Clin Pediatr Endocrinol 2006; **15**(3), 101-107

Original Article

Beneficial Effect of Oral Bisphosphonate Treatment on Bone Loss Induced by Chronic Administration of Furosemide without Alteration of Its Administration and Urinary Calcium Loss

Takuo Kubota[1], Noriyuki Namba[1, 2], Shunji Kurotobi[1], Shigetoyo Kogaki[1], Haruhiko Hirai[1], Taichi Kitaoka[1], Shigeo Nakajima[1] and Keiichi Ozono[1]

[1]*Department of Pediatrics, Osaka University Graduate School of Medicine, Osaka, Japan*

[2]*The First Department of Oral and Maxillofacial Surgery, Osaka University Graduate School of Dentistry, Osaka, Japan*

Abstract. Bisphosphonate is widely used to treat patients with primary and secondary osteoporosis. The chronic administration of furosemide is considered a risk factor for osteoporosis mainly due to the increased urinary excretion of calcium, leading to a long-term negative balance of calcium. We describe two patients with mild heart failure who took furosemide for more than 5 yr and developed hyperparathyroidism and lumbago associated with low bone mineral density. Their serum levels of intact parathyroid hormone and bone mineral density (BMD) of the lumbar spine (L2-L4) were 180.8 and 144.3 pg/ml, and 71% and 80% of the mean of healthy women, respectively. The oral administration of alendronate or risedronate was effective for lumbago and improved BMD, although the urinary excretion of calcium and hyperparathyroidism were not changed. For the medical treatment of lumbago and decreased bone mass secondary to the long-term administration of furosemide, bisphosphonate is proposed when the dose of furosemide cannot be reduced. However, it may be important to give sufficient calcium and vitamin D to patients to improve secondary hyperparathyroidism.

Key word: furosemide, bone mineral density, bisphosphonate, hyperparathyroidism, hypercalciuria

Introduction

Calcium is an essential nutrient for bone and mineral metabolism (1). A positive balance of calcium is required for skeletal development and bone mineral accrual. In Japan, daily calcium intake tends to be lower than the recommended amount, 600 mg for adults (2). Vitamin D is also indispensable to achieve normal skeletal development mainly due to its facilitation of calcium absorption in the intestine, and vitamin D deficiency leads to secondary hyperparathyroidism and rickets or osteomalacia. Vitamin D deficiency is quite common in developing countries and has reemerged in developed countries (3, 4). We have previously reported seven Japanese infant and early childhood cases of vitamin D deficiency (5).

Furosemide belongs to a type of loop diuretics and is often used to increase urine output in the treatment of heart failure and renal failure (6, 7).

Received: February 15, 2006
Accepted: April 25, 2006
Correspondence: Professor Keiichi Ozono, Department of Pediatrics, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita City, Osaka 565-0871, Japan
E-mail: keioz@ped.med.osaka-u.ac.jp

Increased urine output is associated with increased loss of calcium. As a result of hypercalciuria, calcification of the kidney and urinary tract stones may occur. Many reports have described decreased bone mineral density (BMD) in patients treated with furosemide for a long time (8, 9). Thiazide is calcium-retention-type diuretic, but it is weaker than furosemide in urinary effect. In addition, diabetes mellitus may be caused by treatment with thiazide (10). Thus, furosemide is more often used and it is sometimes difficult to substitute thiazide for furosemide.

Bisphosphonate is now considered the first line treatment for primary and secondary osteoporosis (11–14). Bisphosphonate is administered to patients with osteoporosis secondary to glucocorticoid, rheumatoid arthritis, and osteogenesis imperfecta etc. (15, 16). Bisphosphonate containing nitrogen functions directly in osteoclasts and significantly suppresses bone resorption (17). In this report, we describe two patients with heart failure who received long-term furosemide therapy. Both patients showed elevated levels of parathyroid hormone (PTH) and low BMD. Treatment with bisphosphonate successfully increased BMD without obvious side effects, although hypercalciuria and secondary hyperparathyroidism continued.

Case Reports

Case 1

Patient 1 was a 21-yr-old woman. She underwent a curative operation for pulmonary stenosis at the age of 5 and took furosemide for more than 10 yr. She was referred to pediatric endocrinologists with lumbago at the age of 21. She has walked for 20 min every day, although she suffers from mild heart failure. She has a regular menstruation cycle and has reached adult height. At the start of treatment, her height and weight were 149.8 cm and 51.6 kg, respectively (BMI was 23.0). She had a systolic heart murmur and pretibial edema, and her liver was enlarged 1 cm below the right costal margin in the midclavicular line. Her blood pressure was within the normal range. Laboratory data showed that human atrial natriuretic hormone (hANP) and B-type natriuretic hormone (BNP) levels were elevated as a heart failure marker (Table 1). Serum levels of calcium, phosphate and alkaline phosphatase (ALP) were within the normal range, 8.8 mg/dl, 3.4 mg/dl and 181 U/l, respectively. Blood cell count and liver and kidney functions were normal. Urinary calcium was increased judging from 0.71 of urinary calcium/creatinine (Ca/Cr). The ratio of maximal renal tubular reabsorption to the glomerular filtration rate (TmP/GFR) was not reduced. Dual-energy X-ray absorptiometry (DXA) with Lunar DPX-L densitometer model detected low BMD of the lumbar spine (L2-L4), 0.795 g/cm^2. Since the BMD was 71% of the young adult mean (YAM) and no fragility fracture was found, a diagnosis of decreased bone mass was made, and the oral administration of 5 mg of alendronate daily was started. Lumbago disappeared two months after treatment. The serum level of calcium, 8.8 mg/dl, in the eleven months from the start of treatment with alendronate, did not fall below the normal range (8.4–10.0 mg/dl).

With regard to other laboratory data, which were obtained eleven months after treatment with alendronate, the serum level of intact parathyroid hormone (PTH) was elevated to 180.0 pg/ml; the 25-hydroxyvitamin D (25OHD) level was relatively low, 15.8 ng/ml; and the 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) level was elevated, 120 pg/ml (Table 1). The urinary excretion of calcium per day increased to 6.2 mg/kg/day. On the other hand, calcium intake was calculated as 390 mg per day, suggesting a negative balance of calcium because the calcium absorption rate is usually less than 50%. Vitamin D intake was calculated as 136 IU per day. In the analyses of biochemical markers of bone turnover, urinary deoxypyridinoline (DPD) level was elevated, 10.1 nmol/mmolCr, while urinary

Table 1 Patient data

	Patient 1	Patient 2
Ca (8.4–10.0 mg/dl)	8.8	9.4
IP (2.9–4.8 mg/dl)	3.4	4.4
ALP (69–185 U/l)	181	125
Intact-PTH (10–60 pg/ml)	180.8*	144.3
$1,25(OH)_2D$ (20–60 pg/ml)	120*	65
25OHD (9.0–33.9 ng/ml)	15.8*	16.0
BAP (13.0–33.9 U/l)	NA	56.9
Osteocalcin (2.9–12.3 ng/ml)	10.9*	16.8
hANP (0–43 pg/ml)	37.0	116
BNP (0–18.4 pg/ml)	31.0	114
Urinary Ca/Cr (<0.20)	0.71	0.31
Urinary Ca (<4 mg/kg/day)	6.2*	1.46
TmP/GFR (2.3–4.3 mg/dl)	3.0	4.7
Urinary DPD (2.8–7.6 nmol/mmolCr)	10.1*	10.1
Urinary NTx (<55 nmolBCE/mmolCr)	46.7*	87.0
L2-L4 BMD (g/cm^2) (% of the mean**)	0.795 (71)	0.923 (80)

The reference ranges in adults are shown in parentheses. *Levels 11 mo after treatment with bisphosphonate. **The young adult mean (YAM) was adopted for Patient 1, and the mean for same-age healthy girls for Patient 2 (19). NA, not available.

NTx and serum osteocalcin levels were normal, 46.7 nmolBCE/mmolCr and 10.9 ng/ml, respectively. Ultrasonography showed no hyperechoic lesion in the kidneys.

Alendronate and subsequent risedronate increased the bone mineral content of L2-L4 (Fig. 1). However, urinary Ca/Cr showed significant variance from 0.03 to 1.19, and no persistent decrease in urinary calcium was observed during bisphosphonate therapy for two years. Increased levels of PTH were maintained between 135 and 244.9 pg/ml during the therapy. We tried to replace furosemide with thiazide, but this was discontinued because of increased complaints of fatigue.

Case 2

Patient 2 was a 17-yr-old girl with restrictive cardiomyopathy and pulmonary hypertension. She took 60 mg furosemide daily for 5 yr. She was also referred to pediatric endocrinologists with lumbago at the age of 17. She went out for an hour every three days, although she suffers from mild heart failure, and her menstruation is regular. At the first consultation, her height and weight were 152.5 cm and 45.1 kg, respectively (BMI was 19.4). The liver was not palpable and no edema was detected.

Laboratory tests showed elevated levels of hANP and BNP (Table 1). Before treatment with alendronate, serum levels of calcium, phosphate and ALP were within the normal range, 9.4 mg/dl, 4.4 mg/dl and 125 U/l, respectively. The serum level of PTH was elevated at 144.3 pg/ml. Blood cell count and liver and kidney functions were normal. The 25OHD level was relatively low, 16.0 ng/ml, while the $1,25(OH)_2D$ level was slightly elevated, 65 pg/ml. Urinary calcium was slightly elevated judging from 0.31 of urinary Ca/Cr, although the urinary excretion of calcium per day was not increased, 1.5 mg/kg/day. Calcium intake was calculated as 300 mg per day,

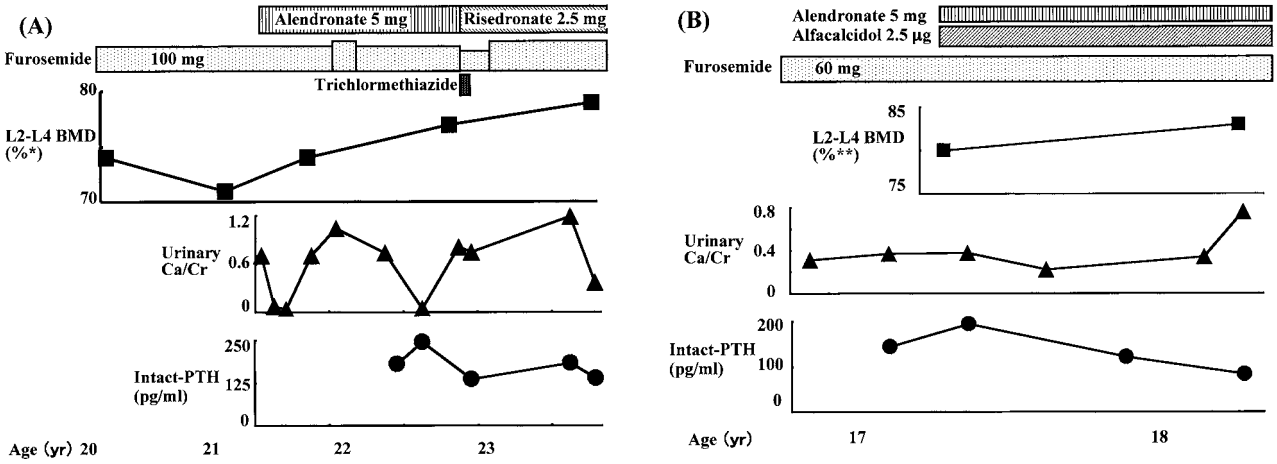

Fig. 1 Changes in BMD (L2-L4), urinary Ca/Cr, and PTH during treatment with bisphosphonates. In Patient 1 (A), alendronate and subsequent risedronate increased the BMD of L2-L4. However, decreased urinary calcium was not observed and increased levels of PTH were maintained during bisphosphonate therapy, although urinary Ca/Cr showed significant variance. The replacement of furosemide with thiazide was tried, but was discontinued because of increased complaints of fatigue. In Patient (B), BMD of L2-L4 was increased after treatment with alendronate and alfacalcidol, although its slightly increased urinary Ca/Cr and elevated levels of PTH were maintained during therapy. *Percentage of the young adult mean (YAM). **Percentage of the mean in same-age healthy girls (19).

suggesting a negative balance of calcium because the calcium absorption rate is usually less than 50%. Vitamin D intake was calculated as 160 IU per day. Urinary DPD and NTx levels, markers of bone resorption, were elevated, 10.1 nmol/mmolCr and 87.0 nmolBCE/mmolCr, respectively. Serum bone-specific ALP (BAP) and osteocalcin, markers of bone formation, were also elevated, 56.9 U/l and 16.8 ng/ml, respectively. TmP/GFR was not reduced. DXA detected relatively low BMD of L2-L4, 0.923 g/cm^2. Since her BMD was 80% of the mean in same-aged healthy girls and she suffered from lumbago, oral alendronate, 5 mg daily, and alfacalcidol, 2.5 μg daily, were started (18). Lumbago disappeared two months after the treatment and the BMD of L2-L4 was increased. However, elevated levels of PTH were maintained between 84.2 and 194.8 pg/ml during therapy. The serum level of calcium, 8.8 mg/dl, in the two months from the start of treatment with alendronate did not fall below the normal range.

Discussion

Treatment with furosemide is recognized as a risk factor of osteoporosis due to increased excretion of calcium (7). Indeed, Patient 1 showed hypercalciuria and a low intake of calcium. Patient 2 showed an increased level of urinary Ca/Cr, but the total amount of daily calcium excretion was not remarkable. This was probably because of incomplete collection of urine judging from the falsely low levels of creatinine clearance when Cr excretion levels were considered. Thus, these cases support the previous observation that a long-term negative balance of calcium associated with furosemide treatment may lead to secondary hyperparathyroidism and low levels of BMD. Thiazide is a diuretic that affects calcium retention. Thus, the replacement of furosemide with thiazide is an alternative to avoid a negative balance of calcium. However, it is sometimes impossible to change furosemide to thiazide,

partly because furosemide has a stronger effect as a diuretic.

The diagnostic criteria of decreased bone mass in adolescence have not been defined at present. We judged that it was appropriate for the diagnostic criteria of decreased bone mass in adult to be applied to Patient 2 in adolescence (18). BMD was measured by DXA with a Lunar DPX-L densitometer model in both patients, and therefore standard reference values of lumbar spine in normal adolescents, measured by the same densitometer, were adopted in Patient 2, although the described subjects were white Mediterranean Spanish adolescents (19). Since BMD of lumbar spine in Patients 1 and 2 were 71% and 80% of the mean in healthy women, respectively, and they had no fragility fracture in spite of lumbago, a diagnosis of decreased bone mass was made.

The recommended daily calcium intake is 600 mg in Japan (20). The intake of calcium was very low in both of our patients. A low intake of calcium was a factor in the deterioration of hyperparathyroidism and low BMD of these patients (21). As it is another deterioration factor in hyperparathyroidism and low BMD, we should be aware of the vitamin D status of these patients. The levels of 25OHD were 15.8 and 16.0 ng/ml, respectively. These levels do not indicate a vitamin D-deficient status, but a vitamin D-insufficient status, which may cause hyperparathyroidism and rickets in infancy and early childhood as we and others have reported (5, 22). However, our patients were older and vitamin D insufficiency at these levels would have been unlikely to have been the main cause of hyperparathyroidism and low BMD.

Immobilization is another factor in increased calcium loss and low BMD, but both of our patients walked around every day or every three days, respectively. Probably the activities of our patients were not major sources of increased calcium loss and low BMD. Congestive heart failure and cyanosis are also harmful to bone health, but our patients did not suffer from severe heart failure or a low saturation level of oxygen (23). In addition, hypogonadism in late adolescence is associated with low BMD (24). Both of our patients had regular menstruation cycles, although their serum levels of E2, LH and FSH were unclear. It is unlikely that their gonad function contributed to their low BMD.

Bisphosphonate increased BMD in spite of high levels of urinary Ca/Cr. Bisphosphonate inhibits bone resorption induced mainly by hyperparathyroidism. Large control studies have shown that alendronate and risedronate are effective at preventing bone loss in patients with primary and secondary hyperparathyroidism (12). An observational follow-up showed that alendronate was well tolerated over a 10-yr period for osteoporosis in postmenopausal women (25). However, it was reported that severe suppression of bone turnover and non-spinal fractures developed during long-term alendronate therapy (26). Bisphosphonates should be used carefully, with measurement of BMD and biochemical markers of bone turnover. Although a consensus on the time to discontinue bisphosphonates has not currently been achieved, we are planning to discontinue them, once BMD reaches 100% of the mean of healthy women or before excessive suppression of bone turnover is observed.

Besides, intravenous administration of bisphosphonates often leads to a symptomatic or symptomatic hypocalcemia. It was reported that vitamin D deficiency resulted in severe hypocalcemia, coupled with an intravenous bisphosphonate (27). However, oral administration of alendronate is seldom related to hypocalcemia (28). Neither of our patients had developed hypocalcemia at several months after the initiation of oral alendronate, although the levels of 25OHD were vitamin D-insufficient statuses.

Furosemide inhibits transcellular NaCl reabsorption in the thick ascending loop of Henle,

and then suppresses the transepithelial potential difference and calcium, magnesium and sodium reabsorption. Since the target of furosemide in the kidney is not affected by bisphosphonate, it is highly likely that hypercalciuria continues after the administration of bisphosphonate. However, it is necessary to examine whether the long-term of administration of bisphosphonate ameliorates hypercalciuria. Although bisphosphonate could not reduce the excretion of calcium in urine, it increased BMD in our patients, probably due to the inhibition of bone resorption.

In conclusion, two patients with mild heart failure who had received long-term furosemide therapy developed secondary hyperparathyroidism and low BMD. Treatment with bisphosphonate successfully increased BMD without obvious side-effects, although hypercalciuria and secondary hyperparathyroidism remained.

References

1. Abrams SA, Atkinson SA. Calcium, magnesium, phosphorus and vitamin D fortification of complementary foods. J Nutr 2003;133:2994S–9S.
2. Iso H, Date C, Noda H, Yoshimura T, Tamakoshi A; JACC Study Group. Frequency of food intake and estimated nutrient intake among men and women: the JACC Study. J Epidemiol 2005;15(Suppl 1):S24–S42.
3. Pettifor JM. Nutritional rickets: deficiency of vitamin D, calcium, or both? Am J Clin Nutr 2004;80(Suppl):1725S–9S.
4. Fitzpatrick S, Sheard NF, Clark NG, Ritter ML. Vitamin D-deficient rickets: a multifactorial disease. Nutr Rev 2000;58:218–22.
5. Kubota T, Kotani T, Miyoshi Y, Santo Y, Hirai H, Namba N, *et al.* A spectrum of clinical presentations in seven Japanese patients with vitamin D deficiency. Clin Pediatr Endocrinol 2006;15:23–8.
6. Prandota J. Clinical pharmacology of furosemide in children: a supplement. Am J Ther 2001;8:275–89.
7. Constant J. Pearls and pitfalls in the use and abuse of diuretics for chronic congestive heart failure. Cardiology 1999;92:156–61.
8. Stein MS, Scherer SC, Walton SL, Gilbert RE, Ebeling PR, Flicker L, *et al.* Risk factors for secondary hyperparathyroidism in a nursing home population Clin Endocrinol (Oxf) 1996;44:375–83.
9. Venkataraman PS, Han BK, Tsang RC, Daugherty CC. Secondary hyperparathyroidism and bone disease in infants receiving long-term furosemide therapy. Am J Dis Child 1983;137:1157–61.
10. Messerli FH, Grossman E. Therapeutic controversies in hypertension. Semin Nephrol 2005;25:227–35.
11. Rosen CJ. Clinical practice. Postmenopausal osteoporosis. N Engl J Med 2005;353:595–603.
12. Delmas PD. The use of bisphosphonates in the treatment of osteoporosis. Curr Opin Rheumatol 2005;17:462–6.
13. Raisz LG. Clinical practice. Screening for osteoporosis. N Engl J Med 2005;353:164–71.
14. Geusens PP. Review of guidelines for testing and treatment of osteoporosis. Curr Osteoporos Rep 2003;1:59–65.
15. Rauch F, Glorieux FH. Bisphosphonate treatment in osteogenesis imperfecta: which drug, for whom, for how long? Ann Med 2005;37:295–302.
16. Maricic M. Glucocorticoid-induced osteoporosis: treatment options and guidelines. Curr Osteoporos Rep 2005;3:25–9.
17. Rogers MJ. New insights into the molecular mechanisms of action of bisphosphonates. Curr Pharm Des 2003;9:2643–58.
18. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, *et al.* Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 2001;19:331–7.
19. Rio LD, Carrascosa A, Pons F, Gusinye M, Yeste D, Domenech FM. Bone mineral density of the lumbar spine in white Mediterranean Spanish children and adolescents: Changes related to age, sex, and puberty. Pediatr Res1994;35:362–4.
20. Hirota T, Nara M, Ohguri M, Manago E, Horota K. Effect of diet and lifestyle on bone mass in Asian young women. Am J Clin Nutr 1992;55:1168–73.
21. South-Paul JE. Osteoporosis: part I. Evaluation and assessment. Am Fam Physician 2001;63:897–

904, 908.
22. Nakamura K, Ueno K, Nishiwaki T, Okuda Y, Saito T, Tsuchiya Y, *et al.* Nutrition, mild hyperparathyroidism, and bone mineral density in young Japanese women. Am J Clin Nutr 2005;82:1127–33.
23. Nishio K, Mukae S, Aoki S, Itoh S, Konno N, Ozawa K, *et al.* Congestive heart failure is associated with the rate of bone loss. J Intern Med 2003;253:439–46.
24. Takahashi Y, Minamitani K, Kobayashi Y, Minagawa M, Yasuda T, Niimi H. Spinal and femoral bone mass accumulation during normal adolescence: comparison with female patients with sexual precocity and with hypogonadism. J Clin Endocrinol Metab 1996;81:1248–53.
25. Bone HG, Hosking D, Devogelaer J-P, Tucci JR, Emkey RD, Tonino RP, *et al.* Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189–99.
26. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CYC. Severely suppressed bone turnover: A potential complication of alendronate therapy. J Clin Endocrinol Metab 2005;90:1294–301.
27. Rossen CJ, Brown S. Severe hypocalcemia after intravenous bisphosphonate therapy in occult vitamin D deficiency. N Engl J Med 2003;348:1503–4.
28. Biswas PN, Wilton LV, Shakir SAW. Pharmacovigilance study of alendronate in England. Osteoporos Int 2003;14:507–14.