Lecture 4

drugs used in calcium & vitamin D disorders

Objectives:

★ **Recognize the common drugs used in calcium & vitamin D disorders**

★ **Classify them according to sources & pharmacological effects**

★ **Detail the pharmacology of each drug regarding; mechanism, clinical utility in affecting calcium & vitamin D**

- Additional Notes
- Important
- Explanation –Extra-

★ before starting, please check our endocrine block correction

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com

calcium metabolism

- Calcium plays an essential role in many cellular processes, including muscle contraction, hormone secretion, cell proliferation, and gene expression.
- Calcium balance is a dynamic process that reflects a balance between calcium absorption by the **intestinal tract,** calcium excretion by the **kidney**, and release and uptake of calcium by **bone** during bone formation and resorption.

- **three principal hormones and three principal tissues regulate Ca homeostasis:**

hormones

- ★ **Parathyroid hormone (PTH)**
- ★ **Vitamin D**
- ★ **Calcitonin**

tissues

- ★ **bone**
- ★ **kidney**
- ★ **intestine**

Bone

- The dominant site of calcium storage in the body is bone, which contains nearly 99.9% of body calcium.
- Most body calcium is stored in bone (~1000 g), which is a very dynamic site as bone is remodeled continuously by resorption of old bone by osteoclasts & formation of new bone by osteoblasts.
- Although only a small fraction of total body calcium is located in the plasma, it is the plasma concentration of ionized calcium that is tightly regulated, primarily under the control of PTH and vitamin D.

Parathyroid hormone

About the Hormone	• PTH: a hormone that plays a critical role in controlling calcium and phosphate balance. • PTH is released from the parathyroid gland in response to low plasma Ca^{2+} level • Secretion of PTH is inversely related to [Ca^{2+}].
Its Action	★ The overall action of PTH is to increase plasma Ca^{2+} levels in response to hypocalcemia: ❖ First, PTH enhances intestinal calcium absorption in the presence of permissive amounts of vitamin D. ❖ Second, PTH stimulates bone resorption by stimulating osteoclasts to increase the outward flux of calcium. ❖ Third, PTH stimulates the active reabsorption of calcium from the kidney.

Parathyroid hormone

Its Response	Daily, **intermittent** administration of recombinant human **PTH** SC in the thigh (alternate thigh every day) leads to a net **stimulation of bone formation** and bone mass/strength by **increasing osteoblast function and number**	**Continuous** or **chronic** exposure to high serum **PTH** concentrations (as seen with primary or secondary hyperparathyroidism) results in **bone resorption** by **increase the activity of osteoclast** leading to **increase serum calcium**
clinical uses	★ **Treatment of severe osteoporosis** ★ **Resistant cases failed to respond to other medications**	

Teriparatide

characteristic	• Synthetic polypeptide form of PTH (PTH analogue). • It belongs to a class of anti-osteoporosis drugs, the so-called “anabolic” agents. . • Given, once / daily by subcutaneous injection	
Its Response	Once-daily administration of teriparatide stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity.	By contrast, continuous administration of teriparatide , may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

Teriparatide

Therapeutic uses

- Good for postmenopausal osteoporosis.
- For treatment of osteoporosis in people who have a risk of getting fracture (increased bone mass & strength)
- Used in severe osteoporosis or patients not responding to other drugs.
- Should not be used routinely due to carcinogenic effects.

Adverse effects

- Carcinogenic effect (osteosarcoma)
- Diarrhea, heart burn, nausea
- Headache, leg cramps
- Hypotension when standing (orthostatic hypotension)
- Elevated serum calcium which may occur in some cases can lead to kidney stones

Contraindications

Teriparatide should not be used by people with increased risk for bone tumors (osteosarcoma) including:

★ People with Paget's disease* of bone. abnormal metabolic bone disease unknown etiology (excessive bone destruction and abnormal bone repair)more liable to fracture

★ People who had radiation treatment involving bones

★ Not recommended in children

Vitamin D

- **Vitamin D is a steroid hormone that is intimately involved in the regulation of plasma calcium levels.**
- **Its role in calcium metabolism first was recognized in the childhood disease rickets, which is characterized by hypocalcemia and various skeletal abnormalities**

important note:

- **Exposure to the ultraviolet rays in the sunlight convert 7-dehydrocholesterol(in skin) to cholecalciferol.**
- **Vitamin D3 is metabolically inactive until it is hydroxylated in the liver then the kidney to the active form 1,25 Dihydroxycholecalciferol.**

remember that:

- 1,25-dihydroxyvitamin D (calcitriol) is The most active form of vitamin D.
- 25-hydroxyvitamin D (calcidiol, 25-hydroxycholecalciferol): an inactive form of vitamin D.
- 1alpha-hydroxylase: The enzyme that converts the inactive form of vitamin D.

Vitamin D mechanism :

- **increases bone resorption**
- **increases Ca^{2+} absorption from intestine, increases renal Ca^{2+} reabsorption**
- **decreases the production of PTH by the parathyroid glands.**
- **The overall effect of vitamin D is to increase plasma Ca^{2+} concentrations**

Vitamin D

Vitamin D: it has 2 forms:

- ★ **Ergocalciferol (Vitamin D2) in plants. is the prescription form of vitamin D & is also used as food additive (milk).**
- ★ **Cholecalciferol (Vitamin D3) in skin. is usually for vitamin D- fortified milk & foods & also available in drug combination products.**
- ★ *Both of them are routinely added to calcium supplements and milk for the purpose of preventing rickets in children and osteomalaciea in adults.
- ★ **Vit D2 and Vit D3 have equal biological activities.**

Therapeutic use of Vit D

- Rickets & Osteomalacia
- Osteoporosis
- Psoriasis
- Cancer prevention (prostate & colorectal

Deficiency of Vit D

- Rickets in small children
- Osteomalacia
- Osteoporosis

Calcitonin

characteristic	•synthesized and secreted by the parafollicular cells (C cells) of the thyroid gland. •It is released when there is a *rise in plasma Ca2+ levels,* While PTH and vitamin D act to *increase plasma* Ca^{2+} •has lower efficacy compared to other drugs.
MOA	•Inhibiting bone resorption by ***inhibiting osteoclast activity*** ***(the target of calcitonin)*** •Decreasing reabsorption of Ca2+ & PO4 by the kidney, thus increasing their excretion **NOTE:**Calcitonin does not appear to be critical for the regulation of calcium homeostasis even if thyroid gland is **removed**.
Clinical uses	★ Osteoporosis. major indication ★ Hypercalcemia ★ Paget's disease. ★ Milk-alkali syndrome (increased calcium absorption) ★ decreased calcium excretion (thiazide use).
Routes of administration	• Subcutaneous • Nasal spray • Solution (Calcitonin Salmon) from salmon fish has more affinity towards human calcitonin receptors
Adverse effects	•Nausea •Local inflammation at site of injection •Flushing of face & hands specific for calcitonin •Nasal irritation specific for calcitonin

MCQs

1.Continuous administration of PTH will lead to which one of the following?
A.Bone formation
B.Bone resorption
C.Increase bone mass
D.Activation of osteoblast

2.56 years old women suffering from osteoporosis, her doctor prescribe teriparatide as one dose daily What is the mechanism of this drug in her condition?
A.Stimulate osteoclast
B.Stimulate osteocyte
C.Stimulate osteoblast
D.Stimulate chondrocyte

3.Which drug used in treatment of Paget's disease?
A.Calcitonin
B.Teriparatide
C.PTH
D.Artemesinin

4.Which of the following is PTH function?
A.Increase Ca absorption from intestine
B.Stimulation of bone resorption
C.Stimulates reabsorption of calcium from the kidney
D.All of the above

5.Which drug is contraindicated in patient with Paget's disease?
A.calcitonin
B.Aspirin
C.Toradol
D.Teriparatide

6.Deficiency of vitamin D leads to which one of the following?
A.Osteosarcoma
B.Osteoarthritis
C.Osteomalacia
D.osteomyelitis

7.Teriparatide has which one of the following?
A.Diabetogenic effect
B.Immunological effect
C.Inflammatory effect
D.Carcinogenic effect

8.What is the mechanism of action of calcitonin?
A.inhibition osteoclast activity
B.Decreasing reabsorption of Ca^{2+} & PO_4 by the kidney
C.Decrease Ca absorption from GIT
D.All of the above

1-B
2-C
3-A
4-D
5-D
6-C
7-D
8-D

Good luck!

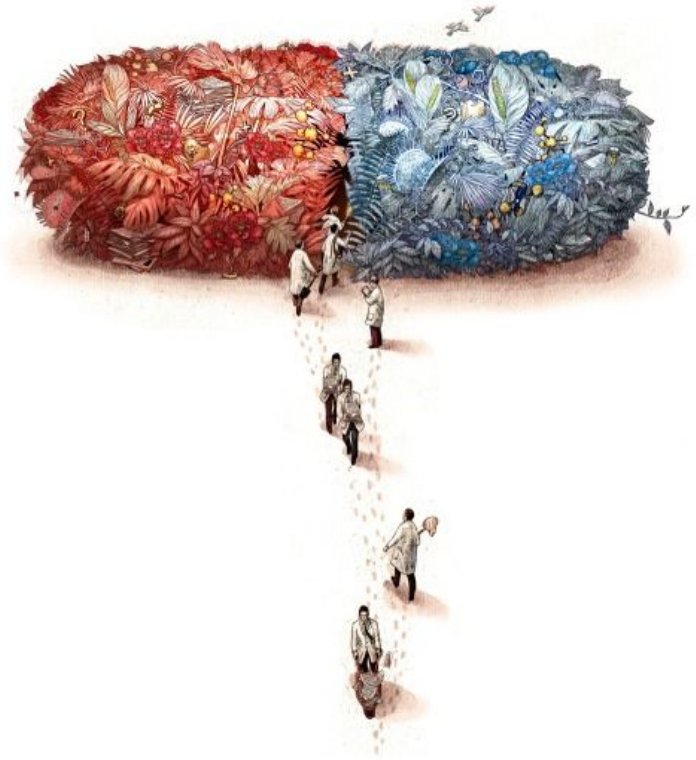
Done by Pharmacology team 434

Done by:

- ★ Ahmed Alsaleh
- ★ Abdulrhman Almutairi
- ★ Abdullah Althuniyan

reviewed by:

- ★ Rawan Ghandour
- ★ Ahmed Alsaleh



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