

Ibandronate - Clinical utility and Pharmacological properties

*Dangroo Mushtaq Ahmad, **M Ashraf Ganie

*Departments of Medicine and **Endocrinology, *Government Medical College associated SMHS Hospital, Srinagar, **Sher-i-Kashmir Institute of Medical Sciences, Soura Srinagar, J & K.

ABSRTACT

Bisphosphonates are currently the most important class of anti resorptive agents used in the treatment of metabolic bone diseases including osteoporosis; Paget's disease; tumour-associated osteolysis and hypercalcaemia(1). Remarkable progress has been made in increasing the potency of bisphosphonates as inhibitors of bone resorption. Ibandronate is nitrogen containing bisphosphonate available in oral and parenteral preparations. It is as effective medication as other bisphosphonates and current data suggests that monthly ibandronate is at least as effective and well tolerated as the currently approved daily ibandronate regimens. [IJEM 2008;12(5):15-17]

Key Words: Bisphosphonates, Ibandronate, osteoporosis, BMD, Hypercalcemia

INTRODUCTION

Bisphosphonates are chemically stable analogs of inorganic pyrophosphates, which are resistant to breakdown by enzymatic hydrolysis. The first bisphosphonate to be developed for clinical use was Etidronate. Since then 2nd and 3rd generation Bisphosphonates have been developed for clinical use.

Pharmacological properties of bisphosphonates

1. Nitrogen-containing bisphosphonates (the most potent class) act by inhibiting the Mevalonate pathway in osteoclasts, thereby preventing prenylation of small GTPase signaling proteins required for osteoclast function.

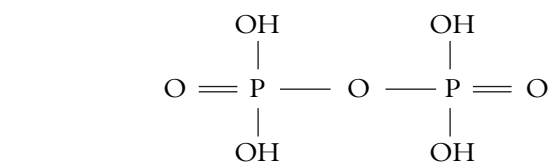
2. Non-nitrogen containing bisphosphonates do not inhibit protein prenylation but involve the formation of cytotoxic metabolites in osteoclasts or inhibition of protein tyrosine phosphatases.

The first bisphosphonate developed for clinical use i.e., Etidronate is the most potent mineralization inhibitor of this group. Subsequent clinical experience has shown that inhibition of mineralization actually constitutes a disadvantage, leading over time to osteomalacia. Thus, 2nd and 3rd generation Bisphosphonates have been developed that minimize this action.

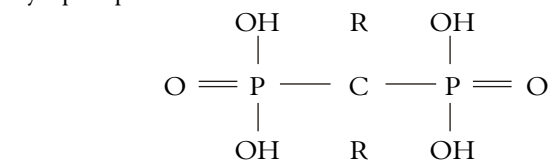
The two phosphate groups covalently linked to carbon determine both the name Bisphosphonates and the function of the drugs. The long side chain (R2) determines the chemical properties, the mode of action and strength of bisphosphonates drugs. The short chain (R1) often called the hook, mainly influences chemical properties and pharmacokinetics.

Bisphosphonate structure

The bisphosphonates are formed by substitution of oxygen by carbon in pyrophosphates. The pyrophosphate is a product of cellular metabolism (ATP → AMP + PPi), pyrophosphate which is a natural circulating inhibitor of mineralization in the blood can't get inside the bones because of destruction by alkaline phosphatase.



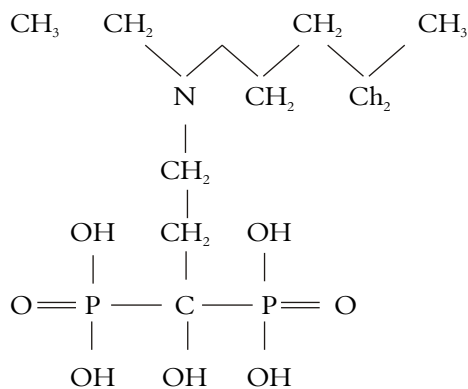
Pyrophosphate



Bisphosphonate

Address for correspondence:

Dr. M. Ashraf Ganie, Department of Endocrinology
Sher-i-Kashmir Institute of Medical Sciences, Srinagar - 190011
E-mail: ashraf.endo.ijem@gmail.com



Ibandronate

Ibandronate is a nitrogen-containing bisphosphonate available in oral and parenteral preparations. It is most potent aminobisphosphonate and directly inhibit multiple steps in the path way from Mevalonate to cholesterol and isoprenoid lipids, such as geranylgeranyl diphosphate, that are required for the prenylation of various proteins that are important for osteoclast function(3).

Anti resorptive potency with respect to other bisphosphonates

Drugs	Potency
1. Pamidronate	100
2. Alndronate	1000
3. Risedronate	5000
4. Ibandronate	10000

Dosage

Dosage of the drug is 150mg /month oral, 3mg /3 months IV, 2.5mg oral daily. Ibandronate should be taken with water when the patient will be able to remain upright for 1 hour following the dose, and should not be taken within one hour of eating or ingesting any other medication products containing calcium, aluminium, magnesium, or iron (e.g; milk, many foods, anti acids) which interfere with absorption of ibandronate, thus monthly dosing may be more convenient for some patients.

Pharmacokinetics

Absorption of oral ibandronate occurs in the upper gastrointestinal tract. Plasma concentrations increase in a dose – linear manner up to 50mg oral intake and increases non-linearly above this dose. Following oral dosing, the time to maximum observed plasma ibandronate concentrations ranged from 0.5 to 2hours (median one hour) in fasted state. The mean oral bioavailability of 2.5mg ibandronate was about 0.6% compared to intravenous dosing. The extent of absorption is impaired by food or beverages (other than plain water). The oral bio-availability of ibandronate is reduced by about 90% when it is administered concomitantly with a standard breakfast in comparison with bio-availability observed in fasted subjects. After absorption ibandronate either rapidly binds to bone or is excreted into urine. The amount of dose removed from circulation via the bone is estimated to be 40-50% of circulating dose. The portion of ibandronate that is not removed from circulation via bone

absorption is eliminated unchanged by the kidney (approximately 50 – 60% of absorbed dose). Unabsorbed ibandronate is eliminated unchanged in the feces. There is no evidence that ibandronate is metabolized in humans.

Adverse effects

Adverse effects with ibandronate most commonly are gastrointestinal and include dyspepsia, gastroenteritis and nausea. They are comparable to the adverse effects of other drugs in the same class(3,4). In two clinical trials 7% and 7.5% of participants in ibandronate 2.5mg daily groups dropped out because of medication related adverse effects. Adverse effects that were reported in greater than 5% of patients taking ibandronate included back pain, headache, bronchitis, and myalgias. The overall adverse effect profiles of the daily and monthly preparations were similar.

Precautions and warnings

Osteonecrosis of the jaw is a rare but possible complication that may occur with the use of ibandronate. It should be taken with water and upright (sitting or standing) posture maintained for 1 hour.

Ibandronate And Pregnancy

It may not be safe in pregnancy, although the full risks are not known at this time (FDA category C).

Clinical efficacy

In MOBILE study (5) 1609 women with postmenopausal osteoporosis were assigned to one of four oral Ibandronate regimens; monthly 50/50 (50mg on 2 consecutive days); 100; 150 and daily 2.5mg. After 1 year lumbar spine BMD increased by 3.9%, 4.3%, 4.1% and 4.9% in the 2.5,50/50,100 and 150mg arms, respectively. All monthly regimens were proven non inferior and 150mg regimen superior to the daily regimen.

All monthly regimens produced similar hip BMD gains which were larger than those with daily regimen. All regimen similarly decreased serum levels of C- telopeptide, a biochemical marker of bone resorption compared with the daily regimens, a significantly larger proportion of women receiving the 100mg and 150mg monthly regimens achieved predefined threshold levels for percent change from baseline in lumbar spine (6%) or total Hip BMD (3%). All regimens were well tolerated. Two year results from the MOBILE study (6) revealed that lumbar spine BMD increased in all arms: 5.0%, 5.3%, 5.6%, and 6.6% in the daily and once monthly groups [50+50mg,100mg and 150mg] respectively. All once monthly regimens were confirmed at least as effective as daily, and in addition 150mg was proven superior [$p < 0.001$]. Substantially increases in proximal femur BMD [total hip, femoral neck, trochanter] were increased; 150mg produced the most pronounced effect [$p < 0.05$ versus daily]. Independent of the regimens most participants [70.5%-93.5%] achieved increases above base line in lumbar spine BMD, total hip BMD or both, pronounced decreases in the biochemical marker of bone resorption, SCTX, observed in all arms after 3 months, were maintained throughout. The 150mg regimen consistently produced greater increases in BMD and SCTX suppression than the 100mg and daily regimens. Ibandronate was well tolerated with similar incidents of adverse events across groups. In a study of 80 post renal transplants for osteoporosis prevention, Ibandronate

injection was given to 40 before and at 3,6 and 9 months after renal transplantation(7). Loss of spongy and cortical bone after transplantation was prevented by ibandronate. Changes of BMD (Ibandronate versus controls) were as follows : lumbar spine, $-0.9 \pm 6.1\%$ versus $-6.5 \pm 5.4\%$ ($p < 0.0001$); femoral neck $+ 0.5 \pm 5.2\%$ versus $-7.7 \pm 6.5\%$ ($p < 0.0001$); and mid femoral shaft $+ 2.7 \pm 12.2\%$ versus $-4.0 \pm 10.9\%$ ($p = 0.024$). Fewer spinal deformities developed with Ibandronate (7 patients with 7 deformities versus 12 patients with 23 deformities, $p = 0.04$). There were fewer acute rejection episodes with Ibandronate (11 versus 22; $p = 0.009$). Graft function after 1 year was comparable. Bone loss, spinal deformation, and loss of body height during 1st year after kidney transplantation are prevented by injection of ibandronate at intervals of 3 months. The smaller number of rejection episodes of the ibandronate treated groups needs further confirmation and the mechanism studied. In a study on 629 patients (8) of post menopausal women in a multicentre, double blind, placebo controlled trial 1 year treatment with 3 monthly IV ibandronate 2mg, 1mg and 0.5mg produced a dose dependent gain in BMD compared with a loss of BMD in placebo. DIVA study(9) was conducted on 1395 post menopausal women with osteoporosis. 2 and 3 monthly IV ibandronate was given 2 and 3mg respectively. At 2 years 2 and 3 monthly IV regimens achieved statistically superior increase in BMD compared with daily regimens 6.4% and 6.3% versus 4.8% respectively ($p < 0.001$).

Effects of long term intravenous ibandronate therapy on skeletal related events, survival and bone resorption markers in patients with advanced Multiple myeloma was studied by Hans D. Manssen *et al* (10). Patients with multiple myeloma stage II or III were randomly assigned to receive either 2mg ibandronate or placebo as monthly IV bolus injection for 12 to 24 months in addition to conventional chemotherapy. 99 patients per treatment group were assessable for efficacy analysis. The occurrence of SRE was found between the two treatment groups. In overall evaluation no differences were found between the groups regarding bone pain, analgesic drug use, quality of life and median survival (33.1 V 28.2 months respectively). Explorative post hoc analysis revealed that ibandronate patients with strongly suppressed bone turn over markers (30% and 50% mean reduction of serum osteocalcin and urinary c-terminal telopeptides) developed significantly less bone morbidity. Ibandronate was tolerated well during as many 25 therapy cycles. Chronic corticosteroid therapy, causes osteoporotic fractures in approximately 30-50% of patients treated. To prevent this oral bisphosphonate is recommended. However daily or weekly doses are associated with inconvenience, less frequent dosing given by IV in established corticosteroid induced osteoporosis [C10; Lumbar spine (L2-L4) bone mineral density(BMD) T- score d"-2.5] was given in a study of 115 participants. The patients were assigned to receive daily calcium 500mg plus either ibandronate [2mg] injection every 3 months or daily alfacalcidol [1mg] for 3years. IV ibandronate produced significantly greater increases in mean BMD at lumbar spine [13.3% versus 2.6%, respectively; $p < 0.001$] and femoral neck [5.2% versus 1.9% respectively; $p < 0.001$] versus daily oral alfacalcidol, after 3 years, relative to baseline. After 36 months frequency of patients with new vertebral fractures was significantly lower in the patients

receiving ibandronate relative to those taking alfacalcidol [8.6% versus 22.6% respectively $p = 0.43$]. This is the first time significant vertebral fracture reduction has been demonstrated with an IV bisphosphonate in C10. Patients treated with IV ibandronate injections also experienced less back pain [$p < 0.001$] and less height loss [$p = 0.001$] than those receiving oral alfacalcidol.

CONCLUSION

Sub optimal adherences to daily and weekly oral bisphosphonates (ibandronate) can potentially compromise therapeutic outcomes. Monthly bisphosphonates (ibandronate) is at least as effective and well tolerated as the currently approved daily ibandronate regimens. Thus, monthly oral regimens are preferred in conditions were indicated.

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