

1-34 PTH Could Reverse Impaired Bone Mineralization Induced By the Overdose of Bisphosphonate

Kyeong Hye Park, Kwang Joon Kim¹, Han Seok Choi², Kyoung Min Kim, Eun Young Lee, Seonhui Han³, Hyun Sil Kim³, Daham Kim, Hannah Seok, Eun Yeong Choe, Yumie Rhee, Sung-Kil Lim

Department of Internal Medicine, Yonsei University College of Medicine, Seoul; Executive Healthcare Clinic¹, Yonsei University Health System, Seoul; Division of Endocrinology and Metabolism², Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang; Department of Oral Pathology³, Yonsei University College of Dentistry, Seoul, Korea

Bisphosphonates are the mainstay of osteoporosis treatment. Despite the fact that bisphosphonates have a relatively good safety record and are tolerated well by the majority of patients, serious adverse events have been associated with their use. A 41-year-old man had been diagnosed with osteoporosis and had taken etidronate 200 mg/day daily for 2 years due to the judgmental error. He was referred for the management of refractory bone pain and generalized muscle ache. Serum calcium, phosphate, 25-hydroxyvitamin D (25(OH)D), and immunoreactive parathyroid hormone (iPTH) were within normal range. Plain X-ray showed multiple fractures. Whole body bone scan confirmed multiple sites of increased bone uptakes. Tetracycline-labeled bone biopsy showed typical findings of osteomalacia. He was diagnosed with iatrogenic, etidronate-induced osteomalacia. The patient received daily parathyroid hormone (PTH) injection for 18 months. PTH effectively reverses impaired bone mineralization caused by etidronate misuse. Currently, he is doing well without bone pain. Bone mineral density significantly increased, and the increased bone uptake was almost normalized after 18 months. This case seems to suggest that human PTH (1-34) therapy, possibly in association with calcium and vitamin D, is associated with important clinical improvements in patients with impaired bone mineralization due to the side effect of bisphosphonate. (*Endocrinol Metab* 27:247-250, 2012)

Key Words: Etidronate, Iatrogenic osteomalacia, Parathyroid hormone

INTRODUCTION

Bisphosphonates are the mainstay of osteoporosis treatment. The efficacy of bisphosphonates has been well demonstrated [1-3]. Though bisphosphonates have a relatively good safety record and are tolerated well by the majority of patients, serious adverse events have been associated with their use. Hence, some unadvertised aspects of bisphosphonates, including their long half-life and their effects on bone physiology need to be addressed. Furthermore, clinicians need to know how to treat a patient who has experienced side effect of this drug. Recently, many studies have emphasized a long-term side effect of bisphosphonate [4-6]. It has been reported that etidronate, one of the first generation of bisphosphonate medication rarely used now, may lead impairment of bone mineralization and subsequent drug-induced osteomalacia [6-8].

We report a case of a patient who developed osteomalacia because of etidronate misuse and was treated effectively by using parathyroid hormone (PTH), an anabolic agent.

CASE REPORT

A 41-year-old man with a history of cerebral palsy presented with a 1-year history of proximal muscle weakness and generalized bone pain. The symptom of general pain began 1 year ago, especially at the hip and the leg. The pain progressively worsened, and for the past 3 months, the pain interfered with the patient's sleep. The patient had no history of alcohol, smoking, or hypertension. The patient was previously diagnosed with cerebral palsy, and used wheelchair to move. The patient was diagnosed with osteoporosis at another hospital 3 years ago and since then took eti-

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Corresponding author: Sung-Kil Lim

Division of Endocrinology, Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea
Tel: +82-2-2228-1983, Fax: +82-2-393-6884, E-mail: lsk@yuhs.ac

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dronate disodium (Dinol, Chodang Pharmaceuticals, Seoul, Korea) 200 mg/day daily for 2 years without interval. The patient discontinued the medication 1 year ago. Whole-body bone scan (WBBS) and magnetic resonance imaging (MRI) were performed in another hospital. WBBS showed increased bone remodeling, and MRI of the lower extremities suggested osteoid osteoma at the right distal fibula. However, bone biopsy revealed no malignancy. There was no history of use of steroid, oriental medicine, or other health products. Family history was negative for specific disease.

A review of system of the patient upon the visit revealed general fatigue, as well as pain at the hip and both lower extremities. There was tenderness at cervical spine, lumbar spine, bilateral tibia, and bilateral fibula. Chemistry showed increased alkaline phosphatase (487 IU/L), but was otherwise normal (calcium, 9.1 mg/dL; phosphorus, 4.2 mg/dL; BUN/creatinine, 16.3/0.95 mg/dL; uric acid, 4.7 mg/dL; protein/albumin, 6.9/4.7 mg/dL; Na/K/Cl/tCO₂, 143/4.2/107/25 mmol/L). The results of blood tests were as follows: PTH 15.48 pg/mL (10-57), PTH-related peptide < 1.1, 25-hydroxy-vitamin D (25(OH)D) 21.7 ng/mL (9-37.6), osteocalcin 1954 ng/mL (5.8-33.8). Serum C-terminal telopeptide of collagen type I (CTX) was increased to 2.080 ng/mL (> 0.584). All serum tumor markers were within normal range. The 24-hour urine test revealed a normal tubular reabsorption of phosphorus (TRP = phosphate clearance/creatinine clearance) of 95%.

The dual energy X-ray absorptiometry (DEXA) suggested osteopenia, with T-score of lumbar spine and femur -2.0 and -1.6, respectively. WBBS showed multiple sites with increased uptake, includ-

ing bilateral rib, cervical spine, lumbar spine, bilateral femur, right fibula, and right sacrum (Fig. 1).

Including the above findings, there were no evidence of malignancy and other causes of osteomalacia, and the patient was suspected with metabolic bone disease; therefore, tetracycline double labeling was planned, but since the patient could not wait 3 weeks due to severe pain, single labeling bone biopsy was performed at the iliac crest in September 16th, 2009. The findings of bone biopsy were consistent with osteomalacia (Fig. 2). After combining the above findings, the patient was ultimately diagnosed with osteomalacia due to etidronate misuse. We first prescribed (Cal-D-vita, Bayer Korea, Seoul, Korea) (calcium carbonate 1,500 mg and cholecalciferol 400 IU) to supplement calcium and vitamin D; however, it was replaced by Calico (Hanmi Pharmaceuticals, Seoul, Korea) (calcitriol 1 µg) for its strong potency and quick response.

In addition, 20 µg of Forsteo (Eli Lilly and Company, Indianapolis, IN, USA) (teriparatide-hPTH [1-34]) was administered subcutaneously to normalize bone mineralization. After 6 months of use, the patient stated that muscle weakness and bone pain has markedly improved. A WBBS performed in March 2010 showed significant decrease in multiple bone remodeling, and both serum CTx and osteocalcin were elevated (Fig. 3). In February 2011, after 18

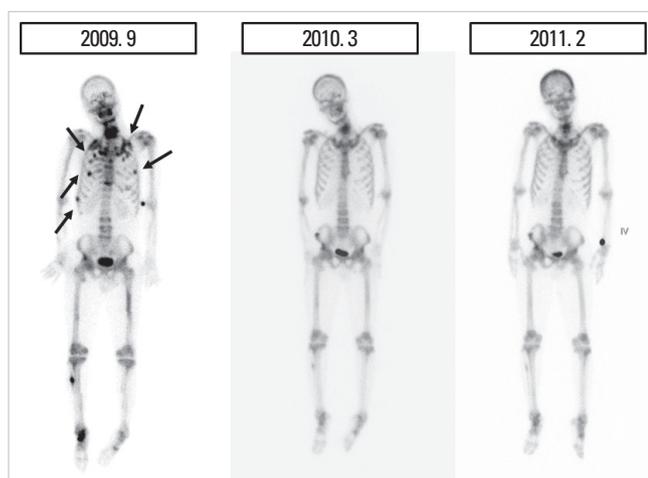


Fig. 1. Whole body bone scan. Administer intermittent human parathyroid hormone (1-34) for 6 and 18 months, increased uptake of multiple bone site was completely resolved.

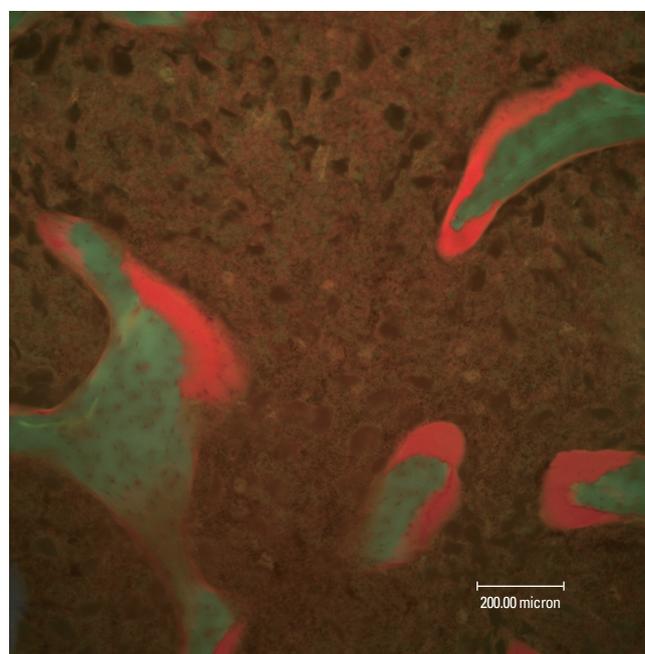


Fig. 2. Tetracycline labeled bone biopsy. The findings of single tetracycline labeled bone biopsy was consistent with osteomalacia (mean osteoid thickness, 68.56 µm; trabecular bone volume, 12.43%; osteoid volume, 32.52%; osteoid surface, 51.58%).

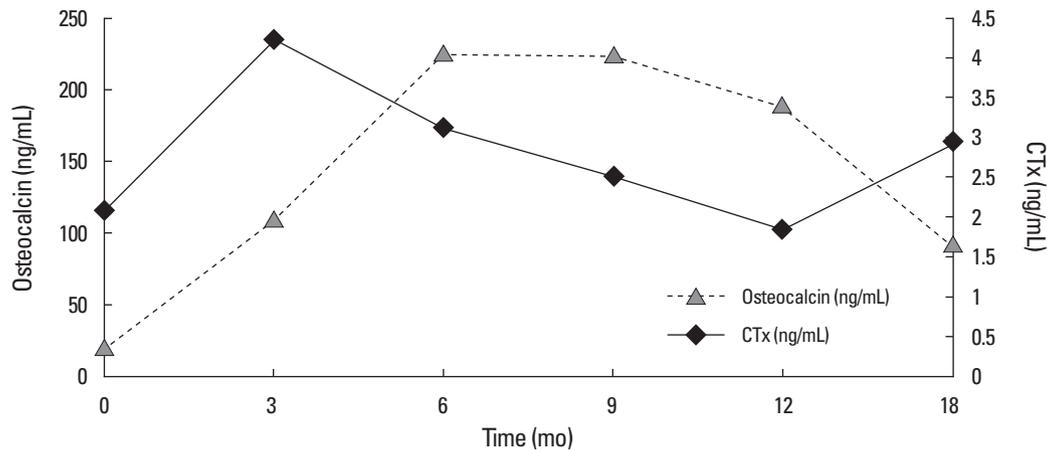


Fig. 3. Changes of serum bone turn over markers. This graph shows the changes of serum bone turn over markers (c-terminal telopeptide and osteocalcin) during follow-up. CTx, collagen type I.

months of Forsteo use, DEXA showed significant increase in bone mineral density (T-score of lumbar spine from -2.0 to 0.5, femur from -1.6 to -0.4), and WBBS showed multiple abnormal uptake was almost normalized. He is currently followed up as an outpatient without any bone pain.

DISCUSSION

Etidronate, analogues of inorganic pyrophosphate and a natural inhibitor of bone mineralization, strongly binds to hydroxyapatite, a component of bone mineral, thus inhibiting resorption and potentially affecting mineralization as well [9]. Due to its lesser potency of osteoclast killing, very high dose of etidronate is required for treatment of osteoporosis. The recommended dose is 400 mg/day for 2 weeks every 3 months [1]. However, continuous oral treatment with high doses of etidronate may lead to impairment of bone mineralization (osteomalacia) and the cessation of bone remodeling. Hence, etidronate treatment needs a medication-free-period to prevent impaired mineralization.

In our patient, it is likely that the abnormal bone mineralization was caused by etidronate misuse. This patient had kept taking etidronate 200 mg/day for 2 years without interval (total dose of etidronate was 146,000 mg). The serum calcium, phosphorus, 25(OH) D and PTH level were within normal range. Furthermore, there was no evidence of any malignancy, hyperparathyroidism, renal phosphorus wasting, renal disease such as renal tubular acidosis or chronic kidney disease, or vitamin D deficiency. Baseline alkaline phosphatase level was elevated but decreased after calcium and vi-

tamin D replacement. Based on a combination of clinical features, laboratory results, radiological findings, and bone histomorphometry [10], we could diagnose him as osteomalacia.

Mineralization defect caused by bisphosphonate could be reversed after drug cessation; however, as etidronate is a first-generation bisphosphonate, it may remain in the bone for several years, or even permanently [11]. The patient still suffered from bone pain with multiple rib fractures even 1 year after cessation of etidronate despite adequate serum level of vitamin D. Therefore, treatment options in addition to spontaneous recovery with vitamin D and calcium replacement should be considered.

In this patient, bone turnover was extremely suppressed and the function of osteoblast, as well as osteoclast, was severely impaired. We considered intermittent PTH treatment [12] as the next approach because many previous report already showed that it could reverse bisphosphonate-related low bone turnover and some disease with impairment of mineralization [6,13,14]. Recently, Jamal and Hodsmann [15] also suggested that anabolic agents would be a more plausible approach to the management of adynamic bone disease, an example of very low bone turnover state. Furthermore, there was one case report which improved skeletal mineralization effectively by hPTH (1-34) in adult hypophosphatasia characterized by severe impairment of mineralization [6]. Meanwhile, we believe that hPTH (1-34) was not the only responsible agent for reversing the impaired mineralization of bone in this patient, even though it played the main role. Vitamin D supplement also has some limited beneficial effects on differentiation of osteoblast and remineralization [10].

This case indicates that bone that has been treated with bisphos-

phonate is still able to show an anabolic response to intermittent PTH and normalize mineralization. Thus, fortunately, the profound bisphosphonate suppression of bone mineralization is at least partly reversible via using PTH.

요 약

비스포스포네이트는 골다공증 치료의 중심인 약물이다. 비록 상대적으로 좋은 안정성 정보를 가지고 있고 대다수의 환자에서 약물 순응도가 양호하나, 비스포스포네이트 사용은 심각한 부작용을 보이기도 한다. 본 증례는 골다공증으로 진단된 41세 남자 환자로, 일차 진료기관의 판단미숙으로 인해 etidronate를 2년간 매일 200 mg 씩 복용해왔다. 이 환자는 골성 통증 및 전신 근육통이 해결되지 않아 세브란스병원으로 의뢰되었다. 혈청 칼슘, 인, 25-hydroxy-vitamin D 및 부갑상선호르몬 수치는 정상이었다. X-ray상 전신에 다발성 골절이 확인되었고 전신 뼈 스캔검사상에서도 광범위한 방사성 동위원소 흡수가 관찰되었다. Tetracycline으로 표시하여 시행한 골조직검사는 전형적인 골연화증 소견을 보여주었다. 위의 결과들을 종합하여 상기 환자는 etidronate에 의한 골연화증으로 진단되었다. 환자는 진단 후 18개월 동안 매일 부갑상선호르몬 주사(teriparatide) 치료를 받았고 부가적으로 칼슘, 비타민 D를 복용하였다. 환자는 최근까지 외래 추적 관찰 중으로, 골통증 및 전신 상태가 모두 호전되었다. 골밀도는 뚜렷하게 증가하였고 골스캔검사상 보이던 골흡수 증가 소견은 18개월 뒤 정상화되었다. 환자에게 시행된 부갑상선호르몬 치료는 etidronate 오용으로 인한 골무기질화 장애를 효과적으로 회복시켰음을 보여주었다. 본 증례는 부갑상선호르몬 치료에 비스포스포네이트로 인한 골무기질화 장애를 보이는 환자들에서 매우 효과적일 수 있음을 시사하고 있다.

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