Chapter 24 Hormones and 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. About 98% of this is stored in bones, the rest being distributed in plasma and all tissues and cells. Calcium serves important physiological roles in several cellular functions.

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, *viz.* glucocorticoids, sex steroids, thyroid hormone, growth hormone affect calcium homeostasis, and can be considered its secondary regulators. Many other signal molecules and drugs also influence calcium handling (*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

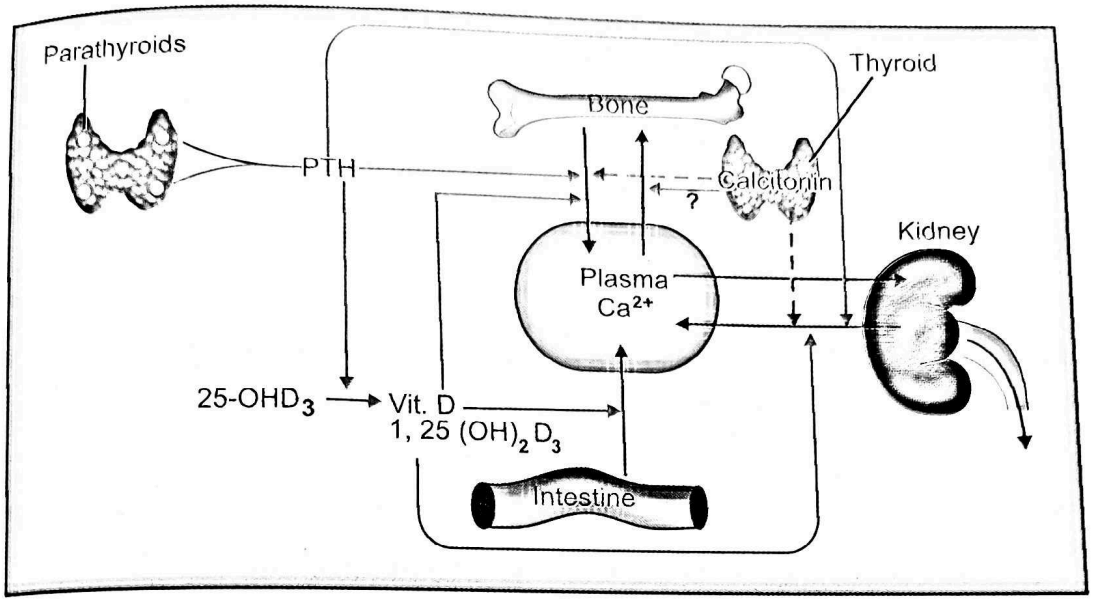


Fig. 24.1: Regulation of plasma level of calcium
→ stimulation, - - - - - → Inhibition; Bold arrow indicates—major action.
PTH—Parathormone; $25\text{-}OHD_3$—Calcifediol; $1,25\ (OH)_2D_3$—Calcitriol.

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 life-time 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.

Absorption and excretion Calcium is absorbed by facilitated diffusion from the entire small intestine. In addition, a carrier-mediated active transport under the influence of vit D occurs in the duodenum. Calcium is secreted as well in the ileum, limiting net absorption. 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 its 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 lower, but 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 mildly irritating to 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 to tissues; therefore not given orally. However, very dilute solution can be infused i.v.

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 D_3 250 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 D_3 400 IU tab, also syrup: Cal. phos 240 mg per 5 ml containing Vit D_3 200 IU and B_{12}.

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 D_3 200 IU tab.; also syrup cal. carb. (150 mg cal) with magnesium, zinc and vit D_3 200 IU per 5 ml syrup.

Uses

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 in 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 the 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 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. 47).

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 fall in plasma calcium levels; parathormone (PTH) was isolated in 1925.

Parathyroid hormone (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 PTH 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 triggered 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. In the kidney, PTH also promotes 1α-hydroxylation of 25-OHD_2 to generate calcitriol, the active form of vit D.

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 the 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.

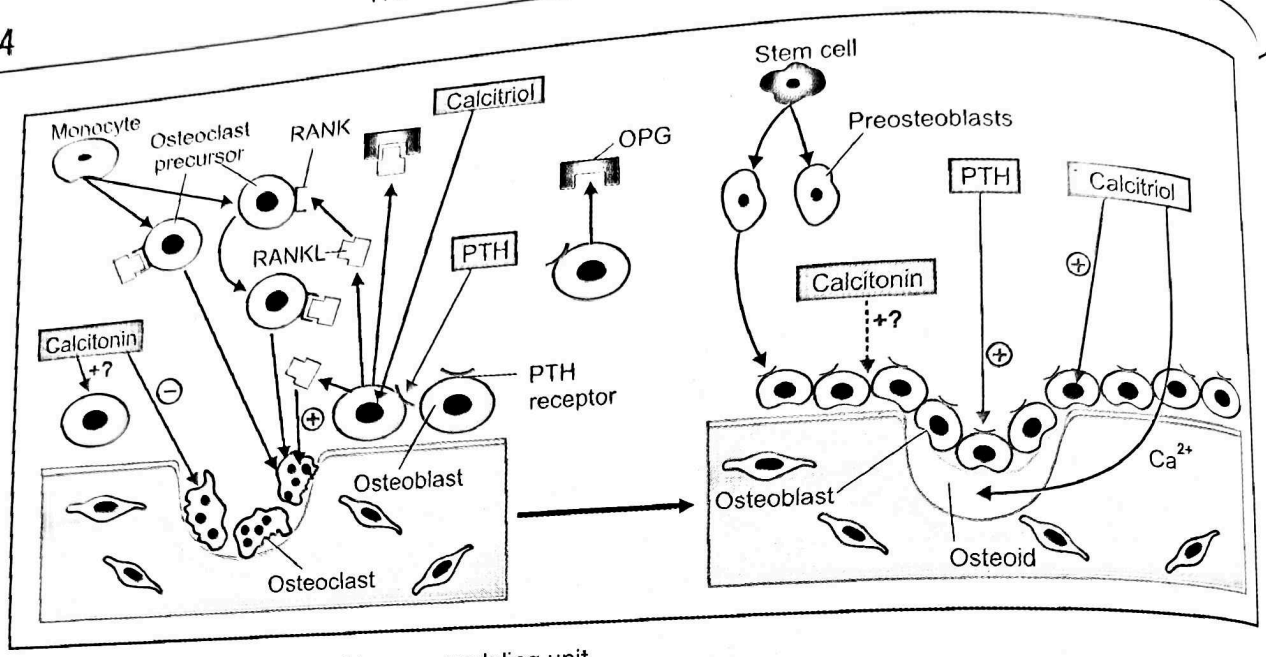


Fig. 24.2: Hormonal regulation of bone remodeling unit
The monocyte osteoclast precursor cells in the marrow near the bony surface are activated to proliferate and fuse to form multinucleated osteoclasts. The osteoclast-precursors express a 'receptor for activation of nuclear factor-κ B' (RANK) on their 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.

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.

PTH is not used to treat hypoparathyroidism because plasma calcium can be elevated and kept in the normal range more conveniently by vit D therapy. PTH has to be given parenterally, while vit D can be given orally. Vit D is inexpensive. However, recombinant human PTH (1–84 amino acid) has been produced and is being clinically evaluated for use in hypoparathyroidism.

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 is an orally active calcimimetic fluorinated compound which allosterically activates the calcium sensing receptor (CaSR) on parathyroid cells and in other body tissues. The primary action is to inhibit PTH secretion and thus decrease plasma levels of PTH, Ca^{2+} and phosphate. The biological t½ of cinacalcet is 30–40 hours. It is indicated in secondary hyperparathyroidism due to renal

disease and in patients undergoing long-term dialysis. Cinacalcet can also be used to lower plasma Ca^{2+} in inoperable cases of parathyroid cancer. Hypocalcaemia is a risk, and dose has to be adjusted carefully.

Dose: 30 mg BD with meals, increase to 60 mg BD or 90 mg BD, if needed.

SETZ 30, 60, 90 mg tab; PTH-30, SENACEPT 30 mg tab.

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 the 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 new 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. When given only once daily, action produced is intermittent, 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 with teriparatide beyond 2 years is not recommended, but BPNs may be continued thereafter. Side effects include dizziness, headache and leg cramps. Pagets disease and hypercalcaemia are the contraindications.

TEREOS 750 µg/3 ml vial for inj.

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.

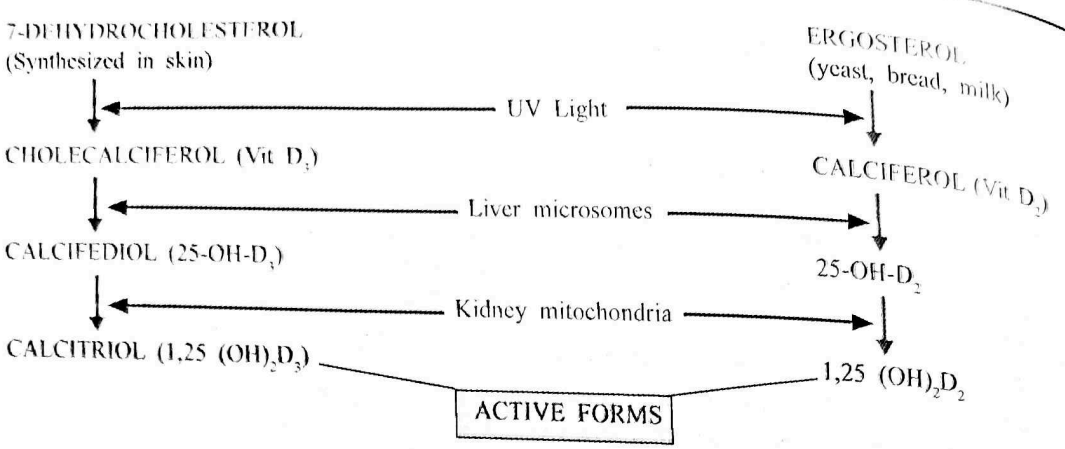
1 IU = 4 µg of the standard preparation.

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* A nasal spray formulation delivering 200 IU per actuation has been employed in osteoporosis.

MIACALCIN NASAL SPRAY, OSTOSPRAY CALCINASE 2200 IU/ml metered dose nasal spray, 200 IU per actuation. 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. However, British guidelines no longer recommend use of calcitonin for postmenopausal osteoporosis, because of risk of malignancy associated with its long term use outweighs the benefit.

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 deficiency, 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) and translocates to the nucleus where it increases synthesis of specific mRNA that in turn regulates 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) by affecting calcium flux across intestinal mucosal cell. This 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, as well as by inducing proteins like osteocalcin. The 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* Since VDR is expressed in many tissues, actions of calcitriol on immunological cells, lymphokine production, proliferation and differentiation of epidermal cells and certain malignant cells, neuronal and skeletal muscle function have also been demonstrated.

Vit D deficiency Plasma calcium and phosphate tend to fall in vit D deficiency due to inadequate intestinal absorption. As a consequence PTH is secreted and calcium is mobilized from bone in order to restore plasma Ca^{2+}. The bone fails to mineralize normally in the newly laid areas, becomes soft producing 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, vit D is bound to vit D binding protein (DBP), which is 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 of vit D 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 60,000 IU sachet/soft gel caps/chewable tabs, 1000 IU/5 ml syr, 800 IU/ml drops. CALCIBEST SACHET

60,000 IU in 1 g granules, to be suspended in milk/water and taken at 3–4 weeks intervals, and then every 2–6 months. LUMINA 60,000 IU caps.

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, which 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. 362 and in Table 69.2.

Use

1. *Prophylaxis* (400 IU/day) *and treatment* (3000–4000 IU/day) *of nutritional vit D deficiency* Prophylactic dose or therapeutic dose of vit D is given to prevent or 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. Prophylaxis (oral or parenteral as appropriate) 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 (which takes place in kidney) 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. 362). 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 or 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. 66). Systemically it has been tried in skin cancer and immunological disorders.

Interactions

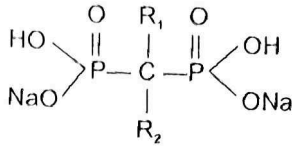
1. Cholestyramine and habitual use of liquid paraffine can reduce vit D absorption.
2. Phenytoin and phenobarbitone reduce the responsiveness of target tissues to calcitriol; their prolonged use (for epilepsy) can cause rickets/osteomalacia. It was believed earlier that these drugs enhance degradation 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

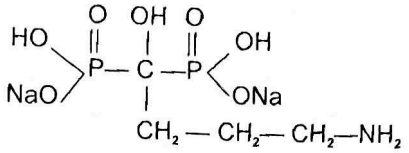
Bisphosphonates (BPNs) are analogues of pyrophosphate: carbon atom replacing oxygen in the P-O-P skeleton. They inhibit bone resorption and have attracted considerable attention because of their ability to prevent osteoporosis in addition to their usefulness in metabolic bone diseases and hypercalcaemia. They are the most effective antiresorptive drugs. Chronologically and according to their 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.

Biphosphonate	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



Alendronate

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 the second and third generation potent amino-BPNs 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 antitumour activity on bony metastasis.

Pharmacokinetics All oral BPNs are poorly absorbed and produce gastric irritation, esophagitis as the major side effect. Alendronate, ibandronate and risedronate are administered orally. Oral BPNs are contraindicated in gastroesophageal reflux, peptic ulcer and renal impairment. The alternate route for BPNs is i.v. infusion, by which large amount of BPN can be made to enter the body. This also permits frequency of dosing to be reduced to as less as once a year, because about 50% of the absorbed/injected drug is sequestrated in the bone. The remaining 50% is excreted unchanged in the urine. Pamidronate and zoledronate are available for i.v. infusion.

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

1. *Osteoporosis* The second and third generation BPNs (e.g. alendronate, ibandronate, risedronate) are effective in preventing and treating postmenopausal 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%. However, BPNs do not directly stimulate bone formation.

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, ibandronate 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 dehydration and altered consciousness. Rapid rehydration with i.v. saline infusion is the first step, which itself lowers serum Ca^{2+} to some extent. 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. Potent BPNs, especially zoledronate, have shown independent antitumour property. They have shown adjuvant value as add-on drugs in reducing breast carcinoma recurrences as well as in delaying skeletal events in women with bony metastasis.

Oral administration of BPNs All oral BPNs are to be taken on empty stomach in the morning with a full glass of water and the patient is instructed not to lie down or take food for at least 30 min. The tab/cap should not be chewed. These measures are needed to prevent contact of the drug with esophageal mucosa which results in esophagitis, erosions and ulcers. Calcium, iron, antacids, mineral water, tea, coffee, fruit juice interfere with BPN absorption, because metal salts and other

food constituents form nonabsorbable complex with BPNs. NSAIDs accentuate gastric irritation caused by BPNs.

Etidronate This is the first BPN to be used clinically. It has been employed in hypercalcaemia, Paget's disease and heterotopic ossification (deposition of bone in skeletal muscles and other soft tissues). However, it also interferes with bone mineralization: continuous therapy produces osteomalacia. Therefore, it has been largely replaced by second or third generation BPNs.

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 in men, as well as for Paget's disease. Adverse effects are esophagitis, 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 equally 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. Dose reduction is needed in patients with renal impairment. The terminal elimination t½ of alendronate has been measured as 10.5 years.

Ibandronate This is another amino-BPN, similar in properties to alendronate. Though its efficacy has not been directly compared with other BPNs in clinical trials, it has been reported to reduce the risk of vertebral fractures, but not nonvertebral fractures among osteoporotic patients. It has also been used in Paget's disease and by i.v. infusion (2–4 mg over 1–2 hours) for hypercalcaemia of malignancy.

Dose: 2.5 mg daily or 150 mg once a month

BONIVA, BONRONIC 150 mg tab.

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: 5 mg daily or 35 mg/week or 150 mg once a month oral in the morning with a full glass of water.

RISOFOS 5, 35, 75, 150 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 antitumour 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 and 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 for a maximum of 5 years 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 osteoporosis

1. Denosumab: It is a fully human monoclonal antibody against RANKL. By binding to and neutralizing RANKL, denosumab prevents RANK activation thereby inhibiting proliferation and differentiation of osteoclast precursors as well as

osteoclast function. As a result, bone resorption is inhibited to an extent equal to or greater than potent BPNs. It is now being used as a treatment option for osteoporosis in both women and men, as well as to limit bony metastasis in breast and prostate cancers. The bone loss caused by gonadal suppressant therapy of these tumours is also counteracted.

In osteoporotic patients with high fracture risk, denosumab has been found to lower vertebral as well as hip fracture risk by 40–68%. It can be given to patients with severe renal disease, in whom BPNs are contraindicated. Adverse effects of denosumab are flu-like symptoms, initial fall in serum Ca^{2+} level, dermatitis, susceptibility to infections (because RANKL is a signal molecule for many immune cells as well), rarely osteonecrosis of the jaw.
Dose: 60 mg s.c. once every 6 months (max. 3–5 years).

2. Strontium ranelate: This organic compound of strontium inhibits bone resorption by preventing osteoclast differentiation and promoting their apoptosis. In addition, it stimulates bone formation. In clinical trials it has been found to increase bone mineral density and to decrease the risk of vertebral as well as hip fracture. However, it can increase the risk of serious cardiovascular disease like MI, stroke and thromboembolism. Therefore, it is indicated only as a reserve drug for severe osteoporosis in elderly women and in men at high risk of fracture in whom BPNs and other drugs are contraindicated or not tolerated. Other adverse effects are headache, g.i. upset, rashes and serious skin reactions.
Dose: 2 g/day; avoid food for 2 hours before and after the dose.

STRONAT 2 g oral granules sachet.

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 malignancy associated 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 other glucocorticoids) enhance calcium excretion, decrease calcium absorption and lower plasma Ca^{2+} level, but act slowly. They have adjuvant role in hypercalcaemia due to lymphoma, myeloma, leukaemia, carcinoma breast, etc. Administered over several days, glucocorticoids play more important role in normalizing plasma Ca^{2+} level in hypercalcaemia due to hypervitaminosis D and sarcoidosis.