Safety and Antisorptive Power of Ibandronate Applied in the Real-Life Setting

Narong Bunyaratavej MD*, Wiwat Wajanavisit MD**,
Prayook Pauvilai MD***, Tassanee Kitumnuoypong MD****,
Nipat Kittimanon MD*****, Songkiat Lektrakoon MD******

** Department of Orthopedic Surgery, Siriraj Hospital, Bangkok, Thailand*
*** Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
**** Lerdsin General Hospital, Ministry of Public Health, Bangkok, Thailand*
***** Rajavithi Hospital Ministry of Public Health, Bangkok, Thailand*
****** Budhachinaraj Hospital Ministry of Public Health, Phitsanulok, Thailand*
******* Sapprasithiprasong Hospital Ministry of Public Health, Ubon Ratchayhani, Thailand*

This study involved 78 participants taking 150 mg of Ibandronate once a month for the investigation of the drug efficacy and safety. Ibandronate had a strong antiresorptive action that decreased 67.9 per cent of bone resorption. The total cases of unwanted effect were 21 that showed the common adverse events like other bisphosphonate. The most common events were flu-like symptom (8.75%) and dyspepsia (7.5%) which occurred at the first tablet. Most participants subsided after the following months, but only one case persisted in these symptoms through the study period while the others had a myalgia, diarrhea and burning of epigastric in percent of 6.25, 2.5, 1.25 respectively. Ibandronate (150mg) showed the strong antiresorptive effect and good compliance for taking once a month.

Keywords: *Ibandronate*

J Med Assoc Thai 2009; 92 (Suppl 5): S72-5
Full text. e-Journal: *http://www.mat.or.th/journal*

Ibandronate is aminobisphosphonate containing nitrogen in its molecule which disturbs the mevalonate pathway[1] that can affect the osteoclast metabolism leading to the cell fatalities. Ibandronate is recommended for decreasing bone resorption in osteoporosis. Taking 150 mg orally once a month is a good compliance. In Thailand, this kind of bisphosphonate is readily available. Thus, the study of Ibandronate efficacy and safety should be performed.

Material and Method

Eighty enrolled participants were from 6 Medical Centers: Siriraj Hospital, Ramathibodi Hospital, Lerdsin General Hospital, Rajavithi Hospital, Budhachinaraj Hospital and Sapprasithiprasong Hospital. The subjects were recruited by the qualification criteria for inclusion and exclusion.

Correspondence to: Bunyaratavej N, Department of Orthopedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. Phone: 0-2419-7962. E-mail: todrnarong@yahoo.com

Inclusion criteria

1. Males or females were diagnosed as osteoporosis patients under the definition of WHO criteria[2].

2. They experienced the na□ve or unsuccessful osteoporosis treatment of the previous regimen.

Exclusion criteria

1. People had no history of bisphosphonate allergy.

2. People were bed bidden.

3. Their blood calcium level was lower than the normal limit with impairment of renal function.

Every case was screened by blood test for obtaining the data of resorptive markers as the baseline control. The blood test was repeated every three months to the sixth month.

Schedule of Study

Parameter	Baseline visit	Visit 2 (end of month 3)	Visit 3 (end of month 6)
Diagnosis	x		
Physical examination	x	x	x
Biochemistry test*	x		x
Hematology test**	x		x
Serum bone marker (CTx)	x		x
Safety evaluation		x	x
Ibandronate (Bonviva®)	x	x	x

Table 1. Baseline characteristic

Gender	
Female, n (%)	79 (98.8)
Male, n (%)	1 (1.2)
Age, mean ± SD	61.6 (10.3)
Weight, mean ± SD	51.76 (8.26)
Height (cm), mean ± SD	1.53 (0.05)
BMI, mean ± SD	22.10 (3.51)
Menopausal history	
Reach menopausal, n (%)	75 (93.75)
Not reach menopausal, n (%)	4 (5)
Not applicable (male), n (%)	1 (1.25)

Table 2. Change of bone resorption marker (CTx)

Parameter	Mean (SD)
Baseline CTx (n = 78)	0.486 ± 0.298
End of month 6 (n = 70)	0.156 ± 0.166
Absolute CTx reduction (n = 70)	-0.304 ± 0.265
	p < 0.0001*
% CTx reduction (n = 70)	-67.90 ± 42.20

Table 3. Adverse events after study

Event	n (%)
Flu-like symptom	7 (8.75)
Dyspepsia	6 (7.5)
Myalgia	5 (6.25)
Diarrhea	2 (2.5)
Epigastric buming	1 (1.25)

One Ibandronate tablet of 150 mg per month had to be taken before meal at least one hour ahead with one glass of plain water only. After taking this medicine, the lying posture on bed was prohibited.

Results

The efficacy of Ibandronate could suppress the bone resorption as CTx or BetacrossLap increased. CTx was 67.9% when it was checked at the sixth month. The mean of this marker at the end of the study was 0.156 nanogram per milliliter that was below the normal value (0.312 nanogram/milliliter).

The adverse events interpreted by the following data mainly showed the symptoms of flu-like and dyspepsia (Table 3).

The common adverse events during the intake of Ibandronate were shown below (Table 3). Three cases were withdrawn due to some accidental events: spinal cord tumor, hip fracture and vertigo

Discussion

The efficacy of Ibandronate was valuable as it did not extremely suppress bone resorption that could interfere the bone function. It suppressed bone resorption approximately 67 percent after the 6-month treatment. The principle of using bisphosphonate was to adjust the dose for obtaining the optimal bone condition resulted from the values of CTx bone resorption marker. If this bone marker value was too low, bone fatigue and microcrack could not be prevented. Tanko[3] mentioned that the agents, such as estrogen, calcitonin, estrogen plus progesterone and bisphosphonate, are the most potent antiresorption required for careful application when adjusting them. The power of antiresorptive agents suppressed the bone resorption state into the optimal level.

Mashiba et al[4] showed that the prolonged use of bisphosphonate caused micro damage in dog bones. Stepan et al[5] reported that the micro damage was accumulated after using the bisphosphonate in postmenopausal women. This study supported that bone damage was assuredly increased by prolonged bisphosphonate intake. Thus, the length of using bisphosphonate should be as short as possible while Ibandronate did not severely suppress bone. Its CTx bone marker was only beyond the physiologic level of CTx (0.293-0.328 nanogram/milliliter)[6]. After controlling bone resorption through pharmaceutical intervention, both enhancing bone formation and decreasing the risk factors are the additional steps that certainly lead to success of the osteoporosis treatment.

The side effects of Ibandronate were the same as the ones of other bisphosphonate: flu-like symptoms and dyspepsia; this study showed no esophageal ulcers.

Acknowledgements

The authors would like to thank not only Roche Company for supporting the project on the commemoration of His Majesty the King's 80th birthday but also the Roche personnel: Yuwadee Jaruthumporn, Pichet Kamolrungsantisuk and Patchara Pamornpiboon who collected all data from each center.

Reference

1. Fleisch H. Basic biology of bisphosphonates. In: Marcus R, Feldman D, Kelsey J. editors. Osteoporosis. 2nd ed. San Diego, CA: Academic Press; 2001: 449-70.
2. World Health Organization risk and its assessment of fracture application to screening for postmenopausal women. WHO Technical Report Series 843.Geneva: WHO; 1994.
3. Tanko LB, Christiansen C. Hormone replacement therapy. In: Genazzani AR, editor. Postmenopausal osteoporosis. London: Taylor & Francis; 2006: 185-92.
4. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res 2000; 15: 613-20.
5. Stepan JJ, Burr DB, Pavo I, Sipos A, Michalska D, Li J, et al. Low bone mineral density is associated with bone microdamage accumulation in post-menopausal women with osteoporosis. Bone 2007; 41: 378-85.
6. Bunyaratavej N, Kitimanon N, Boonthitikul S. Study of the level of biochemical bone markers: NMID osteocalcin and bone resorptive marker (beta CTx) in Thai women. J Med Assoc Thai 2001; 84 (Suppl 2): S560-5.

การศึกษาผลของยา ibandronate ในการลดการสลายตัวของกระดูกและความปลอดภัยของยาจาก 6 โรงพยาบาล

ณรงค์ บุณยะรัตเวช, วิวัฒน์ วจนะวิศิษฐ, ประยุกต์ พัววิไล, ทัศนีย์ กิตอำนวยพงษ์, นิพัธ กิตติมานนท์, ทรงเกียรติ์ เล็กตระกูล

รายงานการศึกษาความปลอดภัยและประสิทธิภาพของยา ibandronate 150 มิลลิกรัม เดือนละครั้ง ต่อเนื่องกัน 6 เดือนโดยใช้ bone marker ชนิด CTxเป็นหลักในการติดตามและประเมินผลการลดการสลายตัวของกระดูกในผู้ป่วยอาสาสมัคร 80 ราย จากโรงพยาบาล 6 แห่งได้แก่ โรงพยาบาลศิริราช, โรงพยาบาลรามาธิบดี, โรงพยาบาลเลิดสิน, โรงพยาบาลราชวิถี, โรงพยาบาลพุทธชินราช และโรงพยาบาลสรรพสิทธิประสงค์ พบผลข้างเคียงของยาไม่รุนแรง อาการที่พบมากได้แก่ อาการเหมือนเป็นไข้หวัด และอาหารไม่ย่อย ซึ่งพบเช่นเดียวกันกับยากลุ่มบิสฟอสฟอเนตที่ใช้ในปัจจุบัน อาการหลอดอาหารเป็นแผลไม่พบ ผลข้างเคียงที่รุนแรงไม่ปรากฏแต่มีเพียงสองรายที่จำหน่ายออกจากโครงการเนื่องจากมีโรคที่ไม่เกี่ยวกับยา ได้แก่ เนื้องอกไขสันหลัง และกระดูกสะโพกหักหลังเข้าโครงการได้เพียงหนึ่งเดือน และจากการติดตามผลด้วย CTx ด้านการห้ามการสลายตัวของกระดูก พบว่าหลังหกเดือนสภาพดังกล่าวลดลง ร้อยละ 67.9 โดยค่าเฉลี่ยของ CTx ก่อนได้รับยา 0.486 $\pm$ 0.298 นาโนกรัม/มิลลิลิตร หลังหกเดือนค่าเฉลี่ยลดลงเหลือ 0.156 $\pm$ 0.166 นาโนกรัม/มิลลิลิตร ซึ่งแสดงว่าตัวยาสามารถลดการสลายตัวของกระดูกได้ดี และค่าของ CTx ลดลงต่ำกว่า ค่าปกติไม่มาก (ค่าปกติของ CTx = 0.293-0.328 นาโนกรัม/มิลลิลิตร) นับว่าเป็นผลดีที่ยาไม่กดการทำงานของเซลล์กระดูกมากเกินไป