

BISPHOSPHONATES: (BRN) (ANTIRESORPTIVE DRUGS)

- They are analogues of pyrophosphate
- They inhibit bone resorption and have attracted ability to prevent osteoporosis.

MECHANISM OF ACTION:

Osteoporosis: - low bone mass

↓
Skeletal fragility.

↓
Microarchitectural disruption.

↓
Reduced fracture.

⇒ Osteoblast (Bone Building).

PTH hormone bind to osteoblast receptors.

They form RANK ligand

which bind to osteoclast (bone resorption)

↓
cell

↓
bone formation is boosted by

hypoxia and PTH.

↑ in osteoclast activity → Bone Resorption

↓

↓ Bone density

↓

osteoporosis

TSR < -2.5

Drug:

1st gen: Etidronate, Tiludronate

2nd gen: Pamidronate, Alendronate, Ibandronate

3rd gen: Risedronate, Zoledronate

MOA: ① They have high affinity for hydroxyapatite in bone.

(acidic)

- They localize at site of Active bone Remodelling, particularly where osteoclasts are Active, due to high

Affinity for Ca^{2+} ion.

↓

so, when Ca^{2+} ions are Released from the bone

sulfate due to high acidity the BPM's are Also

Released And is internalized into osteoclasts by endocytosis.

Result: → Accumulated Apoptosis of osteoclast Reduces their number

→ Dismantling of cyto-skeleton And Ruffled Border of osteoclast

→ Suppression of osteoclast precursor differentiation by

Inhibition of IL-6

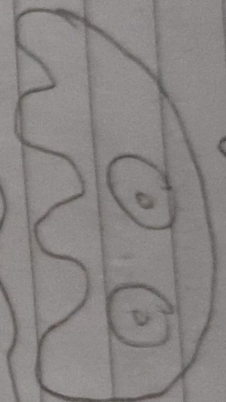
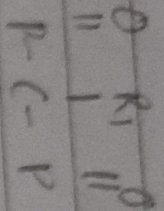
② They Also interfere with mevalonate Pathway of

cholesterol synthesis which is Required for

normal function of osteoclasts. (2nd & 3rd gen drugs)

Supraphosphate

glycolysis



hydrolysis

ATP

Apoptosis

BRM have two phenotypes. One may bind strongly to

hydrolysis, the other component of bone

They Accumulate sites of Adipose

Resorption when osteoclasts

BRM (bone remodeling) (bone resorption)

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Apoptosis

↓ Bone Resorption

Uses:

1) Osteoporosis: 2nd & 3rd generation are unfull to prevent postmenopausal osteoporosis in women.

→ 1st choice of drug
→ better than cipro and ceftriaxone.

2) Pay 15 divorce: divorce due to abnormal behavior
producing honey comb like bone

→ BPN assist collogne unions, Reduce bone pain

3) Hypocalcaemia of malignancy:
↓
Irisalene is given Along with

1st hydation - IV
Zeladronate And celibain in
Threonide bottle 121 given supplyment.

$$+ \text{BRN}(\text{iv}_1)$$

4.) Endoligite bare metastasis: IV, zele domete anul "ololite lenia

ORAL ADMINISTRATION OF BPNs

→ taken on empty stomach taken with a glass of water, ask the patient not to lie down
chances of esophagitis lesser And ulcers.

ALENDRONATE:

- 2nd gen BPN
- used for t/t of osteoporosis, Paget's disease.
- extend in use.

so dose adjustment needed for renal failure patient
t $\frac{1}{2}$ $\rightarrow$ 10-15 years.

Same H0A

ADR

esophagitis, gastric ulcers, headache, body ache

ZOLEDRONATE:

- $\rightarrow$ highly potent - 3rd gen BPN
- $\rightarrow$ t/t of hypercalcaemia: bone metastases, osteolytic lesions,

Paget's disease.

$\rightarrow$ Additional anti-tumor effect.

$\hookrightarrow$ prediction of tumor cell may be hampered
 $\rightarrow$ DOL of hypercalcaemia

$\rightarrow$ long iv dose every 12 months for systemic
for osteoporosis in PMW.

Same H0A

ADR

- flu like symptoms:
- renal toxicity
- Osteonecrosis of the jaw