Osteoporos Int (2006) 17: 225–230
DOI 10.1007/s00198-005-1976-3

ORIGINAL ARTICLE

Safety and tolerability of subcutaneous PTHrP(1–36) in healthy human volunteers: a dose escalation study

Mara J. Horwitz · Mary Beth Tedesco · Susan M. Sereika
Adolfo Garcia-Ocaña · Alessandro Bisello
Bruce W. Hollis · Caren Gundberg · Andrew F. Stewart

Received: 22 February 2005 / Accepted: 12 June 2005 / Published online: 7 September 2005

Abstract Parathyroid hormone-related protein (PTHrP) is an anabolic skeletal agent in mice, rats and humans. In previous studies, we have demonstrated that PTHrP can be administered to osteoporotic postmenopausal women at a dose of 6.56 ug/kg/day (or approximately 400 ug/day) for 3 months to yield a 4.7% increase in lumbar spine BMD. This regimen was free of hypercalcemia or adverse effects. Moreover, PTHrP appeared to stimulate bone formation selectively, without stimulating bone resorption. This efficacy in the absence of adverse effects, as well as the apparent "pure anabolic" action of PTHrP, prompted us to attempt to define the complete therapeutic window for PTHrP. In this study, we gradually escalated the dose of PTHrP(1–36) from 9 to 28 ug/kg (or approximately 570 ug to 1,946 ug) administered as a single subcutaneous dose to 22 healthy young adult subjects. PTHrP(1–36) was well tolerated even at the highest dose, just under 2.0 mg, some five times higher than we have previously demonstrated to be effective in increasing bone mass, and some 100 times higher than the maximal approved dose of PTH(1–34). Despite the large dose of PTHrP, the highest serum calcium achieved was 10.6 mg/dl, and this was observed in only one subject at the highest dose. The mean serum calcium in subjects receiving the highest dose was 9.6 mg/dl. Only one subject experienced adverse symptoms/signs, and this was at the highest dose. We conclude that subcutaneous PTHrP(1–36) is safe when administered in single doses approaching 2.0 mg. These findings indicate that the therapeutic window for PTHrP(1–36) in humans is wide and permit the design and implementation of longer safety and efficacy trials.

Keywords Dose escalation study · Subcutaneous PTHrP · Tolerability

This study was supported by NIH grants DK 51081 and RR 00056, The University of Pittsburgh General Clinical Research Center and the Multiple Myeloma Research Foundation. Dr Stewart is CEO of Osteotrophin, LLC.

M.J. Horwitz (✉) · M.B. Tedesco · A. Garcia-Ocaña
A. Bisello · A.F. Stewart
Division of Endocrinology, University of Pittsburgh
School of Medicine, Falk 580 3601 Fifth Ave., Pittsburgh,
PA 15213, USA
E-mail: horwitz@pitt.edu
Tel.: +1-412-5869714
Fax: +1-412-5869726

S.M. Sereika
School of Nursing and Graduate School of Public Health,
University of Pittsburgh, Pittsburgh, PA, USA

B.W. Hollis
The Medical University of South Carolina, Charleston, SC, USA

C. Gundberg
Yale University School of Medicine, New Haven, CT, USA

Introduction

Parathyroid hormone (PTH) is a potent skeletal anabolic agent. PTH(1–34) and PTH(1–84) when administered on a daily subcutaneous basis result in increases in both bone resorption and formation and lead to rapid and quantitatively large increases in bone mineral density in postmenopausal women and in men with osteoporosis [1, 2, 3, 4, 5, 6, 7]. PTH treatment results in a marked reduction in skeletal fracture rates [1]. The availability of PTH represents the beginning of a new era in the anabolic therapy of osteoporosis, complementing more traditional anti-resorptive therapies such as the bisphosphonates, estrogens and SERMs. The dose of PTH(1–34) approved by the United States FDA is 20 ug/day. Higher doses result in increasing toxicity, including nausea, headache, dizziness, muscle cramps and other adverse events. Indeed, even the approved dose of 20 ug/day may result in mild hypercalcemia. For example, at the 20 ug/day dose, 11% of women developed hypercalcemia (defined as a serum calcium greater than 10.6 mg/dl), and this increased to 28% in women receiving the 40 ug/day dose [1]. Thus, despite the efficacy and promise of PTH as a skeletal anabolic agent,

increases in bone resorption, hypercalcemia and other adverse effects occur.

Parathyroid hormone-related protein (PTHrP) was initially identified as the humoral factor that causes humoral hypercalcemia of malignancy. Recently, work from the Miao, Karaplis and Goltzman group has demonstrated that PTHrP is the endogenous ligand for the PTH/PTHrP or PTH-1 receptor in bone, and is a native anabolic factor for bone [8, 9, 10, 11]. For example, mice haploinsufficient for PTHrP develop osteoporosis [8], and conditional disruption of PTHrP production by osteoblasts results in osteoporosis [9]. Conversely, mice null for PTH develop increases in bone mass, and this increase in bone density results from a local increase in PTHrP production [10]. Thus, whereas both PTH and PTHrP can interact with the PTH-1 receptor in bone, one can reasonably argue that PTHrP, and not PTH, is the native anabolic skeletal ligand.

Complimenting these observations in osteoporotic PTHrP-deficient mice, we have shown that PTHrP administration is capable of increasing bone mass in postmenopausal women with osteoporosis. For example, daily subcutaneous administration of PTHrP(1–36) for 3 months to women with postmenopausal osteoporosis resulted in a mean increase in lumbar spine density of 4.7% [12]. Similarly, 6 months of daily administration of PTHrP(1–36) to ovariectomized rats resulted in a 22% increase in bone mass [13]. While there are no human PTHrP studies with a fracture endpoint, the rat studies demonstrated that PTHrP leads to markedly enhanced biomechanical properties in the femur and vertebrae [13].

PTHrP administration in humans is associated with four unique features. First, the doses required and tolerated are large. For example, we have shown that doses ranging from 0.82 to 6.56 ug/kg, approximately equivalent to 50 to 400 ug/day in a 60 kg postmenopausal woman, are well tolerated [12, 14, 15], and that doses in the range of 6.56 ug/kg are required for the anabolic effect in humans [12, 15]. Second, despite the large doses employed, PTHrP is well tolerated. Despite using doses some 20 times higher than the approved dose of PTH(1–34), subjects receiving PTHrP(1–36) have not displayed subjective adverse effects, nor objective adverse effects such as hypercalcemia [12, 14, 15]. Third, the increments in spine BMD are large and rapid [12]. Indeed, some subject receiving PTHrP(1–36) displayed increases in spine BMD of 6–8% in 3 months [12]. And, fourth, whereas PTHrP administration is associated with increases in bone formation (as measured using bone formation markers in humans [12, 15], and histomorphometric markers of bone formation in rats [13]), it is not associated with increases in bone resorption [12, 13, 15]. Thus, PTHrP(1–36) in doses used to date appears to be a pure skeletal anabolic agent.

Since PTHrP has beneficial effects on skeletal mass and is well tolerated, even at large doses, we wondered if even larger doses might be well tolerated, and if so, whether larger doses might be more efficacious than the 6.56 ug/kg/day (or approximately 400 ug/day) dose employed previously [12, 15]. In the current study, therefore, we explored the maximal tolerable single dose of PTHrP(1–36) in healthy young adults.

Materials and methods

Study subjects

Twenty-two subjects (7 males and 15 females) between the ages of 24 and 45 years old (mean age $=28.4 \pm 0.8$) were studied. All subjects were healthy, on no medications and had no cardiac, renal, hematological, endocrine or other diseases. The baseline blood pressure, physical exam, serum calcium, phosphorus, creatinine, 25(OH)vitamin D and electrocardiogram were normal. Pregnancy tests were negative in females.

Protocol design

The purpose of this study was to define the maximal single subcutaneous dose of PTHrP(1–36) that can be safely tolerated by healthy young adults. Subjects were admitted for 10 h to the Adult General Clinical Research Center at the University of Pittsburgh School of Medicine after fasting overnight. An intravenous line was inserted for blood sampling, and subjects were allowed to have breakfast. PTHrP was administered at the doses indicated below at approximately 8:00 a.m. Supine and standing pulse and blood pressure were measured at 15-min intervals for the first hour, then at 30-min intervals for the next hour, and then hourly. Serum calcium, ionized serum calcium, serum phosphorus, $1,25(OH)_2$ D, plasma amino-terminal peptide of collagen-1 (NTX), plasma carboxy-terminal peptide of procollagen-1 (CTX), and procollagen-1 amino-terminal peptide (P1NP) and urine for calcium, creatinine and phosphorus, were obtained at the times indicated in Figs. 1 and 2. An adverse effect questionnaire [12, 16] was administered every 15 min for the first 60 min, then every 30 min for 2 h, then every 2 h for the remainder of the study. Informed written consent was provided by each subject, and the studies were approved by the University of Pittsburgh Human Subjects Institutional Review Board.

Human PTHrP(1–36) was administered in sterile saline in volumes between 0.4 and 0.8 ml into the subcutaneous abdominal fat. The highest dose of PTHrP employed in our prior studies [12, 15] was 6.56 ug/kg. Therefore, the initial dose in this study was 9 ug/kg, and the dose was then escalated to 12, 16, 21 and 28 ug/kg. When expressed in ug/subject, the mean doses were 570, 879, 1,192, 1,499 and 1,946 ug per subject, respectively. For the lowest four doses, each dose was administered to groups of three different subjects, increasing the dose serially if no adverse effects were observed. Finally, the 28 ug/kg dose was given to a group of ten additional

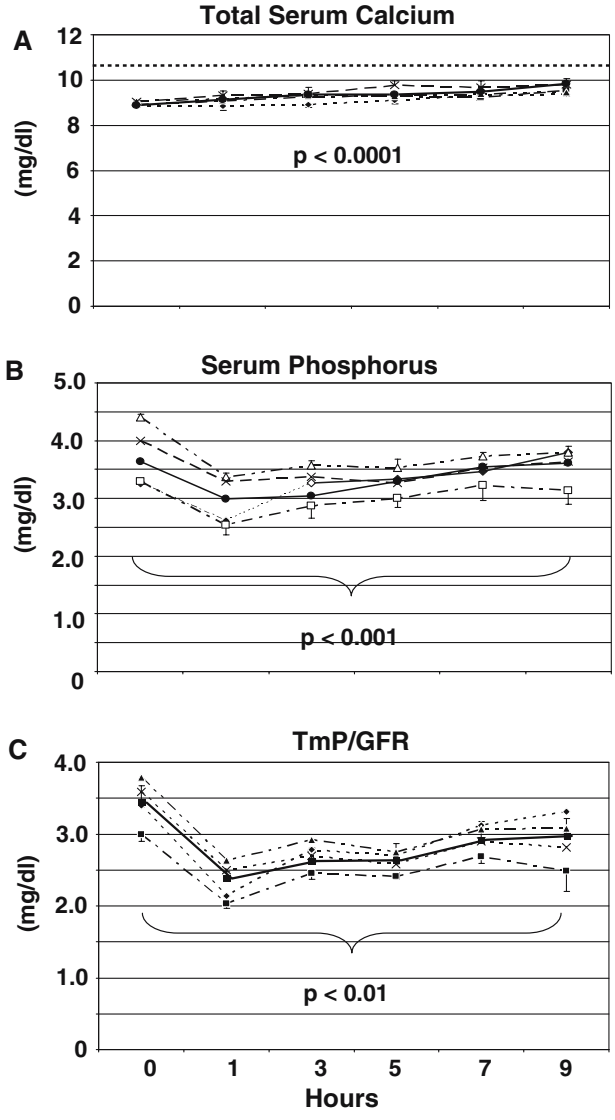

Fig. 1 Total serum calcium, serum phosphorus and the renal tubular maximum for phosphorus (TmP/GFR) responses to PTHrP dose escalation. *Open triangles*: 9.0 ug/kg ($n = 3$, mean dose 570 ug/subject); *open squares* 12 ug/kg (n = 3, mean dose 879 ug/subject); × 16 ug/kg ($n = 3$, mean dose 1,192 ug/subject); *x symbol* 21 ug/kg ($n = 3$, mean dose 1,499 ug/subject); *filled black circle* and *solid black line* 28 ug ($n = 10$, mean dose 1,946 ug/subject). The *dotted line* in the *upper panel* represents the upper normal limit for serum calcium (10.5 mg/dl). Representative standard *error bars* are shown. In each *panel*, the *P* value refers to the changes as compared to baseline in the 28 ug/kg group

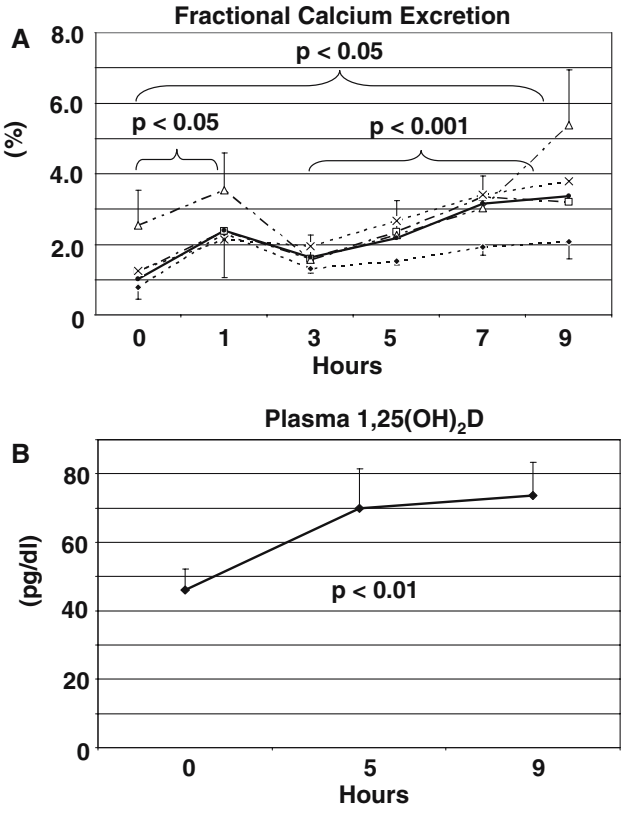

Fig. 2 Fractional calcium excretion and plasma $1,25(OH)_2$ D responses to subcutaneous PTHrP. The symbols are the same as in Fig. 1. See text for details

subjects. Subjects were not aware of the dose they were receiving. Study subjects were observed for 9 h following the dose of PTHrP(1–36).

Peptide

Human PTHrP(1–36) was prepared and administered as described in detail previously [12, 13, 14, 15, 16, 17, 18, 19]. Briefly, hPTHrP was synthesized by solid phase synthesis, aliquotted into sterile vials under sterile conditions, and lyophilized. Purity was confirmed using analytical scale reversed-phase HPLC, and accuracy of synthesis by amino acid analysis and mass spectroscopy. Vials were tested for amino acid content to confirm the quantity of PTHrP per vial, and were assayed for bioactivity using the SaOS-2 adenylyl cyclase bioassay [16, 17, 18]. The PTHrP(1–36) preparation used in these studies displayed comparable bioactivity to hPTH(1–34) (Bachem, Torrance, Calif.) in the SaOS-2 adenylyl cyclase bioassay, and was comparable in potency to PTHrP(1–36) employed in our prior studies [12, 13, 14, 15, 16, 17, 18, 19]. Sterility was confirmed by routine bacterial culture, and pyrogenicity was assayed using a standard endotoxin assay. The use of PTHrP was approved by the FDA under IND no. 49,175.

Analyses

Serum, plasma and urine for calcium, phosphorus and creatinine was analyzed in the University of Pittsburgh Clinical Chemistry Laboratory. Fractional calcium excretion and the renal tubular maximum for phosphorus (TmP/GFR) were calculated as described previously [19]. Plasma NTX, CTX and P1NP were assayed using commercially available kits (Osteomark ELISA, Ostex International, Seattle, Wash.; Crosslaps ELISA,

Nordic Bioscience Diagnostics, Inc., Herlev, Denmark; Orion Diagnostics RIA, Espoo, Finland, respectively). Plasma 1,25$(OH)_2$ D was measured using the Diasorin Kit (Stillwater, Minn.).

Statistics

Changes in the measured parameters in the group receiving the highest PTHrP dose, 28 ug/kg, were evaluated using mixed modeling methods. Mixed modeling was employed since it allows for a correlational structure among the repeated measures other than compound symmetric, which is the correlational structure assumed for repeated measures analysis of variance. The level of significance was pre-established at 0.05 for two-sided hypothesis testing.

Results

The changes in total serum calcium are shown in Fig. 1A. There was a mild, but statistically significant, increase in total serum calcium over the 10 h of the study. The subjects receiving the lower doses also displayed similar mild increases. No group approached the upper limits of normal in our laboratory (10.5 mg/dl), and only one subject in any group achieved a serum calcium concentration over 10.0 mg/dl. This was a single subject in the 28 ug/kg dose, who reached 10.6 mg/dl at 5 h. Similar results were observed for ionized calcium (baseline in the 28 ug/kg group 4.5 ± 0.04 vs. 5.0 ± 0.04 mg/dl at 9 h, mean ± SE, $P = 0.0001$). Serum creatinine did not change significantly (baseline in the 28 ug/kg group 0.85 ± 0.05 vs. 0.81 ± 0.04 mg/dl at 9 h, mean ± SE, P = ns).

As anticipated, each group displayed a transient decline in serum phosphorous (Fig. 1B) and in the TmP/GFR (Fig. 1C). Fractional calcium excretion increased transiently, but reproducibly in each group at the first (1 h) time point (Fig. 2A). Fractional calcium excretion rapidly declined at 3 h, and then gradually increased over the ensuing 6 h. Plasma NTX and CTX, markers of bone resorption, remained stable during the study, as did plasma P1NP (mean ± SE, CTX baseline = 17.9 ± 9.2 vs. 9 h = 18.5 ± 7.8 ng/ml; NTX baseline = 16.9 ± 1.0 vs. 9 h = 16.3 ± 1.5 nM BCE; P1NP baseline 68.6 ± 10.5 vs. 9 h 61.2 ± 10.1 ug/l). Plasma 1,25$(OH)_2$ D was measured in the subjects receiving the 28 ug/kg dose, or approximately 2.0 mg of PTHrP(1–36). As can be seen in Fig. 2B, plasma 1,25$(OH)_2$ D increased progressively, approximately doubling over the 9 h of the study.

Supine and standing systolic and diastolic blood pressure and heart rate were measured throughout the study. Baseline supine and standing systolic blood pressures in the 28 ug/kg group were 111 ± 5.9 and 115 ± 4.4 mgHg, respectively. There was a transient, 45–60 min increase in systolic blood pressure of approximately 15–20 mmHg, in both supine and standing positions in the subjects receiving the 28 ug/kg dose, and similar changes were observed in the subjects receiving the lower doses. The highest systolic blood pressure in any subject was 158 mmHg. No significant changes were observed in standing or supine diastolic blood pressure. Supine heart rate increased during the study from a baseline of 63 to 78 bpm. Standing heart rate also increased from a baseline of 77 to 90 bpm. Both peaked at approximately 60 min and returned to baseline by 120 min. The highest pulse in any subject was 133 bpm.

In the subjects receiving the 9, 12, 16 and 21 ug/kg doses, no significant adverse effects were observed. Among the ten subjects who received the 28 ug/kg dose, one subject experienced significant nausea, flushing and diaphoresis, accompanied by postural dizziness (lowest recorded supine BP was 93/63 mmHg, with a baseline BP of 84/55 supine, and 99/66 standing) not accompanied by tachycardia (pulse of 76 bpm with a baseline pulse of 80 supine and 96 standing) between 4 and 5 h following injection of PTHrP. She recovered without specific treatment and was symptomatically and hemodynamically normal within 9 h.

Discussion

These studies demonstrate that the maximum tolerable single subcutaneous dose of PTHrP(1–36) is in the approximate range of 2.0 mg. More specifically, the maximal tolerable subcutaneous dose was at least 28 ug/kg, or, on average, 1,946 ug (1.95 mg) in ten healthy young adults. This dose is some five times higher than the dose we employed previously in postmenopausal women with osteoporosis [12, 15], and some 100 times higher than that approved for hPTH(1–34) [1, 2, 3, 4, 5, 6, 7].

PTHrP administration increased circulating concentrations of 1,25$(OH)_2$ D, as has been reported previously [14, 15, 16, 18, 19, 20]. Despite the ten-fold higher dose of PTHrP in the current study as compared to our earlier study [14], the kinetics of plasma 1,25$(OH)_2$ D were almost identical. These results suggest either that PTHrP absorption is limited, or that 1,25$(OH)_2$ D synthesis was already maximal at the lower dose. In prior studies, the increase in 1,25$(OH)_2$ D was transient, returning to baseline values within 24 h [15]. The increase in 1,25$(OH)_2$ D suggests that intestinal calcium absorption could be elevated in the several hours following PTHrP administration.

Fractional calcium excretion (FECa) increased in the 1st hour following the administration of PTHrP. This transient increase has been reported previously both for PTH and PTHrP [16, 18, 19, 21, 22] and is believed to represent a proximal tubular PTH- or PTHrP-induced calciuresis. This initial increment at 1 h was followed by a subsequent decline at the 3-h time point that could either reflect the waning calciuric effects of PTHrP, the well-documented anti-calciuriuc effects of PTHrP

[16, 19], or a combination of both. Between the 3- and 9-h time points, there was a statistically significant increase in FECa. This could, in theory, reflect an increase in bone resorption or an increase in intestinal calcium absorption mediated by the increase in circulating $1,25(OH)_2$ D.

The total serum calcium increased marginally in quantitative terms, but significantly in statistical terms. The mean serum calcium in the ten subjects receiving the highest (28 ug/kg) dose rose from 8.9 mg/dl at baseline, to 9.8 mg/dl at 9 h. A similar increase was observed in the subjects receiving the four lower doses as well. The increase in serum calcium does not appear to be related to postural or fluid redistribution effects, since the ionized serum calcium also increased comparably. In theory, the mild increase in serum total and ionized calcium could represent a diurnal change in serum calcium, but this seems unlikely in that in our prior studies, subjects receiving placebo treatment under the same conditions on the same research center did not display such changes [19]. The increase in serum calcium at 9 h is not likely due to renal calcium retention mediated by PTHrP, for subjects were more calciuric at 9 h than at baseline. It is not likely reflective of bone resorption, since NTX and CTX did not change. It seems likely, therefore, that the mild increase in serum calcium reflects the substantial and contemporaneous increase in plasma $1,25(OH)_2$ D described above.

The primary outcome measures in this study were safety measures. From a safety standpoint, the mean serum calcium in the subjects receiving all of the doses of PTHrP remained well within the normal range. Only one subject of the 22 in the study reached the 10.5 mg/dl upper normal limits value, and this subject rose only to 10.6 mg/dl. This is in accord with prior studies employing subcutaneous PTHrP, none of which have revealed significant increases in serum calcium [12, 15].

PTHrP and PTH are both well-described vasodilatory agents, and intravenous administration of either PTH or PTHrP to laboratory animals causes essentially immediate, dramatic but transient declines in systolic and diastolic blood pressure [23, 24, 25]. This decline in blood pressure is mediated by a direct vasorelaxant effect on arterial smooth muscle cells in small arterial resistance vessels [23, 24, 25]. Intravenous administration of PTH and PTHrP to intact animals also leads to an immediate increase in heart rate [23, 24, 25]. In part, some of this may be a reflex tachycardia in response to hypotension. However, Ogino et al. have demonstrated that PTHrP has direct chronotropic effects in the isolated perfused rat heart [25]. In humans, Wolzt et al. have performed progressive intravenous infusions of PTHrP(1–34) into healthy normal volunteers, up to a maximal dose of 14.9 nmol/min, or approximately 900 ug, administered over 15 min [26]. Infusion of this large dose resulted in increases in heart rate and renal blood flow, but no important decline in mean arterial pressure. Given these considerations, we had anticipated that single subcutaneous doses of PTHrP(1–36) in the range of 1 to 2 mg might cause systemic hypotension due to vasodilatation. We also anticipated that if they occurred, they would occur at the time of peak plasma PTHrP(1–36) concentrations, which we had previously demonstrated to occur at 15 min following a subcutaneous dose [14]. With this background, the hemodynamic responses observed were surprising, for instead of the anticipated decline in systemic blood pressure, we observed a transient, but statistically significant increase in systolic blood pressure. The heart rate also transiently increased following administration of PTHrP(1–36), perhaps reflecting a reflex tachycardia in response to PTHrP-mediated vasodilatation, a direct chronotropic response of PTHrP, or a response to the stress or anxiety accompanying experimental hospitalization and/or drug administration. From a safety standpoint, the changes were of modest clinical significance.

At the highest dose employed, one of the ten subjects experienced nausea, dizziness, diaphoresis, slight bradycardia and postural hypotension some 4–5 h following the dose, or some 4–5 h after the peak of PTHrP absorption (15 min) [14]. The relative bradycardia was more suggestive of a non-specific vagal reaction than a specific PTHrP-related adverse event, for two reasons. First, PTHrP administration in animals is associated with tachycardia, not bradycardia. Second, as noted above, the event occurred hours after PTHrP had likely disappeared from the circulation.

In summary, these studies demonstrate that PTHrP(1–36) can be administered to healthy young volunteers in surprisingly large doses. Although these large doses were safe when administered as a single dose, it remains fully possible that sustained administration over multiple days to weeks may very well elicit skeletal resorptive responses and hypercalcemia, or other adverse effects. Thus, the significant finding here is that the optimal therapeutic window for PTHrP(1–36) likely lies somewhere between 400 ug/day, the dose used in our two previous studies, and 2,000 ug/day, the approximate maximal dose employed in the current study. Future studies can now be designed to define the pharmacokinetics of absorption of these large doses of PTHrP(1–36) and the safety of doses in this window over longer periods of time.

Acknowledgements The authors wish to thank the members of our Data Safety and Monitoring Board, Drs. Robert M. Neer, Susan L. Greenspan, Olivier Blondel, Steven Wisniewski, Steven Reis and J. Philip Kistler. We also thank the staff of the University of Pittsburgh Adult General Clinical Research Center (NIH grant no. RR 00056) and the volunteers who participated in this study.

References

1. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster J-Y, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH (2001) Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–41

2. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, Garnero P, Bouxsein ML, Bilezikian JP, Rosen CJ (2003) The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 349:1207–1215
3. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM (2003) The effects of parathyroid hormone, alendronate or both in men with osteoporosis. N Engl J Med 349:1216–1226
4. Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP (2000) Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. J Clin Endocrinol Metab. 85:3069–3076
5. Marx J (2004) Coming to grips with bone loss. Science 305:1420–1422
6. Khosla S (2003) Parathyroid hormone plus alendronate—a combination that does not add up. N Engl J Med 349:1277–1279
7. Rosen CJ, Bilezikian JP (2001) Anabolic therapy for osteoporosis. J Clin Endocrinol Metab 86:957–964
8. Amizuka N, Karaplis AC, Henderson JE, Warshawsky H, Lipman ML, Matsuki Y, Ejiri S, Tanaka M, Izumi N, Ozawa H, Goltzman D (1996) Haploinsufficiency of parathyroid hormone-related peptide results in abnormal postnatal bone development. Dev Biol 175:166–176
9. Miao D, He B, Tong XK, Goltzman D, Karaplis AC (2002) Conditional knockout of PTHrP in osteoblasts leads to premature osteoporosis. J Bone Min Res 17 [Suppl 1]:S138
10. Miao D, Li J, Xue Y, Su H, Karaplis AC, Goltzman D (2004) Parathyroid hormone-related peptide is required for increased trabecular bone volume in parathyroid hormone-null mice. Endocrinology 145:3554–3562
11. Bisello A, Horwitz MJ, Stewart AF (2004) Parathyroid hormone-related protein: an essential physiological regulator of adult bone mass. Endocrinology 145:3551–3553
12. Horwitz MJ, Tedesco MB, Gundberg C, Garcia-Ocaña A, Stewart AF (2003) Short-term, high-dose PTHrP as a skeletal anabolic agent for the treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab 88:569–575
13. Stewart AF, Cain RL, Burr DB, Turner CH, Hock JM (2000) Six month daily administration of PTH and PTHrP peptides to adult ovariectomized rats markedly enhances bone mass and biomechanics: a comparison of human PTH(1–34), PTHrP(1–36) and SDZ-PTH-893. J Bone Min Res 15:1517–1525
14. Henry JG, Mitnick MA, Dann PR, Stewart AF (1997) Parathyroid hormone-related protein(1–36) is biologically active when administered subcutaneously to humans. J Clin Endocrinol Metab 82:900–906
15. Plotkin H, Gundberg C, Mitnick M, Stewart AF (1998) Dissociation of bone formation from resorption during 2-week treatment with hPTHrP(1–36) in humans: potential as an anabolic therapy for osteoporosis. J Clin Endocrinol Metab 83:2786–2791
16. Horwitz MJ, Tedesco MB, Sereika S, Hollis B, Garcia-Ocaña A, Stewart AF (2003) Direct comparison of sustained infusion of hPTHrP(1–36) versus hPTH(1–34) on serum calcium, plasma $1,25(OH)_2$ vitamin D concentrations and fractional calcium excretion in healthy human volunteers. J Clin Endocrinol Metab 88:1603–1609
17. Stewart A, Mangin M, Wu T, Goumas D, Insogna KL, Burtis WJ, Broadus AE (1988) A synthetic human parathyroid hormone-like protein stimulates bone resorption and causes hypercalcemia in rats. J Clin Invest 81:596–600
18. Everhart-Caye M, Inzucchi SE, Guinness-Henry J, Mitnick MA, Stewart AF (1996) Parathyroid hormone-related protein(1–36) is equipotent with parathyroid hormone(1–34) in humans. J Clin Endocrinol Metab 81:199–208
19. Syed MA, Horwitz MJ, Tedesco MB, Garcia-Ocaña A, Wisniewski SR, Stewart AF (2001) Parathyroid hormone-related protein (1–36) stimulates renal tubular calcium reabsorption in normal human volunteers: implications for the pathogenesis of humoral hypercalcemia of malignancy. J Clin Endocrinol Metab 86:1525–1531
20. Fraher LJ, Hodsman AB, Jonas K, Saunders D, Rose CI, Henderson JE, Hendy GN, Goltzman D (1992) A comparison of the in vivo biological responses to exogenous parathyrid hormone-(1–34) [PTH-(1–34)] and PTH-related peptide-(1–34) in man. J Clin Endocrinol Metab 75:417–423
21. Law WM, Heath H (1983) Rapid development of renal resistance to low doses of synthetic bovine parathyroid hormone fragment 1–34. J Clin Invest 72:1106–1113
22. Law WM, Heath H (1984) Time- and dose-related biphasic effects of syntetic bovine parathyroid hormone fragment 1–34 on urinary cation excretion. J Clin Endocrinol Metab 58:606–608
23. Massfelder T, Helwig J-J, Stewart AF (1996) PTHrP as a cardiovascular regulatory peptide. Endocrinology 137:3151–3153
24. Mok LLS, Nickols GA, Thompson JC, Cooper CW (1989) Parathyroid hormone as a smooth muscle relaxant. Endocrine Rev 10:420–436
25. Ogino K, Burkhoff D, Bilezikian JP (1995) The hemodynamic basis for the cardiac effects of parathyroid hormone (PTH) and PTH-related protein. Endocrinology 136:3024–3030
26. Wolzt M, Schmetterer L, Dorner G, Zelger G, Entlicher J, Kapiotis S, Eichler H-G (1997) Hemodynamic effects of parathyroid hormone-related protein in humans. J Clin Endocrinol Metab 82:2548–2451