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Review Article

Bisphosphonates-what's new?

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ABSTRACT

Bisphosphonates are chemical-related to pyrophosphate. The oxygen atom in pyrophosphate is substituted by a carbon atom in these compounds, resulting in a P-C-P bond. They are potent antiresorptive medicines because they have a strong inhibitory effect on osteoclasts. It lowers fracture risk by reducing bone turnover, increasing bone mineral density, and decreasing fracture risk in the lumbar spine and hip. Bisphosphonates are strongly attracted to bone surfaces, where they accumulate, primarily at remodeling sites. They are rarely associated with systemic side effects due to their selectivity in action. Irritation of the upper gastrointestinal tract is the most common side effect. A strong third-generation bisphosphonate, zoledronate, is currently approved to treat postmenopausal-induced osteoporosis. This review mainly focuses on the mechanism of action, therapeutic uses, and its adverse effects.

Keywords: Bisphosphonates, Calcium balance, Bone homeostasis

INTRODUCTION

Bisphosphonates are pyrophosphate analogues containing two phosphonate groups attached to a germinal carbon replacing oxygen in pyrophosphate. (i.e., P-0-P to P-C-P).[1]

These agents have high affinity for bone (hydroxyapatite), and targets bone surfaces which undergoes remodeling.[2]

Classification of bisphosphonates

First generation bisphosphonates-Medronate, clodronate, etidronate and tiludronate, these agents are least potent drugs due to presence of chlorophenol group (tiludronate) and modified side chains.

Second generation amino bisphosphonates-Alendronate and pamidronate, these agents are 10-100 times more potent than first generation drugs due to presence of nitrogen group in side chain.

Third generation bisphosphonates-Risedronate and zoledronate, these agents are 10,000 times more potent than other generation because it contains nitrogen atom with a heterocyclic ring.

MECHANISM OF ACTION[2]

Bisphosphonates acts by bone resorption inhibition, (Direct inhibitory mechanism on osteoclasts).

Usually, it accumulates at active bone remodelling sites, stays in the matrix until the remodelling halts and then released in acidic environment of bone resorption lacunae and inducing osteoclasts apoptosis.

Antiresorptive potential has 2 main mechanisms-apoptosis in osteoclasts and inhibition of cholesterol synthesis.

Pharmacokinetics[3]

Almost all oral agents are being poorly absorbed from GI tract and have extremely limited bioavailability of <1% to 6% which is further decreased by the presence of food and drugs containing divalent cations like antacids, calcium and iron supplements. Therefore, these drugs must be

taken with glass of water following overnight fasting or at least 30 min before breakfast. It is widely distributed into bone, less hepatic clearance and excreted by kidneys in unchanged form. The absorbed drug in the bone is slowly released during the process of bone remodelling and has terminal half-life of 10 years.

Therapeutic uses

Paget's disease[4]

Etidronate sodium, zoledronate and pamidronate is commonly used. Newer agents approved for treatment of Paget's disease-tiludronate, alendronate and risedronate.

Alendronate is available in once daily or once weekly oral formulations

Tiludronate-400 mg/day orally-3 days (do not interfere with bone mineralization unlike etidronate) and zoledronate-single dose 5 mg IV infusion.

Tumour associated osteolysis[5,6]

Bisphosphonate IV therapy (pamidronate/ zoledronate) is most effective treatment for bone lesions associated with cancer. Its decreases bone pain and reduces fracture risk.

Hypercalcemia

Etidronate (IV), pamidronate (IV) used in the management of hypercalcemia associated with malignancy, it is usually given as IV infusion of 60-90 mg over 2-24 hr.[1] Zoledronate-4 mg (IV).

Tiludronate-400 mg/day orally-3 days (do not interfere with bone mineralization unlike etidronate) Zoledronate – single dose 5 mg IV infusion

Osteoporosis (postmenopausal and steroid induced)[7,8]

Zoledronate used for the prevention of osteoporosis with breast and prostate cancer patients on hormonal therapy.

Ibandronate-2.5 mg daily or 150 mg once monthly (P.O) approved for the treatment and prevention of postmenopausal osteoporosis

For treatment of osteoporosis, ibandronate (IV) 3 mg every 3 months.

Zoledronate is the first agent approved for yearly once IV in dose of 5 mg annually

Prevent or delay the development of metastasis in breast cancer[9]

Bisphosphonates exert anticancer effects by altering local tissue micro environment that may delay or prevent the establishment of bone metastasis. It also reduce the rate of bone loss associated with breast cancer treatment

ADVERSE EFFECTS OF BISPHOSPHONATES[10]

Most common adverse effects

Upper GI side effects

This is the most common cause of patient's intolerance to oral bisphosphonates. The incidence of upper GI side effects like heartburn, esophageal irritation, esophagitis, nausea, dyspepsia, abdominal pain and diarrhoea symptoms are common.

Reason: Bisphosphonates acts as a local irritant to the gastrointestinal tract leading to inflammation and erosion of the esophagus.

Ways to reduce/ prevent: Remain in upright posture for 30 – 60 minutes after taking oral bisphosphonates with a full glass of water. These adverse effects reduced with the advent of weekly and monthly preparations.

Acute phase reaction

It is a transient acute phase reaction following IV bisphosphonates (pamidronate, zoledronate, ibandronate) therapy usually lasts 24 to 72 hours which is characterized by skin flushing, flu-like symptoms, muscle and joint aches, nausea and vomiting, abdominal discomfort, diarrhoea or constipation especially when given in higher concentrations or at faster rates. This is observed in 1 in 10 patients receiving IV therapy with first time, subsequently the incidence declines with second (1 in 15) and third (1 in 35) infusions.

Reason: Idiosyncratic reaction, mainly due to rapid and excessive production of pro-inflammatory cytokines by activated γδ T cells.

Ways to reduce/ prevent: Usually it resolves spontaneously, treatment with acetaminophen (500-1000 mg before and for 24-48 hour after infusion) may ameliorate the symptoms.

Hypocalcemia

It occurs most commonly following i.v. bisphosphonates therapy and often in patients with impaired kidney function, less calcium intake, hypovitaminosis D and increased bone resorption (Paget's disease of bone or bone tumour).

Reason: Bisphosphonate induced hypocalcemia is caused by demasked vitamin D deficiency.

Ways to reduce/prevent: Advice to take adequate calcium and vitamin D in diet.

Clinical implication: Serum levels of calcium, phosphorus, vit D, parathyroid hormone and urinary calcium levels must be assessed before starting bisphosphonate therapy

Most serious/life- threatening

Osteonecrosis of jaw[11]

The incidence (1 to 10 per 100 patients) is high with the patients who are receiving bisphosphonates for cancer. Risk factors are poor oral hygiene, invasive dental procedures, usage of denture and prolonged use of high doses IV bisphosphonates.

Reason: mainly due to trauma of dentoalveolar structures which has limited capacity for bone healing due to the effects of bisphosphonate therapy**.**

Ways to reduce/ prevent: Mainly supportive like improve oral hygiene with antiseptic oral solution, limited invasive dental surgeries, pain control and use of antibiotics to prevent infections.

Clinical implication: Recently measurement of bone resorption marker carboxy-terminal collagen crosslinks to estimate risk for osteonecrosis of jaw development.

Renal toxicity[12]

Since majority of drug administered is excreted in unchanged form by kidneys, remaining is taken up bone cells. It is associated with both dose ad infusion time.

Reason: Mainly associated with IV bisphosphonates therapy related to maximum drug accumulation.

Ways to reduce/ prevent: Avoid prescribing other agents having nephrotoxic potential like NSAIDS, aminoglycosides and diuretics. By adjusting dose in patients with preexisting renal pathology.

Clinical implication: Patients with an estimated glomerular rate of 30 ml/min or less, these agents must be avoided to prevent renal compromise.

Atrial fibrillation

Incidence of serious atrial fibrillation (events which needs immediate hospitalization/ produce life threatening complications/ disability) is seen with IV bisphosphonate therapy

Reason: No clear mechanism is explained for association between bisphosphonates and atrial fibrillation.

Stress fractures of femur

Bisphosphonates associated stress fractures of femoral shaft or subtrochanteric femur fracture are very uncommon accounts for <1%, occurs spontaneously or low energy trauma in patients who are receiving prolonged therapy. They also have prodrome of symptoms like vague discomfort, thigh pain, fatigue and subjective weakness. Imaging shows cortical thickening and cortical stress reaction.

Reason: Long term therapy leads to bone remodeling over suppression and increased bone fragility

Clinical implication: Patients on bisphosphonates therapy if they develop dull aching bone pain in the thigh or groin refer them to bone mineral specialist for the further evaluation.

Others adverse effects

Severe musculoskeletal pain

Bisphosphonate use may be associated with severe bone, joint and musculoskeletal pain, according to a recent FDA alert.

Reason: Due to direct cytokine-mediated acute phase reactions, pressure changes in bone marrow, localized bone hypoxemia, and direct stimulation of mechanical nociceptors.

Ways to reduce/ prevent: Temporary or permanent drug discontinuation must be considered.

Esophageal cancer

Bisphosphonates therapy seems to be associated with an increased risk of esophageal cancer.

Reason: Repeated and prolonged exposure of esophageal mucosa to inflammation, irritation and erosion leading to tumour growth.

Ways to reduce/ prevent: Avoid prescribing these agents in patients with known esophageal pathology (Barrett's esophagus).

Ocular inflammation

Very rare adverse effect seen with bisphosphonate therapy. E.g., uveitis, conjunctivitis, episcleritis, scleritis, ocular pain and photophobia.

Reason: Idiosyncratic reaction, the exact mechanism of bisphosphonate-associated ocular inflammation is not known.

Clinical implication: Ophthalmologic referral needed if patients develop any eye symptoms and symptomatic management.

Drug interactions

Bisphosphonates+calcium supplements/ antacids-decrease absorption of bisphosphonates.

Clinical implication: Must be taken at-least 2 hours before or after bisphosphonate drug.

CONCLUSION

Since they were first used in medicine, bisphosphonates have revolutionized the treatment of a wide range of skeletal disorders caused by excessive osteoclast-mediated bone resorption. Therefore, for carefully chosen patients, the benefits of using bisphosphonates are clearly clinically superior to the hazards when they are used with knowledge and discretion. All patients receiving bisphosphonate medication must maintain adequate calcium and vitamin D consumption.

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