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Daily nasal spray of hPTH(1–34) for 3 months increases bone mass in osteoporotic subjects: a pilot study

T. Matsumoto · M. Shiraki · H. Hagino · H. Iinuma · T. Nakamura

Abstract

Introduction Although intermittent parathyroid hormone (PTH) injection can lead to strong anabolic effects on bone, daily subcutaneous injection is a disadvantage for patient acceptance. We have developed a nasal spray formula of parathyroid peptide [hPTH(1–34)] with peak serum hPTH (1–34) concentrations by nasal spray of 1,000 μg similar to those by subcutaneous injections of 20 μg hPTH(1–34).

Methods To determine the clinical efficacy and safety of nasal hPTH(1–34) spray, a randomized, open-labeled clinical trial was conducted in subjects with osteoporosis. Ninety osteoporotic subjects age 52–84 years (mean 66.5 years) were randomly assigned to receive either 250 μg (PTH250, $n=31$), 500 μg (PTH500, $n=30$), or 1,000 μg (PTH1000, $n=29$) of daily nasal hPTH(1–34) spray for 3 months. All received daily supplements of 300 mg calcium and 200 IU vitamin D_3.

Results Daily nasal hPTH(1–34) spray for 3 months increased lumbar bone mineral density (L-BMD) in a dose-dependent manner, and the PTH1000 group showed a 2.4% increase in L-BMD from baseline. Only the 1,000-μg dose produced consistent and statistically significant changes in markers of bone turnover; after 3 months, median serum type I procollagen N-propeptide (PINP) and osteocalcin increased 14.8% and 19.4% from baseline, while urinary type I collagen N-telopeptide (NTX) decreased 16.4%. Seven subjects developed transient hypercalcemia at 3 h after nasal hPTH(1–34) spray, but none of the subjects developed sustained hypercalcemia.

Conclusions These observations demonstrate that nasal hPTH(1–34) spray is safe and well tolerated and can rapidly increase L-BMD. The results warrant further studies to examine its long-term efficacy on bone mass and fractures.

Keywords Anabolic agent · Bone mineral density · Bone turnover markers · Osteoporosis · PTH/PTHrP

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Introduction

The development of parathyroid hormone (PTH) as an anabolic agent to stimulate bone formation has rendered a new modality of treatment for osteoporosis. A large randomized clinical trial in postmenopausal patients with osteoporosis demonstrated that daily subcutaneous injections of 20 μg and 40 μg parathyroid peptide [hPTH(1–34)] increased lumbar bone mineral density (L-BMD) by 9.7% and 13.7%, reduced the risks of vertebral fracture by 65–69%, and suppressed nonvertebral fracture incidence by

53% and 54%, respectively, after only about 21 months of treatment [1]. A smaller study with daily subcutaneous injections of hPTH(1–84) also demonstrated a 7.8% increase in L-BMD within 12 months of treatment [2]. In both of these studies there was an increase in bone resorption markers along with a marked increase in bone formation markers.

Daily subcutaneous injection is a considerable disadvantage for patient acceptance, and it would be preferable for PTH to be delivered in a less invasive way. One of the approaches to this problem is to reduce the frequency of injections, and a weekly injection formula of hPTH(1–34) is under development [3]. Another approach to this problem is to deliver PTH via a less invasive way than subcutaneous injection. To explore the possibility of whether PTH can be delivered safely and effectively via intranasal spray, we developed a nasal spray formula of hPTH(1–34). This formula at a dose of 1,000 μg exhibited a higher C_{max} (364±374 vs. 260±120 pg/ml, means ± SD, n=6) and shorter T_{max} (0.23±0.05 vs. 0.67±0.26 h, means ± SD, n=6) and $T_{1/2}$ (0.50 vs. 1.16 h, median values) compared with subcutaneous injection of 20 μg hPTH(1–34) (unpublished data from phase I study). Compared with subcutaneous hPTH(1–34), intranasal hPTH(1–34) exhibited greater variability in these outcomes.

The present study was undertaken to examine whether a nasal spray formula of hPTH(1–34) can increase BMD and to study the time course of skeletal turnover during the 3 months of treatment.

Subjects and methods

Subjects

We studied 90 subjects (89 women and one man, all Japanese) age 52–84 years (mean 66.5 years) who had osteoporosis, defined as low BMD [<70% or T-score -2.6 of the young adult mean (YAM), <0.708 g/cm², measured by a Hologic QDR], or osteopenia (<80% or T-score -1.7 of the YAM, <0.809 g/cm², measured by a Hologic QDR) with at least one vertebral fracture, according to the criteria of the Japanese Society for Bone and Mineral Research (JSBMR) [4, 5]. Vertebral fractures were assessed by x-ray examination of the vertebrae and were diagnosed according to the criteria of the JSBMR [4]. In brief, vertebral fractures were diagnosed if there was more than a 20% reduction in the middle compared with the anterior or posterior height, or more than a 25% reduction in the anterior compared with the posterior height. Female subjects were at least 3 years after menopause or 60 years or more of age, and the male subject was 84 years of age. Subjects were excluded if they had fractures in any of the lumbar vertebrae L2–L4 or if

they had disorders such as primary or secondary hyperparathyroidism, Cushing's syndrome, gonadal insufficiency, poorly controlled diabetes mellitus or other causes of secondary osteoporosis, or a history or suspicion of active urolithiasis at any time. Subjects were also excluded if they had taken bisphosphonates within 12 months before entry; had taken glucocorticoids, calcitonin, vitamin K, active vitamin D compounds, or hormone replacement therapy within the previous 2 months; had serum calcium (Ca) levels above 10.4 mg/dl (2.6 mmol/l); had serum creatinine levels above 1.3 mg/dl (0.12 mmol/l); had clinically significant hepatic disorders; or had New York Heart Association grade III or IV cardiac failure or clinically significant arrhythmias. The subjects were enrolled at eight centers in Japan. None of the enrolled subjects reported taking bisphosphonates or selective estrogen-receptor modulators (SERMs) at any time. The protocol was approved by the internal human studies review board at each center, and each subject gave informed consent.

Treatment

Subjects were randomly assigned to receive either open-labeled 250 μg (PTH250 group), 500 μg (PTH500 group), or 1,000 μg (PTH1000 group) of nasal hPTH (1–34) spray once a day for 3 months. Randomization was performed by a computerized system. Subjects were supplemented with 200 IU/day vitamin D_3 and 300 mg elemental calcium during the treatment. To minimize the development of hypercalcemia or hypercalciuria, the amounts of calcium and vitamin D supplementation were kept at low levels.

We planned to discontinue hPTH(1–34) therapy if hypercalcemia over 11 mg/dl (2.75 mmol/l) developed. However, none of the subjects developed hypercalcemia over 11 mg/dl (2.75 mmol/l). Compliance with the study treatment was assessed with the use of medication diaries.

Assessment of bone mineral density

The BMD of the lumbar spine in the posteroanterior projections was measured by dual-energy x-ray absorptiometry (DXA) at baseline and at 3 months of treatment. All the study centers involved in this trial were equipped with the Hologic QDR series for BMD measurements. A central facility (Rehabilitation Center, Tottori University School of Medicine, Tottori, Japan) performed quality assurance of the longitudinal adjustment. Adjustment for DXA machine differences was made by calibrating each machine with standardized phantoms. All the DXA measurements were analyzed at a central site by a radiologist blinded to treatment group assignment.

Table 1 Baseline demographics of study subjects (*BMD* bone mineral density, *PTH* parathyroid hormone, *25 OH-D* 25-hydroxy vitamin D)

	PTH250[a] (n=31)	PTH500[b] (n=30)	PTH1000[c] (n=29)	Total (n=90)
Age (years; mean ± SD)	65.1±5.8	67.3±7.6	67.3±6.9	66.5±6.8
Men [n (%)]	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.1)
Women [n (%)]	31 (100.0)	29 (96.7)	29 (100.0)	89 (98.9)
Years since menopause (years; mean ± SD)	14.0±6.5	16.1±7.8	16.9±6.7	15.6±7.0
Body mass index (kg/m²; mean ± SD)	21.4±2.7	22.0±2.8	21.6±2.5	21.7±2.7
Height (cm; mean ± SD)	150.4±5.7	151.1±4.9	150.1±6.9	150.6±5.8
Weight (kg; mean ± SD)	48.3±6.2	50.4±7.2	48.6±5.5	49.1±6.3
Lumbar spine BMD (g/cm²; mean ± SD)	0.632±0.050	0.641±0.059	0.632±0.068	0.635±0.058
PTH (pg/ml; mean ± SD)	38.8±11.0	39.2±13.3	41.8±12.0	39.9±12.0
25 OH-D (nmol/l; mean ± SD)	51.8±14.0	56.6±14.1	51.1±16.2	53.2±14.8
Prevalent fractures [n (%)]	11 (35.5)	13 (43.3)	7 (24.1)	31 (34.4)

There were no significant differences among the groups based on χ^2 tests for categorical variables and one-way ANOVA for continuous variables
[a]250 μg/day of hPTH(1–34)
[b]500 μg/day of hPTH(1–34)
[c]1,000 μg/day of hPTH(1–34)

Assessment of chemical parameters and bone turnover

Serum and urine samples were collected at baseline and at 1, 2, and 3 months for routine chemical analyses, including hematologic, hepatic, and renal functions. Because the increase in serum Ca after nasal spray of hPTH(1–34) peaked 2–3 h after administration (data from phase I study), we measured serum Ca before and 3 h after nasal spray at baseline and at the 0.5-, 1-, 2-, and 3-month visits. The absolute increase in serum Ca 3 h after nasal spray at each visit was calculated by subtracting the serum Ca value before the spray (0 h) from that at 3 h after the spray. Because the increase in serum Ca at 3 h after nasal spray was similar throughout the five visits, the data for each time point were combined. At each visit, serum samples were collected before the nasal spray of hPTH(1–34) in fasting patients, and subjects took food just before the spray. Urinary Ca was monitored by a spot urine specimen with overnight fasting before nasal hPTH(1–34) spray and was expressed as mg/dl glomerular filtrate (GF).

Markers of bone turnover, including serum osteocalcin (bone Gla protein-radio Immunoasssay; Mitsubishi Kagaku Bio-Chemical, Tokyo, Japan), type I procollagen N-propeptide (PINP; UniQ PINP RIA, Orion Diagnostica, Espoo, Finland), urinary type I collagen C-telopeptide (CTX; urine CrossLaps ELISA, Nordic Bioscience Diagnostic, Herlev, Denmark), and urinary type I collagen N-telopeptide (NTX; Osteomark, Ostex International, Seattle, WA) were determined at baseline and at 1.5 and 3 months. Plasma hPTH (1–34) was measured at baseline and at 3 months using a specific two-site enzyme immunoassay for hPTH(1–34) before and 30 min after nasal spray [6].

Assessment of adverse events

All subjects were questioned about adverse events of treatment at each visit, and all adverse events were analyzed regardless of the investigators' assessments of causality. Occurrence of supraventricular and ventricular extrasystoles was examined by monitoring the Holter electrocardiograph until 4 h after nasal spray at each visit. The Medical Dictionary for Regulatory Activities (MedDRA, version 6) was used to categorize reported adverse events.

Statistical analysis

The endpoint was change in L2-4 BMD and bone turnover markers from baseline, because JSBMR criteria for the diagnosis of osteoporosis use L2-4 BMD instead of L1-4 BMD. Statistical analyses were performed according to the intent-to-treat principle unless otherwise indicated. Elimination of the male subject in the PTH500 group from the analyses did not make any changes in the results. Therefore, all the results are presented, including those for the male subject.

Group means and standard errors of the mean (SE) are given for the percent changes from baseline in L2-4 BMD and for the actual values of serum Ca. Paired *t*-tests and Student's *t*-tests were used to assess the significance of changes within each group and between groups, respectively. Medians are reported for changes in the levels of bone turnover markers. A paired *t*-test was used to determine which hPTH(1–34)-treated groups were significantly different from the baseline, and William's test was used to determine which higher-dose groups (PTH500 and
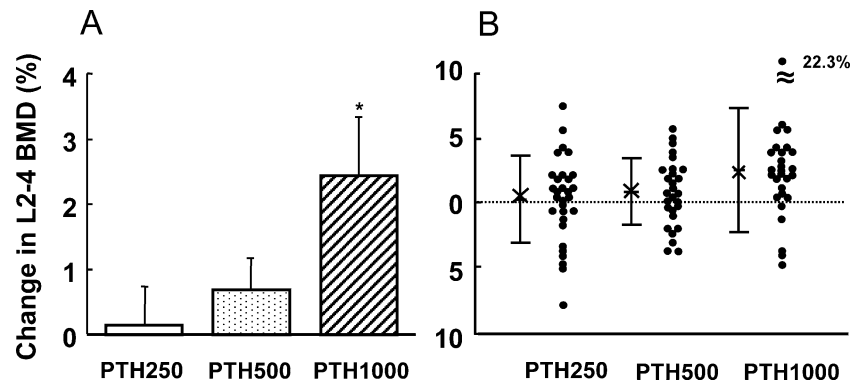
Fig. 1 Effect of 3 months of treatment with hPTH(1–34) on lumbar spine bone mineral density (BMD). BMD of the lumbar spine (L2-4) was measured by dual-energy x-ray absorptiometry at baseline and at 3 months of treatment. **a** Values are expressed as the mean percentage change from baseline, and error bars are standard errors (SE). *Asterisk* indicates significant difference from the baseline by a paired *t*-test ($p<0.05$). **b** Plots are expressed as individual data on the percentage change from baseline, and the mean percentage (-), median percentage (×), and error bars are standard deviation (SD)

PTH1000 groups) in a series were significantly different from the lowest-dose group (PTH250 group). The comparability among the groups for demographic and background information and the incidence rates of adverse events were assessed with the use of one-way analysis of variance (ANOVA) for continuous variables and χ^2 tests for dichotomous variables.

Results

Baseline characteristics of the subjects

Patient demographics are presented in Table 1. Baseline characteristics were similar across all groups, and no statistically significant differences in baseline characteristics were noted among the PTH250, the PTH500, and the PTH1000 groups. No patients reported taking any bisphosphonates or SERMs before starting the study.

Adherence to study treatment

Of the 90 subjects who enrolled in this study, six discontinued treatment: one subject (3.2%) in the PTH250 group, four (13.3%) in the PTH500 group, and one (3.4%) in the PTH1000 group. We found no difference in adherence to treatment among the groups, and all subjects took more than 75% of the nasal spray.

Lumbar spine BMD

L2-4 BMD increased within 3 months of hPTH(1–34) treatment in a dose-dependent manner (Fig. 1a and b). After 3 months of hPTH(1–34) treatment, L2-4 BMD increased from baseline by 0.1%, 0.7%, and 2.4% in the PTH250, the PTH500, and the PTH1000 groups, respectively. The

increase in L2-4 BMD achieved statistical significance from the baseline only in the PTH1000 group ($p=0.012$). The percent change of L2-4 BMD in the PTH1000 group was significantly greater than that in the PTH250 group ($p<0.05$ by William's test). As shown in Fig. 1b, one patient showed an extraordinary increase of L2-4 BMD (22.3%) in the PTH1000 group. We critically rechecked this patient, but no problem was found in BMD measurement of this patient. Therefore, there was no plausible reason to eliminate this patient. If this patient were excluded from the analysis, the increase of L2-4 BMD in the PTH1000 group became smaller (1.7%) but was still statistically significant from the baseline because of more tightening of the results ($p=0.004$).

We also examined whether there was any relationship between plasma hPTH(1–34) levels after nasal spray and changes in L2-4 BMD. Plasma hPTH(1–34) was mostly undetectable before nasal spray. Plasma hPTH(1–34) levels after nasal spray did not differ between baseline and 3 months, and there was no change in bioavailability of hPTH(1–34) with continued use (data not shown). The median values of average plasma hPTH(1–34) for each patient at 30 min after nasal spray on the 1- and 3-month visits were 68 pg/ml [interquartile range (IQR) 45–133] in the PTH250 group, 111 pg/ml (IQR 51–222) in the PTH500 group, and 212 pg/ml (IQR 132–364) in the PTH1000 group. There was a significant difference in plasma hPTH(1–34) levels among all the dosage groups ($p=0.003$ by Kruskal-Wallis test). No statistically significant relationship was found between changes in L2-4 BMD and plasma hPTH(1–34) levels after nasal spray.

Bone turnover markers

Median serum PINP and osteocalcin significantly increased within 1.5 months of treatment with 500-μg and 1,000-μg

Table 2 Adverse events reported in more than 5% of total study subjects

Adverse events (classified by preferred terms)	PTH250 (n=31)	PTH500 (n=30)	PTH1000 (n=29)	p-value[a]
Nasopharyngitis	3 (9.7%)	8 (26.7%)	3 (10.3%)	0.120
Headache	2 (6.5%)	1 (3.3%)	2 (6.9%)	0.807
Supraventricular extrasystoles[b]	5 (16.1%)	4 (13.3%)	2 (6.9%)	0.537
Ventricular extrasystoles[b]	0 (0.0%)	2 (6.7%)	3 (10.3%)	0.206

[a]p-values were calculated by a χ^2 test
[b]All adverse events reported as extrasystoles were detected by Holter monitoring

doses of hPTH(1–34) spray. Only the 1,000-μg dose produced consistent increases in PINP and osteocalcin at 1.5 and 3 months. Osteocalcin and PINP increased by 19.4% (p=0.004) and 14.8% (p=0.048), respectively, after 3 months.

In contrast to the increases it produced in PINP and osteocalcin, the 1000-μg dose reduced NTX (26.1% and 16.4% from baseline after 1.5 and 3 months; p=0.027 and 0.033, respectively) and tended to reduce CTX (28% and 17% from baseline after 1.5 and 3 months; p=0.3 and 0.3, respectively).

Safety

Among the study subjects, 65 (72%) reported at least one adverse event (PTH250, 22; PTH500, 23; PTH1000, 20; p=0.8). There were no dose-dependent increases in any adverse events classified by MedDRA System Organ Classified terms. No death was reported. Two subjects reported serious adverse events (low back pain and cerebral infarction) in the PTH500 group, but these were not considered to be related to the study drug. One subject in the PTH250 group, four in the PTH500 group, and one in the PTH1000 group withdrew from the study because of at least one adverse event. Nasopharyngitis, headache, supraventricular extrasystoles, and ventricular extrasystoles (classified by preferred terms) were reported in more than 5% of total study subjects, but there were no statistically significant differences among the three treatment groups (Table 2). Dizziness known as a PTH-related adverse event was reported by one subject (3.2%) in the PTH250 group, two (6.7%) in the PTH500 group, and one (3.4%) in the PTH1000 group, but the overall incidence (4.4%) among all the study subjects did not exceed 5%. Other possible PTH-related adverse events, such as hot flushes, nausea, vomiting, and leg cramps, were not reported in this study. There were no serious nasal symptoms related to the spray, and only minor symptoms were reported in a small number of subjects, including rhinorrhea, sneezing, and nasal irritation after spray. Although nasal spray has previously been associated with erosion of the nasal conchae, none of the subjects developed such changes in the nasal cavity.

Serum Ca significantly increased 3 h after all doses of hPTH(1–34) spray. Hypercalcemia over 10.4 mg/dl (2.6 mmol/l) was observed 3 h after nasal spray in two patients in the PTH250 group and five patients in the PTH1000 group, but none of the subjects developed hypercalcemia over 11 mg/dl (2.75 mmol/l) throughout the study. The mean increments of serum Ca after 3 h at the five visits were 0.16, 0.13, and 0.29 mg/dl (0.04, 0.03, and 0.07 mmol/l) in the PTH250, PTH500, and PTH1000 groups, respectively. The increase in serum Ca in the PTH1000 group was significantly greater than that in the PTH250 and PTH500 groups (p<0.001 against PTH250 and PTH500). No statistical difference in the increase in serum Ca after 3 h was observed between the PTH250 and PTH500 groups (p=0.5). Serum Ca before nasal hPTH(1–34) spray did not change throughout the study period in any treatment group, and there was no significant difference in serum Ca before nasal spray between the three treatment groups after 3 months of treatment. No subjects developed hypercalciuria. Urinary Ca excretion in the PTH1000 group before the spray at each visit remained almost constant throughout the study [0.073±0.034, 0.072±0.033, 0.074±0.043, 0.074±0.054, and 0.065±0.034 mg/dl GF (mean ± SD) at 0, 0.5, 1, 2, and 3 months, respectively]. There was no relationship between changes in BMD and changes in serum Ca or turnover markers after nasal hPTH(1–34) treatment for 3 months. In addition, there was no apparent link between the occurrence of postspray hypercalcemia and changes in BMD or bone turnover markers, although the number of subjects (four of five subjects completed the study) was too small to draw any conclusions.

Discussion

The present study demonstrates that nasal spray hPTH(1–34) can effectively increase L-BMD in a dose-dependent manner, with daily 1,000-μg hPTH(1–34) spray increasing

L-BMD by 2.4% in 3 months. Therefore, the rate of early increase in L-BMD can be superior to that achieved with bisphosphonates [7, 8] and other antiresorptive agents [9], but it is less than that reported for subcutaneous injections of hPTH(1–34), which showed more than a 4% increase in L-BMD during the initial 3 months of treatment [10]. It should also be pointed out that the cost of hPTH(1–34) does not change much between the 20-μg and 1,000-μg dose ranges because recombinant hPTH(1–34) is produced by a large-scale manufacturing facility.

Previous results demonstrated that subcutaneous injections of either hPTH(1–34) or hPTH(1–84) cause an increase in bone formation markers within 1 month, with a sustained increase to reach a peak at around 6 months of treatment [2, 11]. Among bone formation markers, serum PINP shows the largest and most consistent elevation. Serum osteocalcin and BALP show less responsiveness to PTH treatment. Those results also demonstrated that daily subcutaneous PTH injections increase bone resorption markers as well. Ettinger et al. [12] examined effects of subcutaneous injections of hPTH(1–34) after treatment with raloxifene or alendronate and found similar results with subcutaneous 20 μg hPTH(1–34) injection: an increase in serum osteocalcin and PINP by 200–300% with approximately a 50% increase in urinary NTX after 3 months in the raloxifene-pretreated group. Although the subjects in their study were pretreated with raloxifene, and the increase in resorption markers could be influenced by removal of raloxifene, the changes in bone turnover markers after hPTH(1–34) treatment are comparable to previously reported results for treatment-naïve patients. In a study by Black et al. [13] which examined the effects of 100 μg hPTH(1–84) and alendronate alone or in combination in postmenopausal women with osteoporosis (PaTH Study), hPTH(1–84) treatment alone caused close to a 150% increase in serum PINP along with more than a 70% increase in serum CTX after 3 months. In contrast to those studies, the increase in bone formation markers by nasal 1000-μg hPTH(1–34) spray was only about one-fifth of that by subcutaneous injections of 20 μg hPTH(1–34) or 100 μg hPTH(1–84), whereas nasal hPTH(1–34) spray increased lumbar BMD by about one-half that of the subcutaneous hPTH(1–34) injection. One explanation for this discrepancy may be that nasal hPTH(1–34) spray reduced urinary NTX and CTX by about 17%, while subcutaneous hPTH(1–34) or hPTH(1–84) injection elevated bone resorption markers by 50–70% [11–13]. Taken together, it is plausible to assume that suppressed bone resorption in the face of enhanced bone formation causes a substantial increase in L-BMD after only 3 months of treatment in the PTH1000 group. However, it is unknown from the present study whether bone resorption markers continue to be suppressed and bone formation markers

continue to be elevated to achieve sustained increases in L-BMD after longer nasal spray treatment with hPTH(1–34). Further studies with a longer period of treatment and larger groups of osteoporotic patients are needed to clarify these issues.

It is also unclear why there were marked differences in the effects on bone turnover markers between subcutaneous injection and nasal spray of PTH. However, an earlier phase I clinical study examining pharmacokinetics of nasal spray hPTH(1–34) administration in comparison with subcutaneous injections revealed that the time to achieve peak plasma level after nasal hPTH(1–34) spray was much shorter (14 min), about one-third of that with subcutaneous injection (40 min), and that the plasma half-life for hPTH (1–34) was also shorter after nasal spray compared with subcutaneous injection (0.5 vs. 1.16 h; unpublished data). As a result, the total area under the curve for plasma hPTH (1–34) after nasal administration was less than half that after subcutaneous injection (250 vs. 506 pg·h/ml). Those observations along with the present results are consistent with the notion that the unique pharmacokinetic profile of the nasal spray formula of hPTH(1–34), with a rapid attainment of peak plasma levels with a short half-life, makes it a pure anabolic agent for enhancing bone formation without increasing bone resorption. However, the observed reduction in bone resorption markers could also indicate a negative effect. With reduced bone resorption, there would be less remodeling, less PTH-induced positive bone balance, and ultimately less accretion of new bone. The reasons why bone resorption markers are suppressed and why less increase in bone formation markers and BMD is obtained by nasal hPTH(1–34) spray need to be further clarified.

One of the most frequent and inevitable complications of hPTH(1–34) treatment has been the development of hypercalcemia. Although nasal spray of hPTH(1–34) also elicits an elevation of serum Ca, the increase in serum Ca is transient and peaks between 2 and 3 h after nasal application (unpublished data). In contrast, subcutaneous injections of hPTH(1–34) cause an increase in serum Ca that peaks at 4–6 h after injection [1]. Thus, there appears to be a difference in the time course of elevation in serum Ca as well. In the present study, although there were five subjects in the PTH1000 group who exhibited transient hypercalcemia over 2.6 mmol/l after hPTH(1–34) spray, none of them showed sustained hypercalcemia. In addition, no other serious adverse events related to hPTH(1–34) treatment, as well as well-known PTH-related adverse events such as hot flushes, nausea, vomiting, and leg cramps, were reported. Although our extensive Holter electrocardiographic examination after nasal spray revealed the occurrence of ventricular extrasystoles in two out of 30 subjects in the PTH500 group and three out of 29 subjects

in the PTH1000 group, there was no significant dose-dependent relationship to nasal hPTH(1–34) treatment.

Thus, the nasal spray formula of hPTH(1–34) appears to be safe and well-tolerated, making it a promising candidate as a new bone anabolic agent for treating osteoporotic patients.

The present study also has limitations. First, it was an open-labeled study without placebo controls, in which treatment biases could not be eliminated. Second, the treatment period with hPTH(1–34) spray in the present study was 3 months, and no data on hip BMD or fractures was obtained. Third, because the drug is delivered via the nasal mucosa after being sprayed into the nasal cavity, and because there was a wide variation in plasma hPTH(1–34) levels 30 min after nasal spray, the amount of hPTH(1–34) absorbed each time may vary from day to day. Finally, based on immunoassayed plasma PTH levels in our study participants, we can conclude that greater PTH bioavailability is needed. Although the optimal dose of nasal hPTH(1–34) spray may be higher, there is a limitation in the volume of each spray and soluble concentration of hPTH(1–34). Therefore, the effect of the nasal spray formula will have to be examined with the current highest and safest dose. However, there are also possibilities that the volume limitation can be overcome by a twice-daily spray of 1,000 μg hPTH(1–34), or a different formulation may improve absorption from the nasal mucosa.

In conclusion, this pilot study provides proof of concept for intranasal hPTH(1–34), but it indicates a need for greater dosage or dose frequency or bioavailability to achieve skeletal effects comparable to those seen with standard dosages of subcutaneous PTH. Because the nasal spray can easily be applied without any painful injections, this formula of hPTH(1–34) can be a patient-friendly alternative way of administering bone anabolic hPTH(1–34) to osteoporotic subjects. The present results warrant further studies to examine the formula's long-term efficacy on bone mass and fractures.

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