Alendronate and its Role in Post-Menopausal Osteoporosis

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ABSTRACT

Alendronate (alendronic acid) is a nitrogen-containing drug that belongs to the second generation bisphosphonate class of drug. It binds to bone surfaces and inhibits bone resorption by osteoclasts and has been used as a treatment of choice in postmenopausal women with osteoporosis for many years. It is also a suitable drug for treatment of primary osteoporosis in men and for corticosteroid-induced osteoporosis in both men and women.[1]

Oral alendronate (Alendronic acid) 5 or 10 mg/day has shown to produce an sustained increases in bone mineral density (BMD) in postmenopausal women with or without osteoporosis, in men with primary osteoporosis and in both men and women with or without osteoporosis receiving systemic corticosteroid therapy. Alendronic acid, administered at 70 mg once weekly or 35 mg twice weekly dose, has shown to increase the effective at increasing BMD as 10 mg/day and thus helps in the treatment or prevention of osteoporosis.[1]

In this review, I will be focussing mainly on the properties of oral alendronic acid in the treatment of post-menopausal osteoporosis.
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Key words: Alendronate (Alendronic Acid), Atypical Fractures, Bone mineral density (BMD), Post-Menopausal Osteoporosis, Vitamin D

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INTRODUCTION

Osteoporosis ("porous bones", from Greek: οστούν/ostoun meaning "bone" and πόρος/poros meaning "pore") is a disease of bones that weakens it and leads to an increased risk of fracture. In osteoporosis, the bone mineral density (BMD) is reduced, bone micro architecture deteriorates, and the amount and variety of proteins in bone are altered, [2]which in turn makes the bones in the body, fragile and susceptible to fracture.

Definition: Osteoporosis is defined by the World Health Organization (WHO) as a bone mineral (BMD) density that is 2.5 standard deviations or more below the mean peak bone mass (average of young, healthy adults) as measured by Dual-energy X-ray absorptiometry (DXA); the term "established osteoporosis" includes the presence of a fragility fracture.[3]

Classification: The disease is classified into primary type 1, primary type 2, or secondary osteoporosis. The form of osteoporosis that is most common in women after menopause is referred to as primary type 1 or postmenopausal osteoporosis. Primary type 2 osteoporosis also known as senile osteoporosis occurs after age 75 and is seen in both females and males at a ratio of 2:1.

On the other hand, secondary osteoporosis may arise at any age and affect men and women equally. This form results from chronic predisposing medical problems or disease, or prolonged use of medications such as glucocorticoids, when the disease is called steroid- or glucocorticoid-induced osteoporosis (SIOP or GIOP).[2]

Effect of Menopause in occurrence of Osteoporosis (Pathophysiology): In postmenopausal women, Low estrogen levels or estrogen deficiency accelerates bone loss. Estrogen deficiency can lead to excessive bone resorption accompanied by inadequate bone formation. Osteoblasts, osteocytes, and osteoclasts all express estrogen receptors. In addition, estrogen also affects bones indirectly through cytokines and local growth factors. The estrogen-replete state may enhance osteoclast apoptosis via increased production of transforming growth factor (TGF)–beta.[4]

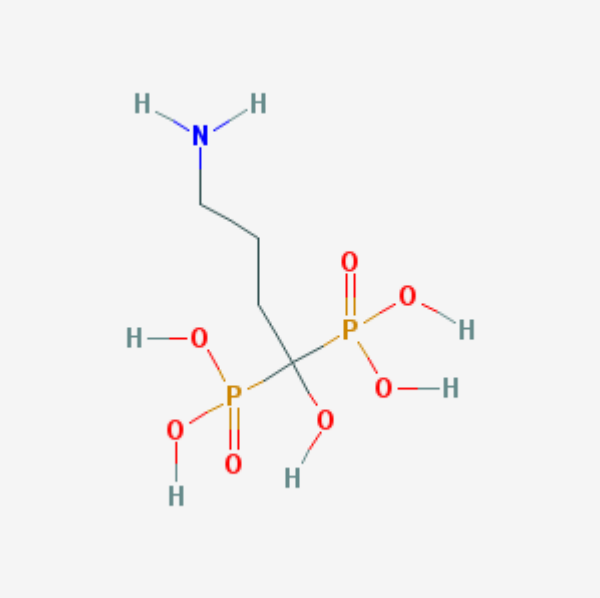
In the absence of estrogen, T cells promote osteoclast recruitment, differentiation, and prolonged survival via IL-1, IL-6, and tumour necrosis factor (TNF)–alpha. A murine study, in which either the mice's ovaries were removed or sham operations were performed, found that IL-6 and granulocyte-macrophage CFU levels were much higher in the ovariectomized mice. This finding provided evidence that estrogen inhibits IL-6 secretion and that IL-6 contributes to the recruitment of osteoclasts from the monocyte cell line, thus contributing to osteoporosis.[4]

IL-1 has also been shown to be involved in the production of osteoclasts. The production of IL-1 is increased in bone marrow mononuclear cells from ovariectomized rats. Administering IL-1 receptor antagonist to these animals prevents the late stages of bone loss induced by the loss of ovarian function, but it does not prevent the early stages of bone loss. The increase in the IL-1 in the bone marrow does not appear to be a triggered event but, rather, a result of removal of the inhibitory effect of sex steroids on IL-6 and other genes directly regulated by sex steroids.[4]

T cells also inhibit osteoblast differentiation and activity and cause premature apoptosis of osteoblasts through cytokines such as IL-7. Finally, estrogen deficiency sensitizes bone to the effects of parathyroid hormone (PTH).[4]

Alendronic acid is a bisphosphonate drug used for treatment and prevention of osteoporosis and several other bone diseases. It is a nitrogen-containing bisphosphonate which binds to bone surfaces and inhibits bone resorption by osteoclasts.[1]It falls under the category of second generation bisphosphonates.

STRUCTURE OF ALENDRONIC ACID



Chemical Formula: $C_4H_{13}NO_7P_2$
Molecular Weight: 249.10
Kingdom: Organic
Drug Class: BISPHOSPHONATES (Second Generation)
Half Life: More than 10 years[5]
Synonyms: Alendronate, Alendronate sodium
Brand Names: Fosamax, Adronat, Alendros, Arendal, Onclast, Fosamax Plus D

PHARMACOKINETICS

Absorption and Bioavailability: Absorption and disposition appear independent of dose. Oral bioavailability is about 0.9 to 1.8%, and food markedly inhibits oral absorption. The oral bioavailability of alendronate in the fasted state is about 0.7%, with no significant difference between men and women. Food substantially reduces the bioavailability of oral alendronate.[6]

Distribution: Although soon after administration the drug distributes widely in the body, this transient state is rapidly followed by nonsaturable redistribution to skeletal tissues.[6]

Metabolism: Preclinically, alendronate is not metabolised in animals.[6]

Clearance and Excretion: It is cleared from the plasma by uptake into bone and elimination via renal excretion. Removal of the drug from bone reflects the underlying rate of turnover of the skeleton. Renal clearance appears to involve both glomerular filtration and a specialised secretory pathway.Clinically, the pharmacokinetics of alendronate have been characterised almost exclusively based on urinary excretion data because of the extremely low concentrations achieved after oral administration. After intravenous administration of radiolabelled alendronate to women, no metabolites of the drug were detectable and urinary excretion was the sole means of elimination. About 40 to 60% of the dose is retained for a long time in the body, presumably in the skeleton, with no evidence of saturation or influence of one intravenous dose on the pharmacokinetics of subsequent doses.[6]

PHARMACODYNAMICS

Alendronate (Alendronic Acid) is a bisphosphonate drug. It binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. It reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.[7]

MECHANISM OF ACTION

The action of Alendronate (Alendronic acid) on bone tissue is based partly on its affinity for hydroxyapatite, which is part of the mineral matrix of bone.[8]

Alendronate also targets farnesyl pyrophosphate (FPP) synthase. Nitrogen-containing bisphosphonates (such as alendronate, pamidronate, risedronate, ibandronate and zoledronate) appear to act as analogues of isoprenoid diphosphate lipids, thereby inhibiting FPP synthase, an enzyme in the mevalonate pathway. Inhibition of this enzyme in osteoclasts prevents the biosynthesis of isoprenoid lipids (FPP and GGPP) that are essential for the post-translational farnesylation and geranylgeranylation of small GTPase signalling proteins. This activity inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.

USES

-Alendronic acid is used in the prophylaxis and treatment of female osteoporosis.[9]

-It is used in the treatment of male osteoporosis.[10]and Paget's disease.[11]

-It is also used in the prevention and treatment of corticosteroid-associated osteoporosis together with supplements of calcium and vitamin D.[12]

Use in Post Menopausal Osteoporosis

Dosage/posology:

Alendronic Acid Once weekly 70 mg Tablets is the recommended dose for treatment of post menopausal osteoporosis.[13]

Method of oral administration

To permit adequate absorption of alendronic acid:

Alendronic acid Tablet must be taken at least 30 minutes before the first food, beverage, or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronic acid.[13]

To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences:-

- Alendronic acid Tablet should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml or 7 fluid ounce).[13]
- Patients should not chew or crush the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.[13]
- Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.[13]
- Patients should not lie down for at least 30 minutes after taking Alendronic acid.[13]
- Alendronic acid Tablet should not be taken at bedtime or before arising for the day.[13]

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.[13]

Use in the elderly: In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronic acid. Therefore no dosage adjustment is necessary for the elderly.[13]

Use in renal impairment: No dosage adjustment is necessary for patients with GFR greater than 35 ml/min. Alendronic acid Tablet is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.[13]

Use in children (under 18): Alendronic acid has been studied in a small number of patients with osteogenesis imperfecta under 18 years of age. Results are insufficient to support its use in children.[13]

Use in Pregnancy: There are no adequate data from the use of alendronic acid in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, or postnatal development. Alendronic acid given during pregnancy in rats caused dystocia related to hypocalcemia. Given the indication, alendronic acid should not be used during pregnancy.[13]

Use during lactation: It is not known whether alendronic acid is excreted into human breast milk. Given the indication, alendronic acid tablet should not be used by breast-feeding women.[13]

SIDE EFFECTS

General: Adverse effects usually have been mild when patients adhered to the prescribing instructions. Fever, asthenia and rare instances of peripheral oedema have been reported with the use of alendronic acid.[14]

Gastrointestinal: Esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation and oropharyngeal ulceration can be seen. The combination of alendronate and naproxen (NSAIDS) has been reported as synergistic for development of gastric ulcers. Gastrointestinal side effects have included abdominal pain, nausea, dyspepsia, constipation, diarrhoea, and flatulence. Regurgitation, esophageal ulcer, vomiting, dysphagia, abdominal distension, and gastritis also have occurred. Rarely, taste perversion has been reported. The frequency of adverse effects increased with higher dosages.

Several cases of ulcerative esophagitis have been reported in patients receiving alendronate. Patients with pre-existing esophageal disorders and those who take alendronate with little or no water and lie down immediately following ingestion may be at an increased risk.[14]

Metabolic: Metabolic side effects have included reductions in serum calcium and phosphate levels as a result of the inhibition of bone resorption. These reductions generally have been mild, asymptomatic, and transient. Symptomatic hypocalcemia has been reported on a few occasions.[14]

Musculoskeletal: Musculoskeletal side effects have included bone, muscle or joint pain in approximately 4% of patients. Severe and occasionally incapacitating bone, joint and/or muscle pain, have been infrequently reported.[14]

Localized osteonecrosis of the jaw generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely. Joint swelling has also been reported on few occasions. Also, low-energy femoral shaft and subtrochanteric fractures have been reported with prolonged use of alendronic acid (generally in treatment more than 5 years) [14]

Nervous system: Nervous system side effects have been rare. Headaches have been reported in fewer than 3% of patients. Dizziness and vertigo have been reported in post marketing experience.[14]

Dermatologic: Dermatologic side effects have included rare reports of rash and erythema. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in post marketing experiences.[14]

Ocular: Ocular side effects have included rare incidences of iritis, scleritis, uveitis, and nonspecific transitory conjunctivitis.[14]

Respiratory: Respiratory side effects have included a case report of an asthma attack induced by alendronate .[14]

Cardiovascular: Although, it is said that usage of alendronic acid may lead to atrial fibrillation,

No clear association between atrial fibrillation and bisphosphonate use has been established.

CONTRAINDICATIONS

Alendronic acid is contraindicated in the following.[13]

- Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypersensitivity to alendronic acid or to any of the excipient.
- Hypocalcaemia

IMPORTANCE OF VITAMIN D LEVELS AND CALCIUM LEVELS ALONG WITH USE OF ALENDRONIC ACID

Ensuring adequate calcium and vitamin D intake both before and after initiation of bisphosphonate therapy is an extremely important but frequently overlooked aspect of providing optimal care of skeletal health. Vitamin D insufficiency is widely acknowledged to be prevalent in nearly all patient populations prescribed bisphosphonate therapy, particularly in the elderly, who are more likely to have limited sun exposure, reduced dietary intake, and renal impairment. Vitamin D levels below the optimal range limit dietary absorption of calcium, lead to secondary hyperparathyroidism with loss of skeletal calcium to maintain normocalcemia, contribute to falling risk in the elderly, and blunt the bone mineral density (BMD) response and antifracture efficacy of bisphosphonates

Bisphosphonates are most effective at limiting fracture risk when taken in conjunction with adequate calcium and vitamin D. All patients for whom bisphosphonates are considered should be counselled on this important requirement before and during bisphosphonate therapy.[15]

INTERACTIONS

Absorption of alendronic acid is decreased with milk due to its chelating action.[16]

Drug–drug interactions are rare in the management of osteoporosis and discussed only briefly here.[17]

Co administration of oral bisphosphonates and calcium or acid-suppressant medication, or indeed any other oral medications containing divalent cations, is known to interfere with absorption of the bisphosphonate.[17]

Calcium supplementation should therefore be distanced from bisphosphonate intake. An apparent increase in the risk of fracture has been reported in individuals receiving acid-suppressant medication (proton pump inhibitors) but not with histamine H_2-receptor antagonists. This increase in risk remained in patients receiving acid-suppressant medication in combination with bisphosphonates vs. bisphosphonate alone.[17]

Caution is also recommended with oral bisphosphonates and the concomitant use of agents that irritate the gastric mucosa (e.g., nonsteroidal anti-inflammatory drugs) due to the GI effects of the bisphosphonate. Renal damage due to bisphosphonates could be exacerbated by nonsteroidal anti-inflammatory agents, amino glycoside antibiotics, antiretroviral therapies, or diuretics Thus, care should be taken to administer IV bisphosphonates to only fully hydrated patients.[17]

OPTIMAL DURATION OF BISPHOSPHONATE (ALENDRONIC ACID) USE

It is reasonable to stop bisphosphonates (alendronic acid) after 5 years of use and then to follow patients with markers of bone turnover. As long as the levels of these markers remain reduced, there is no physiological need to add a antiresorptive drug like alendronic acid.[18]

RISK OF ATYPICAL FRACTURES DUE TO LONG TERM USE OF BISPHOSPHONATES (ALENDRONIC ACID)

Studies have shown that, women taking bisphosphonates for osteoporosis have had unusual fractures ("bisphosphonate fractures") in the femur (thigh bone) in the shaft (diaphysis or sub-trochanteric region) of the bone, rather than at the head of the bone, which is the most common site of fracture. However, these unusual fractures are extremely rare (12 in 14,195 women) compared to the common hip fractures (272 in 14,195 women), and the overall reduction in hip fractures caused by bisphosphonate far outweighed the unusual shaft fractures. There are concerns that long-term bisphosphonate use can result in over-suppression of bone turnover.[19]

The incidence of atypical fractures was estimated to be approximately 78 cases per 100,000 patients taking oral bisphosphonates. These fractures have been described in patients receiving alendronate for more than 5 years .[20]

The half-life of bisphosphonate is more than 10 years and it exerts its effects even after cessation of therapy. It has been suggested that the prolonged suppression of bone turnover under long-term administration may impair the ability of bone to remodel, leading to accumulation of micro damage and compromised bone strength, ultimately progress to insufficiency stress fracture.[20]

CONCLUSION

To conclude, Alendronate (Alendronic acid) is a drug that is effective in the treatment and prophylaxis of post menopausal osteoporosis. The recommended dose of alendronic acid 70 mg once weekly or 35 mg twice weekly shows good results in the treatment of post menopausal osteoporosis.

However, method of administration should be followed correctly and contraindications should be carefully ruled out to avoid adverse complications.

Also, Long term use of alendronic acid should be avoided and the medication therapy should not be prolonged more than five years to avoid complications like atypical stress fractures.

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