drugs, but take 24–48 hours to act. They may be supplemented by i.m. calcitonin 6–12 hourly for 2 days to achieve rapid action. Vigorous i.v. hydration is instituted first. After volume repletion, furosemide is added to enhance Ca^{2+} excretion and to prevent volume overload. This is followed by BPN infusion. This therapy reduces serum calcium within few hours and corrects the attending dehydration. Oral BPNs are not useful. Corticosteroids also lower plasma Ca^{2+}, but are slow to act, take 1–2 weeks.

4. *Osteolytic bone metastasis* Parenteral pamidronate/zoledronate arrests osteolytic lesions and reduces bone pain.

Etidronate This is the first BPN to be used clinically, employed in hypercalcaemia and Paget's disease. However, it also interferes with bone mineralization: continuous therapy produces osteomalacia. Therefore, it has been largely replaced by zoledronate for hypercalcaemia and alendronate/risedronate for Paget's disease. Etidronate is administered both orally and i.v., but is not preferred now.
Dose: 5–7.5 mg/kg/day.
DRONATE-OS 200 mg tab, 300 mg inj.

Pamidronate A second generation potent BPN which is administered only by i.v. infusion in a dose of 60–90 mg over 2–4 hours weekly or monthly depending on the condition. It is used in Paget's disease, hypercalcaemia of malignancy and in bony metastasis. Adverse effects are thrombophlebitis of injected vein, bone pain, fever and leukopenia. A flu-like reaction may occur initially due to cytokine release.
AREDIA 15, 30, 60 mg inj; AREDRONET 30, 90 mg inj. BONAPAM 30, 60, 90 mg inj.

Alendronate This potent orally effective second generation amino-BPN is used primarily for prevention and treatment of osteoporosis both in women and men, as well as for Paget's disease. It is to be taken on empty stomach in the morning with a full glass of water and patient is instructed not to lie down or take food for at least 30 min. These measures are needed to prevent contact of the drug with esophageal mucosa which results in esophagitis. Calcium, iron, antacids, mineral water, tea, coffee, fruit juice interfere with alendronate absorption. NSAIDs accentuate gastric irritation caused by alendronate. Other adverse effects are gastric erosion, retrosternal pain, flatulence, headache, bodyache and initial fall in serum Ca^{2+} level.
Dose: 5–10 mg OD; or 35–70 mg weekly; weekly treatment is as effective, more convenient and better tolerated.
OSTEOPHOS, DENFOS 5, 10, 35, 70 mg tab. RESTOFOS, DRONAL 10, 70 mg tab.

Oral bioavailability of alendronate is ~1%. Up to 50% of the drug entering the body is sequestrated in bone while the rest is excreted unchanged mainly by the kidney. The terminal elimination t½ of alendronate has been measured as 10.5 years.

Risedronate It is an oral 3rd generation BPN, more potent than alendronate, but equally efficacious. Oral bioavailability of 1% and other features are similar to alendronate. It is indicated in the treatment of osteoporosis and Paget's disease.
Dose: 35 mg/week oral in the morning with a full glass of water.
RISOFO 5, 35, 70 mg tabs. GEMFOS, ACTONEL 35 mg tab.

Zoledronate This parenteral highly potent 3rd generation BPN is indicated for hypercalcaemia, bony metastasis, osteolytic lesions, and Paget's disease. Osteoclastic activity is markedly suppressed and an additional antitumor effect may be exerted by interference with mevalonate pathway. Proliferation of bony metastasis of prostate/breast cancer and multiple myeloma cells may be arrested. For hypercalcaemia, it is more effective, faster acting than pamidronate and therefore the drug of choice now. Another advantage is that it can be infused over 15 min (because of less venous irritation), whereas pamidronate needs 2–4 hours. Flu-like symptoms due to cytokine release attend the i.v. infusion. Nausea, vomiting, bodyache, dizziness are also common. Renal toxicity has been encountered. Osteonecrosis of the jaw is a rare complication of i.v. high dose BPN therapy.

Zoledronate 4 mg infused i.v. once every 12 months has been used for osteoporosis in postmenopausal women who do not tolerate oral alendronate/risedronate.
Dose: 4 mg diluted in 100 ml saline/glucose solution and infused i.v. over 15 min; may be repeated after 7 days and then at 3–4 week intervals.
ZOBONE, ZOLDRIA, ZOLTERO 4 mg/vial inj.

Other drugs for hypercalcaemia

1. *Gallium nitrate:* It is a potent inhibitor of bone resorption; acts by depressing ATP-dependent proton pump at the ruffled membrane of osteoclasts. Indicated in resistant cases of hypercalcaemia, it is given by continuous i.v. infusion daily for 5 days. It is nephrotoxic and only a reserve drug.

2. *Glucocorticoids:* High doses of prednisolone (and others) enhance calcium excretion, decrease calcium absorption and have adjuvant role in hypercalcaemia due to lymphoma, myeloma, leukaemia, carcinoma breast, etc.

Other drugs for osteoporosis

1. *Strontium ranelate*: It suppresses bone resorption as well as stimulates bone formation, and has been introduced as a reserve drug for elderly women >75 years age who have already suffered osteoporotic fracture and are unable to tolerate BPNs.

2. *Denosumab:* It is a human monoclonal antibody which inhibits osteoclast differentiation and function as well as promotes their apoptosis. It is a treatment option for postmenopausal osteoporosis when no other drug is appropriate.

SECTION 6

DRUGS ACTING ON PERIPHERAL (SOMATIC) NERVOUS SYSTEM

Chapter 25 Skeletal Muscle Relaxants

Skeletal muscle relaxants are drugs that act peripherally at neuromuscular junction/muscle fibre itself or centrally in the cerebrospinal axis to reduce muscle tone and/or cause paralysis. The neuromuscular blocking agents are used primarily in conjunction with general anaesthetics to provide muscle relaxation for surgery, while centrally acting muscle relaxants are used mainly for painful muscle spasms and spastic neurological conditions.

PERIPHERALLY ACTING MUSCLE RELAXANTS

I. Neuromuscular blocking agents

A. Nondepolarizing (Competitive) blockers

1. *Long acting*: d-Tubocurarine, Pancuronium, Doxacurium, Pipecuronium
2. *Intermediate acting:* Vecuronium, Atracurium, Cisatracurium, Rocuronium, Rapacuronium
3. *Short acting:* Mivacurium

B. Depolarizing blockers

Succinylcholine (SCh., Suxamethonium), Decamethonium (C-10)

II. Directly acting agents

Dantrolene sodium
Quinine

Note: 1. Decamethonium is not used clinically.
2. Aminoglycoside, tetracycline, polypeptide antibiotics interfere with neuromuscular transmission at high doses, but are not employed as muscle relaxants.

NEUROMUSCULAR BLOCKING AGENTS

Curare It is the generic name for certain plant extracts used by south American tribals as arrow poison for game hunting. The animals got paralysed even if not killed by the arrow. Natural sources of curare are *Strychnos toxifera, Chondrodendron tomentosum* and related plants. Muscle paralysing active principles of these are tubocurarine, toxiferins, etc.

Tubocurarine was first clinically used in 1930s; many synthetic compounds including *Succinylcholine* were introduced subsequently. Search has continued for neuromuscular blockers to provide greater cardiovascular stability during surgery and for drugs with differing onset and duration of action to suit specific requirements. The latest additions are *doxacurium, pipecuronium, rocuronium, mivacurium, rapacuronium* and *cisatracurium*.

MECHANISM OF ACTION

The site of action of both competitive and depolarizing blockers is the end plate of skeletal muscle fibres.

Competitive block (Nondepolarizing block)

This is produced by curare and related drugs. Claude Bernard (1856) precisely localized the site of action of curare to be the neuromuscular junction. He stimulated the sciatic nerve of pithed frog and recorded the contractions of gastrocnemius muscle. Injection of curare in the ventral lymph sac caused inhibition of muscle twitches but there was no effect if the blood supply of the hind limb was occluded. This showed that curare acted peripherally and not centrally. Soaking a portion of the sciatic nerve in curare solution did not affect the twitches and a curarized muscle still responded to direct stimulation—thus, nervous conduction and muscle contraction were intact. The only possible site of action could be the neuromuscular junction. This has now been confirmed by close iontophoretic application of d-TC to the muscle end plate and by other modern techniques.

The competitive blockers have affinity for the nicotinic (N_M) cholinergic receptors at the muscle end plate, but have no intrinsic activity. The N_M receptor has been isolated and studied in detail. It is a protein with 5 subunits ($\alpha 2\ \beta\ \varepsilon$ or γ and δ) which are arranged like a rosette surrounding the Na^+ channel (*see* Fig. 4.4). The two α subunits carry two ACh binding sites; these have negatively charged groups which combine with the cationic head of ACh → opening of Na^+ channel. Most of the competitive blockers have two or more quaternary N^+ atoms (Fig. 25.1) which provide the necessary attraction to the same site, but the bulk of the antagonist molecule does not allow conformational changes in the subunits needed for opening the channel. Competitive blockers generally have thick bulky molecules and were termed *Pachycurare* by Bovet (1951). ACh released from motor nerve endings is not able to combine with its receptors to generate end plate potential (EPP). d-TC thus reduces the frequency of channel opening but not its duration or the conductance of a channel once it has opened. When the magnitude of EPP falls below a critical level, it is unable to trigger propagated muscle action potential (MAP) and

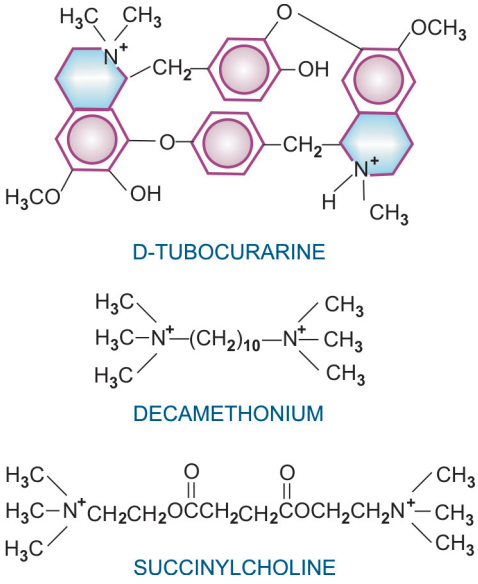


Fig. 25.1: Chemical structure of three neuromuscular blockers. Note the thick, bulky molecule of competitive blocker d-tubocurarine and slender, flexible molecules of depolarizing blockers decamethonium and succinylcholine

muscle fails to contract in response to nerve impulse. The antagonism is surmountable by increasing the concentration of ACh *in vitro* and by anticholinesterases *in vivo*. At very high concentrations, curare like drugs enter the Na^+ channels and directly block them to produce more intense noncompetitive neuromuscular block that is only partly reversed by neostigmine.

The competitive blockers also block prejunctional nicotinic receptors located on motor nerve endings. Since activation of these receptors by ACh normally facilitates mobilization of additional quanta of ACh from the axon to the motor nerve endings, their blockade contributes to depression of neuromuscular transmission. Accordingly, the competitive blockers exhibit the 'fade' phenomenon (Fig. 25.3), i.e. twitch responses during partial block are progressively depressed on repetitive stimulation.

Tetanic stimulation during partial nondepolarizing block increases the response to a subsequent single stimulation (twitch). This is called *'post-tetanic potentiation'*, and is probably due

to a transient increase in prejunctional ACh mobilization following tetanic stimulation.

Depolarizing block Decamethonium and SCh have affinity as well as submaximal intrinsic activity at the N_M cholinoceptors. They depolarize muscle end plates by opening Na^+ channels (just as ACh does) and initially produce twitching and fasciculations. Because in the focally innervated mammalian muscle, stimulation is transient; longer lasting depolarization of muscle end plate produces repetitive excitation of the fibre. In the multiplely innervated contracture muscle (rectus abdominis of frog) stimulation is prolonged resulting in sustained contraction. These drugs do not dissociate rapidly from the receptor and are not hydrolysed by AChE. They induce prolonged partial depolarization of the region around muscle end plate → Na^+ channels get inactivated (because transmembrane potential drops to about –50 mV) → ACh released from motor nerve endings is unable to generate propagated MAP → flaccid paralysis in mammals. In other words a zone of inexcitability is created around the end plate preventing activation of the muscle fibre. In birds, the area of depolarization is more extensive and spastic paralysis occurs.

Depolarizing blockers also have 2 quaternary N^+ atoms, but the molecule is long, slender and flexible—termed *Leptocurare* by Bovet. The features of classical depolarizing block differ markedly from that of nondepolarizing block (*see* Fig. 25.2 and Table 25.1).

However, in many species, e.g. dog, rabbit, rat, monkey, in slow contracting soleus muscle of cat, and under certain conditions in man the depolarizing agents injected in high doses or infused continuously produce dual mechanism neuromuscular blockade which can be divided into two phases:

Phase I block It is rapid in onset, results from persistent depolarization of muscle end plate and has features of classical depolarization blockade. This depolarization declines shortly afterwards and repolarization occurs gradually despite continued presence of the drug at the receptor, but neuromuscular transmission is not restored and phase II block supervenes.

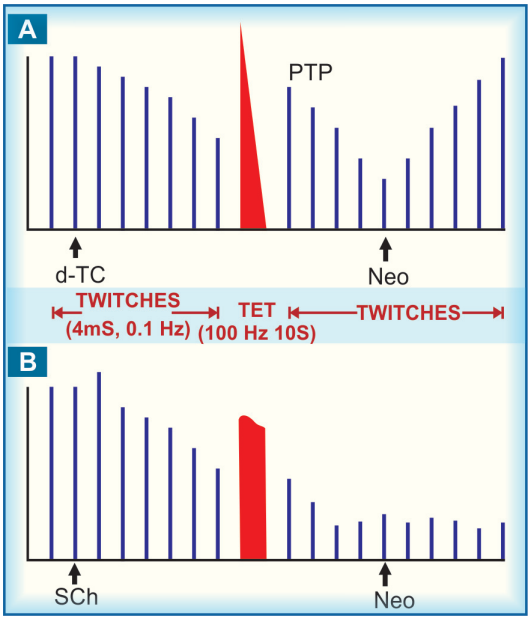


Fig. 25.2: Illustration of characteristics of competitive (A) and depolarizing (B) neuromuscular blockade in sciatic nerve-gastrocnemius muscle of cat
A. Tubocurarine (d-TC) produces progressive decrease in twitch tension; tetanic stimulation (TET) produces poorly sustained contracture, which is followed by post-tetanic potentiation (PTP); Neostigmine (Neo) restores the twitch contractions.
B. Succinylcholine (SCh) produces initial augmentation of twitches followed by progressive block; tetanus is well sustained, but there is no PTP; block is not reversed (rather worsened) by neostigmine.

Phase II block It is slow in onset and results from desensitization of the receptor to ACh. It, therefore, superficially resembles block produced by d-TC. The muscle membrane is nearly repolarized, recovery is slow, contraction is not sustained during tetanic stimulation ('fade' occurs) and the block is partially reversed by anticholinesterases.

In man and fast contracting muscle (tibialis anterior) of cat, normally only phase I block is seen. Phase II block may be seen in man when SCh is injected in high dose or infused

TABLE 25.1 Features of competitive and typical depolarizing block

		Competitive block (d-TC)	*Depolarizing (phase I) block (SCh)*
1.	Paralysis in man	Flaccid	Fasciculations → flaccid
2.	Paralysis in chick	Flaccid	Spastic
3.	Effect on isolated frog's rectus muscle	No contraction, antagonism of ACh	Contraction
4.	Species sensitivity	Rat > rabbit > cat	Cat > rabbit > rat
5.	Human neonates	More sensitive	Relatively resistant
6.	Tetanic stimulation during partial block	Poorly sustained contraction	Well sustained contraction
7.	Neostigmine	Antagonises block	No effect
8.	Post tetanic potentiation	Present	Absent
9.	Ether anaesthesia	Synergistic	No effect
10.	Order of paralysis	Fingers, eyes → limbs → neck, face → trunk → respiratory	Neck, limbs → face, jaw, eyes, pharynx → trunk → respiratory
11.	Effect of lowering temperature	Reduces block	Intensifies block
12.	Effect of cathodal current to end plate	Lessens block	Enhances block

continuously, particularly, if fluorinated anaesthetics have been used. SCh readily produces phase II block in patients with atypical or deficient pseudocholinesterase.

ACTIONS

1. Skeletal muscles Intravenous injection of nondepolarizing blockers rapidly produces muscle weakness followed by flaccid paralysis. Small fast response muscles (fingers, extraocular) are affected first; paralysis spreads to hands, feet—arm, leg, neck, face—trunk—intercostal muscles—finally diaphragm: respiration stops. The rate of attainment of peak effect and the duration for which it is maintained depends on the drug (Table 25.2), its dose, anaesthetic used, haemodynamic, renal and hepatic status of the patient and several other factors. Recovery occurs in the reverse sequence; diaphragmatic contractions resume first. In general, the more potent nondepolarizing blockers have a longer onset of action.

Depolarizing blockers typically produce fasciculations lasting a few seconds before inducing flaccid paralysis, but fasciculations are not prominent in well-anaesthetized patients. Though the sequence in which muscles are involved is somewhat different from the competitive blockers (Table 25.1), the action of SCh develops with such rapidity that this is not appreciated. Apnoea generally occurs within 45–90 sec, but lasts only 2–5 min; recovery is rapid.

Clinical monitoring of neuromuscular block

In anaesthetic practice neuromuscular block (especially during recovery) is monitored by recording contractile responses of thumb muscles to transcutaneous ulnar nerve stimulation. Since single twitch responses have to be interpreted in comparison to twitches before the blocker, and are not reliable, several other protocols are used. One such method is 'train-of-four' (TOF) protocol. Four supramaximal electrical stimuli are applied in 2S (2Hz) and contractions of thumb muscle are recorded (Fig. 25.3A). The TOF-ratio is obtained by dividing the strength of 4th contraction by that of the 1st. In the untreated subject all the 4 contractions remain equal and TOF-ratio is 1.0.

During partial competitive block (as during onset and recovery or reversal) the degree of block corresponds to the decrease in TOF-ratio, because competitive blockers exhibit 'fade' phenomenon. As the muscles recover, the TOF-ratio improves and becomes 1.0 at complete recovery.

On the other hand, classical or phase-I depolarizing block does not exhibit fade; the TOF-ratio remains 1.0, though all the 4 twitches are depressed equally depending on the degree of block. Fade is again seen when phase II or desensitization

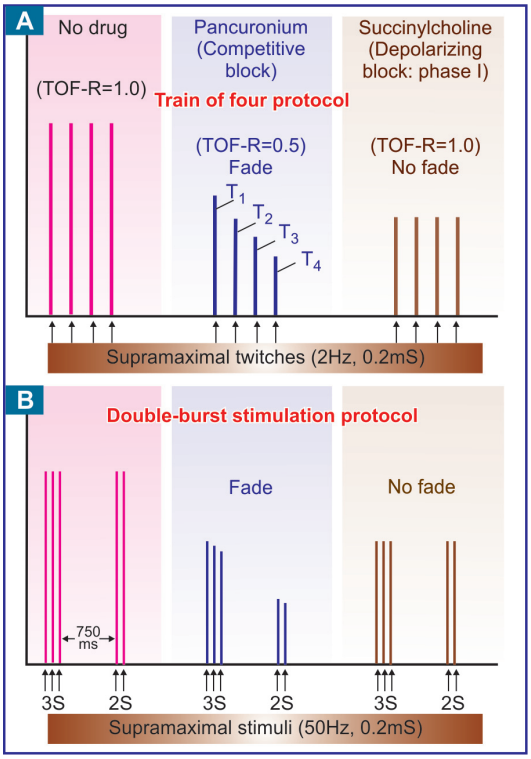


Fig. 25.3: Clinical assessment of neuromuscular block. (A) *Train-of-four (TOF) protocol:* Contractile responses of adductor pollicis muscle to transcutaneous ulnar nerve stimulation with train-of-four protocol of impulses during recovery of neuromuscular block. TOF-R—Train of four ratio (strength of 4th contraction divided by that of the 1st). (B) *Double-burst stimulation ($DBS_{3,2}$):* Evoked responses to burst of three 0.2 ms pulses at 50 Hz followed 750 ms later by a second burst of two similar pulses. Note 'fade' in the second burst after nondepolarizing block.

block occurs with prolonged use of a depolarizing agent and TOF-ratio is depressed as in the case of competitive block. However, SCh generally requires no monitoring.

Rather than measuring each contraction and calculating TOF ratio, in practice, it is easier to simply observe the disappearance (during onset) or reappearance (during recovery) of the successive twitches. Reappearance of 2nd twitch (T_2) corresponds to ~10% recovery (~90% residual block) and that of 4th twitch (T_4) to ~25% recovery.

Because fade is more prominent during sustained stimulation, an alternate method is 'tetanic stimulation' protocol, in which 0.2 ms pulses are applied at 50–100 Hz for 4–5 seconds and presence or absence of fade is noted (*see* fade in Fig. 25.2A).

Many anaesthesiologists prefer to use the less painful variant of tetanic stimulation, *viz* 'double-burst stimulation' (DBS). A burst of three 0.2 ms pulses at 50 Hz is followed after a gap of 750 ms by a second burst of 2 or 3 similar pulses (Fig. 25.3B). The strength of response during the 2nd burst relative to the first is a measure of the recovery from block.

Measurement of 'post-tetanic count (PTC)' is another clinically used method.

2. Autonomic ganglia Because the cholinergic receptors in autonomic ganglia are nicotinic (though of a different subclass N_N), competitive neuromuscular blockers produce some degree of ganglionic blockade; d-TC has the maximum propensity in this regard, while the newer drugs (vecuronium, etc.) are practically devoid of it. SCh may cause ganglionic stimulation by its agonistic action on nicotinic receptors.

3. Histamine release d-TC releases histamine from mast cells. This does not involve immune system and is due to the bulky cationic nature of the molecule. Histamine release contributes to the hypotension produced by d-TC. Flushing, bronchospasm and increased respiratory secretions are other effects. Intradermal injection of d-TC produces a wheal similar to that produced by injecting histamine. Histamine releasing potential of other neuromuscular blockers is graded in Table 25.2.

Heparin may also be simultaneously released from mast cells.

4. C.V.S.

d-Tubocurarine produces significant fall in BP. This is due to—

(a) ganglionic blockade
(b) histamine release and
(c) reduced venous return—a result of paralysis of limb and respiratory muscles.

Heart rate may increase due to vagal ganglionic blockade. Pancuronium and vecuronium also tend to cause tachycardia. All newer nondepolarizing drugs have negligible effects on BP and HR.

Cardiovascular effects of SCh are variable. Generally bradycardia occurs initially due to activation of vagal ganglia followed by tachycardia and rise in BP due to stimulation of sympathetic ganglia. BP occasionally falls on account of its muscarinic action causing

TABLE 25.2 Comparative properties of neuromuscular blocking drugs

Drug	Dose£ (mg/kg)	Onset* (min)	Duration@ (min)	Hist. release	Gang. block	Vagal block
LONG ACTING						
1. d–Tubocurarine	0.2–0.4	4–6	30–60	+++	++	±
2. Pancuronium	0.04–0.1	4–6	60–120	±	±	+
3. Doxacurium	0.03–0.08	4–8	60–120	+	–	–
4. Pipecuronium	0.05–0.08	2–4	50–100	±	–	–
INTERMEDIATE ACTING						
5. Vecuronium	0.08–0.1	2–4	30–60	±	–	±
6. Atracurium	0.3–0.6	2–4	20–40	+	–	–
7. Cisatracurium	0.15–0.2	3–6	20–40	–	–	–
8. Rocuronium	0.6–0.9	1–2	25–40	–	–	±
SHORT ACTING						
9. Mivacurium	0.15–0.2	2–4	15–30	+	–	–
10. Succinylcholine	0.5–0.8	1–1.5	5–8	++	St.	St.

£ Initial paralysing dose for opioid/nitrous oxide + oxygen anaesthesia. In patients anaesthetised with ether/halothane/isoflurane, the dose may be $^1/_3$–$^1/_2$ of the figure given.

* Time to maximal block after i.v. injection.

@ Duration of surgical grade relaxation after usual clinical doses; time to 95% recovery of muscle twitch is nearly double of the figure given (especially for long-acting drugs). Duration is dose dependent as well.

St.—Stimulation

vasodilatation. Prolonged administration of SCh has caused cardiac arrhythmias and even arrest in patients with burns, soft tissue injury and tetanus. Efflux of intracellular K^+ occurs in these conditions which is augmented by prolonged depolarization of skeletal muscles.

5. G.I.T. The ganglion blocking activity of competitive blockers may enhance postoperative paralytic ileus after abdominal operations.

6. C.N.S. All neuromuscular blockers are quaternary compounds—do not cross blood-brain barrier. Thus, on i.v. administration no central effects follow. However, d-TC applied to brain cortex or injected in the cerebral ventricles produces strychnine like effects.

PHARMACOKINETICS

All neuromuscular blockers are polar quaternary compounds—not absorbed orally, do not cross cell membranes, have low volumes of distribution and do not penetrate placental or blood-brain barrier. They are practically always given i.v., though i.m. administration is possible. Muscles with higher blood flow receive more drug and are affected earlier. Redistribution to non-muscular tissues plays a significant role in the termination of surgical grade muscle relaxation, but residual block may persist for a longer time depending on the elimination t½. The duration of action of competitive blockers is directly dependent on the elimination t½. Drugs that are primarily metabolized in the plasma/liver, e.g. vecuronium, atracurium, cisatracurium, rocuronium, and especially mivacurium have relatively shorter t½ and duration of action (20–40 min), while those largely excreted by the kidney, e.g. pancuronium, d-Tc, doxacurium and pipecuronium have longer t½ and duration of action (>60 min). With repeated administration redistribution sites are filled up and duration of action is prolonged.

The unchanged drug is excreted in urine as well as in bile.

SCh is rapidly hydrolysed by plasma pseudocholinesterase to succinylmonocholine and then succinic acid + choline (action lasts 5–8 min). Some patients have genetically determined abnormality (low affinity for SCh) or deficiency of pseudocholinesterase. In subjects who are homozygous for the abnormal enzyme (1 in > 3000 population), SCh causes prolonged phase II blockade resulting in muscle paralysis and apnoea lasting 4–6 hours, because SCh is a poor substrate for the more specific AChE found at the motor end plate. However, duration of paralysis is increased only by 2–3 times in subjects who are heterozygous for the abnormal enzyme (1 in ~ 50), or have only relative deficiency. The prolonged apnoea can be tided over only by mechanical ventilation.

NOTES ON INDIVIDUAL COMPOUNDS

1. d-Tubocurarine Because of its prominent histamine releasing, ganglion blocking and cardiovascular actions as well as long duration of paralysis needing pharmacological reversal, d-TC is not used now.

2. Succinylcholine Despite its propensity to cause muscle fasciculations and soreness, changes in BP and HR, arrhythmias, histamine release and K^+ efflux from muscles causing hyperkalaemia and its complications, SCh is the most commonly used muscle relaxant for passing tracheal tube. It induces rapid, complete and predictable paralysis with spontaneous recovery in ~5 min. Excellent intubating condition *viz.* relaxed jaw, vocal cords apart and immobile with no diaphragmatic movements, is obtained within 1–1.5 min. Occasionally SCh is used by continuous i.v. infusion for producing controlled muscle relaxation of longer duration. It should be avoided in younger children unless absolutely necessary, because risk of hyperkalaemia and cardiac arrhythmia is higher. Risk of regurgitation and aspiration of gastric contents is increased by SCh in GERD patients and in the obese, especially if stomach is full.

MIDARINE, SCOLINE, MYORELEX, ENTUBATE 50 mg/ml inj, 2 ml amp.

3. Pancuronium A synthetic steroidal compound, ~5 times more potent and longer acting than d-TC; provides good cardiovascular stability (little ganglionic blockade), seldom induces flushing, bronchospasm or cardiac arrhythmias because of lower histamine releasing potential. Rapid i.v. injection may cause rise in BP and tachycardia due to vagal blockade and NA release. It is primarily eliminated by renal excretion. Because of longer duration of action, needing reversal, its use is now restricted to prolonged operations, especially neurosurgery.

PAVULON, PANURON, NEOCURON 2 mg/ml in 2 ml amp.

4. Doxacurium A bisquaternary muscle relaxant having the least rapid onset and the longest action: suitable for long duration surgeries. It is primarily eliminated by kidney, though hepatic metabolism also occurs. Cardiovascular changes are less marked.

5. Pipecuronium Another muscle relaxant with a slow onset and long duration of action; steroidal in nature; recommended for prolonged surgeries. It exerts little cardiovascular action, though transient hypotension and bradycardia can occur. Elimination occurs through both kidney and liver.

ARDUAN 4 mg/2 ml inj.

6. Vecuronium A close congener of pancuronium with a shorter duration of action due to rapid distribution and metabolism. It is excreted mainly in bile, recovery is generally spontaneous, but may need neostigmine reversal. Cardiovascular stability is still better due to lack of histamine releasing and ganglionic action; tachycardia sometimes occurs. Currently, it is the most commonly used muscle relaxant for routine surgery and in intensive care units.

NORCURON 4 mg amp, dissolve in 1 ml solvent supplied.
NEOVEC 4 mg amp, 10 mg vial.

7. Atracurium A bisquaternary competitive blocker, 4 times less potent than pancuronium and shorter acting: reversal is mostly not required. The unique feature of atracurium is inactivation in plasma by spontaneous non-enzymatic degradation (Hofmann elimination) in addition to that by cholinesterases. Consequently its duration of action is not altered in patients

with hepatic/renal insufficiency or hypodynamic circulation. It is the preferred muscle relaxant for liver/kidney disease patients as well as for neonates and the elderly. Hypotension may occur due to dose dependent histamine release.

TRACRIUM 10 mg/ml inj in 2 ml vial.

8. Cisatracurium This *R-Cis, R-Cis* enantiomer of atracurium is nearly 4 times more potent, slower in onset, but similar in duration of action. Like atracurium it undergoes Hofmann elimination, but in contrast it is not hydrolysed by plasma cholinesterase. Most importantly, it does not provoke histamine release.

Side effects are fewer.

9. Rocuronium A newer nondepolarizing blocker with a rapid onset and intermediate duration of action which can be used as alternative to SCh for tracheal intubation without the disadvantages of depolarizing block and cardiovascular changes. The same drug also serves as maintenance muscle relaxant, seldom needing reversal. The onset of action is dose-dependent; intubating conditions are attained in 90 sec with 0.6 mg/kg, but within 60 sec at 1.0 mg/kg. Within limits, the duration of paralysis is also dose-dependent. This neuromuscular blocker is gaining popularity for its versatility and more precisely timed onset and duration of action. Infused i.v. (0.3–0.6 mg/kg/hour), it is also being used to facilitate mechanical ventilation in intensive care units. Though little metabolized, it is eliminated mainly in bile. Mild vagolytic action increases HR somewhat.

ROCUNIUM, CUROMID 50 mg/5 ml, 100 mg/10 ml vials.

10. Mivacurium It is the shortest acting competitive blocker; does not need reversal. Dose and speed of injection related transient cutaneous flushing can occur due to histamine release. Fall in BP is possible, but change in HR is minimal. It is metabolized rapidly by plasma cholinesterases. Prolonged paralysis can occur in pseudocholinesterase deficiency, but this can be reversed by neostigmine (unlike paralysis due to SCh).

INTERACTIONS

1. *Thiopentone sod* and SCh solutions should not be mixed in the same syringe—react chemically.

2. *General anaesthetics* potentiate competitive blockers; ether in particular, followed by fluorinated hydrocarbons. Isofluorane, desflurane and sevoflurane potentiate to a greater extent than halothane. Nitrous oxide potentiates the least. Ketamine also intensifies nondepolarizing block. Fluorinated anaesthetics predispose to phase II blockade by SCh. Malignant hyperthermia produced by halothane and isoflurane in rare (genetically predisposed) individuals is more common in patients receiving SCh as well.

3. *Anticholinesterases* reverse the action of competitive blockers. Neostigmine 0.5–2 mg (30–50 µg/kg) i.v. is almost routinely used after pancuronium and other long/intermediate acting blockers to hasten recovery at the end of operation. Though neostigmine also reverses ganglionic blockade to some extent, hypotension and bronchospasm can occur due to muscarinic action of neostigmine; this can be prevented by prior atropinization (atropine or glycopyrrolate 5–10 µg/kg i.v.). Pretreatment with H_1 antihistamines reduces hypotension due to d-TC and others which release histamine.

4. *Antibiotics* Aminoglycoside antibiotics reduce ACh release from prejunctional nerve endings by competing with Ca^{2+}. They interfere with mobilization of ACh containing vesicles from a central location to near the terminal membrane, and have a weak stabilizing action on the postjunctional membrane. In clinically used doses, they do not by themselves produce muscle relaxation, but potentiate competitive blockers. The dose of competitive blocker should be reduced in patients receiving high doses of these antibiotics. Application of streptomycin powder locally at the end of bowel surgery has caused prolonged apnoea if a competitive blocker had been used during the operation. Tetracyclines (by chelating Ca^{2+}), polypeptide antibiotics, clindamycin and lincomycin also synergise with competitive blockers.

5. *Calcium channel blockers* Verapamil and others potentiate both competitive and depolarizing neuromuscular blockers.

6. *Diuretics* may produce hypokalemia which enhances competitive block.

7. *Diazepam*, *propranolol* and *quinidine* intensify competitive block, while high dose of corticosteroids reduces it.

Sugamadex This is a novel reversing agent developed for terminating the action of nondepolarizing muscle relaxants rocuronium and vecuronium. Sugamadex is a modified γ-cyclodextrin with high affinity for rocuronium and vecuronium; encapsulates one molecule of the blocker within its molecule forming an inactive chelate which is excreted in urine with a t½ of ~ 2 hours. As the plasma concentration of free rocuronium falls, it rapidly dissociates from the Nm receptor and neuromuscular transmission is restored. Thus, the mechanism of reversal by sugamadex is entirely different from that of the currently used reversing agents neostigmine and edrophonium. Sugamadex 2–4 mg/kg i.v. reverses rocuronium block within 3 min. in majority of patients. Its side effects are mild precordial pain, nausea, alteration of taste and rarely allergy. No cardiovascular effects have been noted.

TOXICITY

1. Respiratory paralysis and prolonged apnoea is the most important problem.
2. Flushing is common with d-TC (due to histamine release), can occasionally occur with atracurium and mivacurium, rare with others.
3. Fall in BP and cardiovascular collapse can occur, especially in hypovolemic patients. This is less likely with the newer drugs. Muscle relaxants should be used with great caution in patients with severe hepatic and renal disease.
4. Cardiac arrhythmias and even arrest have occurred, especially with SCh, particularly in digitalized patients. SCh releases K^+ from muscles. Intubating dose generally raises serum K^+ by 0.5 mEq/L, but dangerous hyperkalemia can occur, especially in patients with extensive burns and soft tissue injuries.
5. Precipitation of asthma by histamine releasing neuromuscular blockers.
6. Postoperative muscle soreness and myalgia may be complained after SCh.
7. Malignant hyperthermia can be triggered by SCh in patients anaesthetized with fluorinated anaesthetics.

USES

1. The most important use of neuromuscular blockers is as adjuvants to general anaesthesia; adequate muscle relaxation can be achieved at lighter planes. Many surgical procedures are performed more safely and rapidly by employing muscle relaxants. Muscle relaxants also reduce reflex muscle contraction in the region undergoing surgery, and assist maintenance of controlled ventilation during anaesthesia. They are particularly helpful in abdominal and thoracic surgery, intubation and endoscopies, orthopedic manipulations, etc.

Choice of the neuromuscular blocker depends on the nature and duration of the procedure, pharmacokinetics of the blocker and cardiovascular stability that it provides. Vecuronium and rocuronium are the most frequently selected nondepolarizing blockers.

SCh is employed for brief procedures, e.g. endotracheal intubation, laryngoscopy, bronchoscopy, esophagoscopy, reduction of fractures, dislocations, and to treat laryngospasm. For ocular surgery competitive blockers are preferred, because they paralyse extraocular muscles at doses which have little effect on larger muscles. Other factors which should be considered in selecting the relaxant are—onset of action, duration of blockade required, cardiovascular effects of the drug as well as patient's hepatic, renal and haemodynamic status.

Advantages of newer neuromuscular blockers over the older ones

- No or minimal ganglionic, cardiac or vascular effects.
- No or minimal histamine release.
- Many are short acting: easy reversal.
- Some are rapid acting: provide alternative to SCh without the attendant complications.

2. Assisted ventilation: Critically ill patients in intensive care units often need ventilatory support. This can be facilitated by continuous infusion of subanaesthetic doses of a competitive neuromuscular blocker which reduces the chest wall resistance to inflation. Vecuronium is most

commonly used, but after prolonged infusion it can cause blockade lasting 1–3 days due to accumulation of an active metabolite and/or development of neuropathy.

3. Convulsions and trauma from electroconvulsive therapy can be avoided by the use of muscle relaxants without decreasing the therapeutic benefit. SCh is most commonly used for this purpose. The short acting competitive blocker mivacurium is an alternative.

4. Severe cases of tetanus and status epilepticus, who are not controlled by diazepam or other drugs, may be paralysed by a neuromuscular blocker (repeated doses of a competitive blocker) and maintained on intermittent positive pressure respiration till the disease subsides.

DIRECTLY ACTING MUSCLE RELAXANTS

Dantrolene This muscle relaxant is chemically and pharmacologically entirely different from neuromuscular blockers; effect superficially resembles that of centrally acting muscle relaxants. Neuromuscular transmission or MAP are not affected, but muscle contraction is uncoupled from depolarization of the membrane. Dantrolene acts on the RyR1 (Ryanodine Receptor) calcium channels in the sarcoplasmic reticulum of skeletal muscles and prevents Ca^{2+} induced Ca^{2+} release through these channels. Intracellular release of Ca^{2+} needed for excitation-contraction coupling is interfered with. Fast contracting 'twitch' muscles are affected more than slow contracting 'antigravity' muscles. Since Ca^{2+} channels in the sarcoplasmic reticulum of cardiac and smooth muscles are of a different subtype (RyR2), these muscles are affected little by dantrolene.

Dantrolene is slowly but adequately absorbed from the g.i.t. It penetrates brain and produces some sedation, but has no selective effect on polysynaptic reflexes responsible for spasticity. It is metabolized in liver and excreted by kidney with a t½ of 8–12 hours.

Used orally dantrolene (25–100 mg QID) reduces spasticity in upper motor neurone disorders, hemiplegia, paraplegia, cerebral palsy and multiple sclerosis. However, it also reduces voluntary power; the resulting weakness considerably neutralizes the benefit and limits use to bedridden patients.

Used i.v. (1 mg/kg repeated as required) it is the drug of choice for malignant hyperthermia which is due to persistent release of Ca^{2+} from sarcoplasmic reticulum (induced by fluorinated anaesthetics and SCh in genetically susceptible individuals with abnormal RyR1, *see* p. 379). Reversal has also been obtained in neuroleptic malignant syndrome, though this reaction has a different pathogenesis.

Adverse effects Muscular weakness is the dose limiting side effect. Sedation, malaise, light headedness and other central effects occur, but are less pronounced than with centrally acting muscle relaxants. Troublesome diarrhoea is another problem. Long term use causes dose dependent serious liver toxicity in 0.1–0.5% patients. This has restricted its use in chronic disorders.

Quinine (*see* Ch. 59) It increases refractory period and decreases excitability of motor end plates. Thus, responses to repetitive nerve stimulation are reduced. It decreases muscle tone in myotonia congenita. Taken at bed time (200–300 mg) it may abolish nocturnal leg cramps in some patients.

CENTRALLY ACTING MUSCLE RELAXANTS

These are drugs which reduce skeletal muscle tone by a selective action in the cerebrospinal axis, without altering consciousness. They selectively depress spinal and supraspinal polysynaptic reflexes involved in the regulation of muscle tone without significantly affecting monosynaptically mediated stretch reflex. Polysynaptic pathways in the ascending reticular formation which are involved in the maintenance of wakefullness are also depressed, though to a lesser extent. All centrally acting muscle relaxants do have some sedative property. They have no effect

TABLE 25.3 **Comparative features of centrally and peripherally acting muscle relaxants**

Centrally acting	*Peripherally acting*
1. Decrease muscle tone without reducing voluntary power	Cause muscle paralysis, voluntary movements lost
2. Selectively inhibit polysynaptic reflexes in CNS	Block neuromuscular transmission
3. Cause some CNS depression	No effect on CNS
4. Given orally, sometimes parenterally	Practically always given i.v.
5. Used in chronic spastic conditions, acute muscle spasms, tetanus	Used for short-term purposes (surgical operations)

on neuromuscular transmission and on muscle fibres, but reduce decerebrate rigidity, upper motor neurone spasticity and hyperreflexia.

The prominent differences between peripherally and centrally acting muscle relaxants are listed in Table 25.3.

CLASSIFICATION

(i) *Mephenesin congeners* — Mephenesin, Carisoprodol, Chlorzoxazone, Chlormezanone, Methocarbamol.
(ii) *Benzodiazepines* — Diazepam and others.
(iii) *GABA mimetic* — Baclofen, Thiocolchicoside
(iv) *Central α_2 agonist* — Tizanidine

1. Mephenesin It was the first drug found to cause muscle relaxation in animals without producing unconsciousness and was called *internuncial neurone blocking agent* because its primary site of action is the spinal internuncial neurone which modulates reflexes maintaining muscle tone. It is not used clinically because orally it causes marked gastric irritation, and injected i.v., it causes thrombophlebitis, haemolysis and fall in BP. It has been included in counterirritant ointments *(MEDICREME, RELAXYL)* where its irritant rather than muscle relaxant property could be affording relief.

2. Carisoprodol It has a favourable muscle relaxant: sedative activity ratio with weak analgesic, antipyretic and anticholinergic properties. It is used in musculoskeletal disorders associated with muscle spasm.

CARISOMA 350 mg tab; one tab. TDS-QID, SOMAFLAM 175 mg + ibuprofen 400 mg tab.

3. Chlorzoxazone It is pharmacologically similar to mephenesin, but has a longer duration of action and is better tolerated orally.

FLEXON-MR 250 mg + ibuprofen 400 mg + paracetamol 325 mg tab; ULTRAZOX 250 mg + diclofenac 50 mg + paracetamol 325 mg tab; MOBIZOX 500 mg + diclofenac 50 mg + paracetamol 500 mg tab; PARAFON: 250 mg + paracetamol 300 mg tab, 1–2 tab TDS.

4. Chlormezanone It has antianxiety and hypnotic actions as well, and has been used for tension states associated with increased muscle tone.

DOLOBAK 100 mg + paracetamol 450 mg tab, 1–2 tab TDS.

5. Methocarbamol It is less sedative and longer acting than mephenesin. Orally it has been used in reflex muscle spasms and chronic neurological diseases. It can be injected i.v. without producing thrombophlebitis and haemolysis—used for orthopedic procedures and tetanus.

ROBINAX 0.5 g tab, 1 TDS: 100 mg/ml inj. for i.v. or i.m. use. ROBIFLAM 750 mg + ibuprofen 200 mg tab; NEUROMOL-MR 400 mg + paracetamol 500 mg tab.

Clinical efficacy of none of the above drugs as muscle relaxant is well established. Gastric irritation and sedation are the most important side effects.

6. Diazepam (*see* Ch. 29) It is the prototype of benzodiazepines (BZDs) which act in the brain on specific receptors enhancing GABAergic transmission. Muscle tone is reduced by supraspinal rather than spinal action; muscle relaxant: sedative activity ratio is low. No gastric irritation occurs and it is very well tolerated, though

sedation limits the dose which can be used for reducing muscle tone. It is particularly valuable in spinal injuries and tetanus. Combined with analgesics, it is popular for rheumatic disorders associated with muscle spasm.

Dose: 5 mg TDS orally, 10–40 mg i.v. (in tetanus).

7. Baclofen This analogue of the inhibitory transmitter GABA acts as a selective $GABA_B$ receptor agonist. The GABA receptors have been divided into:

$GABA_A$ receptor Intrinsic ion channel receptor which increases Cl^- conductance; blocked by bicuculline; facilitated by BZDs.

$GABA_B$ receptor G-protein coupled receptor; hyperpolarizes neurones by increasing K^+ conductance and altering Ca^{2+} flux; bicuculline insensitive, but blocked by saclofen.

Baclofen does not affect Cl^- conductance and its actions are not antagonized by bicuculline.

The primary site of action of baclofen is considered to be in the spinal cord where it depresses both polysynaptic and monosynaptic reflexes. As such, it does produce muscle weakness, but is less sedative than diazepam. Spasticity in many neurological disorders like multiple sclerosis, amyotropic lateral sclerosis (ALS), spinal injuries and flexor spasms is reduced, and baclofen is the preferred drug for symptomatic relief. However, it is relatively ineffective in stroke, cerebral palsy, rheumatic and traumatic muscle spasms and parkinsonism.

Baclofen is well absorbed orally and is primarily excreted unchanged in urine with a t½ of 3–4 hours.

Side effects are drowsiness, mental confusion, weakness and ataxia; serum transaminases may rise. Sudden withdrawal after chronic use may cause hallucinations, tachycardia and seizures.

Dose: 10 mg BD to 25 mg TDS.

LIORESAL, LIOFEN 10 mg, 25 mg tab.

8. Thiocolchicoside Chemically related to colchicine, this muscle relaxant is believed to act as a GABA mimetic and glycinergic drug. Combined with NSAIDs, it is being used for painful muscle spasms, such as torticolis, sprains, backache, etc. Side effects are gastric upset and photosensitivity reactions

Dose: 4 mg TDS-QID;

NUCOXIA-MR: Thiocolchicoside 4 mg + etoricoxib 60 mg tabs.

9. Tizanidine This clonidine congener is a central α_2 adrenergic agonist—inhibits release of excitatory amino acids in the spinal interneurones. It may facilitate the inhibitory transmitter glycine as well. Polysynaptic reflexes are inhibited resulting in decreased muscle tone and frequency of muscle spasms without reducing muscle strength. Efficacy similar to baclofen or diazepam has been noted in multiple sclerosis, spinal injury and stroke, with fewer side effects.

Tizanidine is absorbed orally, undergoes first pass metabolism and is excreted by the kidney; t½ 2–3 hours. It is indicated in spasticity due to neurological disorders and in painful muscle spasms of spinal origin. Side effects are dry-mouth, drowsiness, night-time insomnia and hallucinations. Dose-dependent elevation of liver enzymes occurs. Though no consistent effect on BP has been observed, it should be avoided in patients receiving antihypertensives, especially clonidine.

Dose: 2 mg TDS; max 24 mg/day.

SIRDALUD 2, 4, 6 mg tab, TIZAN 2, 4 mg tab; BRUFEN-MR, TIZAFEN 2 mg + ibuprofen 400 mg tab; TIZANAC 2 mg + diclofenac 50 mg tab, PROXIVON-MR 2 mg + nimesulide 100 mg cap.

Uses of centrally acting muscle relaxants

1. *Acute muscle spasms* Overstretching of a muscle, sprain, tearing of ligaments and tendons, dislocation, fibrositis, bursitis, rheumatic disorders, etc. cause painful spasm of muscles. The mephenesin-like and BZD muscle relaxants, combined with analgesics, are commonly used, but efficacy is not impressive.

2. *Torticollis, lumbago, backache, neuralgias* These are other conditions in which painful spasm of certain muscles is a prominent feature; respond in the same way as acute muscle spasms.

3. *Anxiety and tension* Increased tone of muscles often attends these states. Diazepam group

of drugs and chlormezanone benefit by their antianxiety as well as muscle relaxant actions.

4. *Spastic neurological diseases* Impairment of descending pathways in the cerebrospinal axis and withdrawal of inhibitory influence over the stretch reflex causes chronic increase in muscle tone or spasticity. Hemiplegia, paraplegia, spinal injuries, multiple sclerosis, ALS and cerebral palsy fall in this category. These conditions are benefited by baclofen, diazepam, tizanidine and dantrolene but not by mephenesin group of drugs. However, therapy of these disorders is far from satisfactory.

5. *Tetanus* Most commonly diazepam is infused i.v. and the dose is titrated by the response. Methocarbamol is an alternative.

6. *Electroconvulsive therapy* Diazepam decreases the intensity of convulsions resulting from ECT, without diminishing its therapeutic effect. Often SCh is used in addition for total suppression of the muscular component of ECT.

7. *Orthopedic manipulations* These procedures may be performed under the influence of diazepam or methocarbamol given i.v.

☞ PROBLEM DIRECTED STUDY

25.1 A 30-year lady brought to the hospital emergency with 40% burn injury has to be operated under general anaesthesia.

(a) Which muscle relaxant should be preferred for tracheal intubation and a brief surgical procedure in this patient? Give reasons.

(see Appendix-1 for solution)