Continuously treatment of hypoparathyroidism with PTH

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ABSTRACT:

Hypoparathyroidism (HypoPT) is the only major hormone deficiency disease that is not usually treated with the missing hormone. Bovine parathyroid hormone (PTH) has been purified and used as experimental treatment, as long back as in 1928 by Fuller Albright. Treatment, however, was abolished mainly because of antibody formation and costs. The recent approval of fully humanized truncated parathyroid hormone (Teriparatide, PTH (1-34)) and intact parathyroid hormone (Preotact, PTH(1-84)) for treatment of osteoporosis, has made the PTH drugs more accessible and thereby made clinical trials with PTH treatment of HypoPT feasible.

Resent clinical trials have shown that treatment with PTH (1-34) and PTH (1-84) can stabilize plasma calcium, normalize plasma phosphate and reduce urine excretion of calcium. Furthermore it seems that some patients experience an improved quality of life when treated with PTH compared with conventional treatment with 1α-hydroxylated vitamin D metabolites and calcium supplements.

Introduction:

Parathyroid hormone (PTH) is of major importance to calcium and bone homeostasis, as it facilitates bone turnover and renewal and the release of calcium from bone when needed. In addition, PTH acts in the kidney by increasing tubular reabsorption of calcium and promoting renal phosphate excretion. In the kidney, PTH also stimulates the renal 25-hydroxyvitamin D-1α-hydroxylase thereby increasing the synthesis of 1.25-dihydroxycholecalciferol ($1.25(OH)_2D$) causing an increased intestinal calcium absorption [1;2]. Accordingly, lack of PTH causes hypocalcemia due to an increased renal calcium loss, decreased intestinal calcium absorption, and a reduced ability to mobilize calcium from bone. Concomitantly, plasma phosphate levels are elevated, which may facilitate extra-skeletal calcifications.

Untreated, hypoparathyroidism (HypoPT) is characterized by an increased neuromuscular irritability including weakness, muscle cramps, paresthesias of the lips, tongue, fingers and feet, loss of memory, headaches, and uncontrollable cramping muscle movements of the wrists and feet (carpopedal spasms) [2]. Other symptoms may be facial spasms provoked by tapping the facial nerve (Chvostek´s sign) and the contraction of hand and forearm muscles produced by upper extremity ischemia (Trousseaus sign or "main d'acoucheur"). In longstanding-HypoPT since childhood symptoms may include cataract, malformations of the teeth, including enamel and root, and malformed fingernails [2].

Surgical removal of or damages to the parathyroid glands are the most common causes of HypoPT, but in rare instances HypoPT may be due to genetic or autoimmune disorder. Unfortunately, no valid data are available on the epidemiology of HypoPT in terms of incidence, prevalence, risk factors, co-morbidity, treatment modalities, or mortality. Accordingly, the reported increased risk of intracranial calcifications (basal ganglia), renal stones, and renal failure in patients with HypoPT is based on case-reports or small series of patients [3- 6]

Currently, standard therapy includes treatment with calcium and usually 1α-hydroxylated-vitamin D metabolites in order to relieve symptoms caused by hypocalcaemia. Treatment focus on maintaining plasma calcium levels stable within or just below the lower normal range [2]. The reasons for keeping plasma calcium levels low are: 1) to minimize urine calcium excretion thereby aiming to prevent nephrocalcinosis and renal stones, 2) to reduce the risk of hypercalcaemia caused by intoxication with active vitamin D; and 3) to stimulate cell proliferation, PTH production and secretion in patients with some intact parathyroid tissue left. Although very high doses of native vitamin D (ergo- or cholecalciferol) has been used previously, 1α-hydroxylated (activated) vitamin D analogues (alphacalcidol, calcitriol, or dihydrotachysterol) are preferred in most instances. Native vitamin D_2 or D_3 have to be given in very high dosages since they cannot undergo 1α-hydroxylation in the kidney because of the lack of PTH. Furthermore, the activated vitamin D analogues have a substantially higher potency as well as a shorter plasma half-life (hours) than 25-hydroxyvitamin D (25OHD), the main circulating metabolite of native vitamin D (2-3 weeks). This is of importance in order to limit the duration of hypercalcemia in case of intoxication. However, not all patients are well regulated when treated with calcium and activated vitamin D analogues. Patients may experience symptoms of either hyper- and/or hypocalcaemia or have fluctuations in plasma calcium levels that may cause discomfort. Also, indices of quality of life (QoL) have been reported to be significantly reduced in HypoPT, including fatigue, reduced endurance and a tendency to depression [7;8]. Accordingly, improved treatment options are warranted.

HypoPT is the only major hormonal insufficiency state that is usually not treated by replacing the missing hormone. This is in striking contrast to e.g. hypothyroidism, type 1 and many cases of type 2 diabetes mellitus, gonadal insufficiency, growth hormone deficiency, diabetes insipidus and adrenal insufficiency. In recent years, several studies have been performed on PTH replacement therapy (PTH-RT) in HypoPT, showing non-inferiority to convention treatment regimes on indices of calcium homeostasis and promising preliminary results on indices of bone metabolism and quality of life (QoL) [9 -14] In the present paper, our aim is to review available data on effects of PTH-RT on calcium-phosphate homeostasis, bone metabolism, and QoL. Published studies are summarized in Table 1.

Parathyroid hormone as a drug

Prior to the development of recombinant DNA technology, PTH was only available as a bovine extract which was tested as a treatment option in a single patients by Fuller Albright in 1929 [15], showing PTH´s ability to increase plasma calcium levels, to discontinue the patients many daily attacks of carpopedal spasms and to turn his positive Chvostek's and Trousseaus signs negative. In 1967 a second paper was published on treatment of 2 patients with bovine PTH, but one of the patients developed neutralizing antibodies against the drug [16]. Following these initial experiments, no further studies with PTH-RT were performed for a long time.

However, the development of recombinant DNA technology has now done it possible, using a strain of Escherichia coli, to synthesize a PTH molecule that is fully identical to human PTH (1-84) or truncated PTH (1-34), thereby minimizing the risk of developing neutralizing antibodies. Moreover, following the results from large scale studies showing a decreased risk of fracture in osteoporotic patients treated with PTH, PTH has been approved as an anabolic anti-osteoporotic agent in the clinical setting.[21-27]. The fact that PTH now is commercially available has eased the access to PTH and thereby facilitated further investigations on effects of PTH-RT in HypoPT.

PTH is a polypeptide hormone with 84 amino acids. Although receptors for both the N- and C-terminal part of the full molecule have been identified, the physiological function of the C-terminal part of the molecule is not yet entirely clear, whereas it is well documented that the N-terminal part is of importance to the effects of PTH on calcium homeostasis [17]. Currently, truncated PTH (1-34), which is the active 34 amino acid N-terminal part of the hormone (teriparatide) and PTH (1-84) (Preotact) which is the intact hormone are manufactured commercially and used in the treatment of osteoporosis [16;18-25]. The pharmacokinetic and dynamic characteristics of the two commercially available PTH metabolites are shown in table 2.

Both drugs have been tested in the treatment of HypoPT (Table 1), but none of them have so far been approved for treatment of HypoPT. In the treatment of osteoporosis, PTH is administrated subcutaneously in the abdominal skin causing a high, but short lived peak concentration in plasma PTH levels. This transient elevation in PTH levels stimulates new bone formation by stimulating osteoblastic activity over osteoclastic activity [26-32], as opposed to continuously elevated PTH levels which causes a catabolic effect on bones as seen in patients with primary hyperparathyroidism [33;34]. However, in the treatment of HypoPT, the aim is not to achieve a very high peak of PTH concentration, but rather to supply the patients with a more stable and constant level of PTH in order to maintain plasma calcium levels close to normal and to relive other possible effects of lack of PTH in tissues expressing the PTH receptor

gene. Therefore, PTH is injected into the thigh, which is a site with a slower absorption rate than the abdomen. This is comparable to the administration of rapid-acting and long-acting insulin in patients with diabetes.

Effects of PTH substitution on calcium-phosphate homeostasis

Effects of PTH (1-34) on calcium-phosphate homeostasis in HypoPT have been investigated in three short term [10;11;13] and two long-term [12;35] open-label randomized studies, including adults [10-12] as well as children [13;35]. Moreover, in a cohort study including 30 patients with HypoPT, effects of two-years of treatment with PTH (1-84) have recently been reported [9].

In 1996, Winer et al. [10] performed the first controlled study on PTH-RT. In a randomized cross-over trial, effects of 10 weeks of treatment with PTH(1-34) administrated as a once-a-day s.c. injection were compared with conventional treatment with calcitriol plus calcium supplements administrated twice-a-day. The study included 10 adult patients with HypoPT. They were admitted to hospital for the first 2 weeks of treatment for dose-adjustment of PTH (1-34) and calcitriol in order to achieve plasma calcium in the low normal range. Moreover, if possible without causing hypocalcaemia, dose was adjusted in order to maintain urinary calcium to creatinine ratio less than 0.25 mmol/mmol (measured as grams per 24 hours). During trial, dietary intake of calcium ranged from 1 to 2 g of elemental calcium. During treatment with calcitriol, a daily supplement with 1000 mg of calcium was administrated in four-divided doses. The study showed that a single morning injection with PTH (1-34) is able to maintain plasma calcium levels within the normal range throughout the 24 hours following the injection. It can also produce a concomitant decrease in plasma phosphate levels and in urinary calcium excretion.

However, a rather large increase in plasma calcium levels with a tendency towards hypercalcaemia was observed 6-10 hours following injection. Therefore, in a subsequent study [11], 14 weeks of treatment with PTH (1-34) administrated once-a-day was compared with 14 weeks of twice-a-day administration in 17 adults. Similar to the first study, this was an open-label randomized, cross-over study with participants admitted to hospital for dose-adjustment during the first two-weeks of treatment. Prior to the study (at baseline), all participants received treatment with calcitriol and calcium. The study included 6 adult patients with autosomal dominant hypocalcaemia (ADH) due to an activating mutation in the calcium sensing receptor (CaSR) gene and 11 patients with idiopathic or acquired HypoPT. As a marked difference was evident between these two groups, results were stratified accordingly. Overall, the dose needed when PTH (1-34) was administrated twice-a-day was approximately half of the dose needed during once a day administration. However, for both dosing schedules, the doses needed by patients with ADH were markedly higher (52 ± 28 vs.141 ± 80 µg/d for twice- vs. once a day, respectively, $p<0.005$) than the doses needed by patients with idiopathic or acquired hypoparathyroidism (45 ± 36 vs. 80 ± 41 µg/d for twice- vs. once a day, respectively, $p<0.005$). The difference in the once-a-day dose between patients with ADH versus idiopathic and acquired (others) were 2.62±1.58 vs 1.00±0.81 µg/kg per day ($p<0.05$) respectively.

In both groups of patients plasma calcium levels peaked 4-5 hours after administration of PTH (1-34) in the once-a-day arm, and in the twice–a-day arm there was another peak 4-5 hours after the 2nd injection. After 14 weeks of treatment with PTH (1-34) and no treatment with calcitriol there was observed a significantly difference in plasma calcium levels between the patients with ADH and the others. In the once-a-day group patients with ADH had a mean serum calcium at

1.67 ± 0.12 mmol/l vs the others 2.02 ± 0.18 mmol/l (p<0.001) and in the twice-a-day group 1.91 ± 0.15 mmol/l vs 2.03 ± 0.15 mmol/l, respectively (p<0.05). Patients with ADH had baseline plasma calcium levels at 2.19 ± 0.26 mmol/l, 14 week's levels in the once-a-day arm were 1.67 ± 0.12 mmol/l (p<0.001) and in the twice-a-day 1.91 ± 0.15 mmol/l(p<0.05). Patients with acquired or idiopathic HypoPT had baseline plasma calcium levels at 2.21 ± 0.22 mmol/l. 14 weeks levels in the once-a-day arm were 2.02 ± 0.18 mmol/l and in the twice-a-day arm 2.03 ± 0.15 mmol/l. None of these values were significantly different from baseline values.

The 24h mean plasma calcium was not significantly different comparing once-a-day with twice-a-day administration. However, a major difference was evident on the 24h profile of plasma calcium levels. Once-a-day compared with twice-a-day administration caused significantly higher plasma calcium levels during the first part of the day and significantly lower levels during the second half of the day. Accordingly, episodes with hypocalcaemia were significantly less frequent in the twice-a-day treatment arm compared to the once-a-day arm. Within the group of patients with acquired or idiopathic HypoPT, no episodes of hypercalcaemia occurred when plasma calcium levels were monitored for 24h during twice-a-day administration, whereas hypercalcaemia was present in 4% of the blood samples obtained during once-a-day administration (p<0.02). Although the frequency of biochemical hypocalcaemia did not differ significantly there was a tendency towards fewer episodes with twice-a-day- (32%) compared with once-a-day- (43%) administration (p=0.4). In contrast, episodes of hypocalcaemia were significantly more frequent during a 24h monitoring in the ADH group during once-a-day- (91%) than during twice-a-day- (63%) administration (p<0.001). There were no episodes of hypercalcaemia in the ADH group.

Both treatment schedules reduced mean 24h-renal calcium excretion by app. 33% independently of whether PTH (1-34) was administrated once- or twice-a-day. Although this decrease in urinary calcium did not reach statistical significance, 24h-urinary calcium was within the normal range for females in the 13 female participants following PTH (1-34) treatment (in contrast to prior to treatment), whereas 24h-urinary calcium remained elevated above the normal range for males in the group of 4 male participants, although a non-significant decrease compared with baseline values was observed.

Following the two short-term studies, Winer et al [12] performed a long-term randomized, parallel group, open-label trial comparing effects of three years of treatment with PTH (1-34) administrated twice-a-day with conventional treatment with calcitriol and calcium in a group of 17 adults with HypoPT. In accordance with the findings from the two studies with a shorter duration of treatment, long term treatment with PTH (1-34) maintained plasma calcium-, phosphate-, and magnesium-concentrations at levels similar to the concentrations during conventional treatment. However, in contrast to conventional treatment, PTH (1-34) normalized the mean 24h renal calcium excretion from year one to three (8.2±0.5 vs. 5.8±0.3 mmol/day). Plasma phosphate and magnesium levels as well as urinary phosphate and magnesium did not differ between groups.

Similar to the findings in adults, a randomized, open-label cross-over trial lasting 28 weeks in children aged 4-17 years (for etiology see table 1).showed that the averages dose of PTH (1-34) needed to maintain plasma calcium levels in the lower part of the reference interval is significantly lower during twice-a-day-administration (25±15 µg/d), as compared with administration once-a-day (58±28 µg/d, p<0.001) [13]. In addition, 24h-profile measurements showed that twice-a-day- administration increased plasma calcium and magnesium levels more effectively than a once-daily dose, which

was especially evident during the second half of the day (12–24 h). Accordingly, episodes of hypocalcemia were less frequent during twice-daily compared with once-daily administration. Renal 24h-excretion of calcium, phosphate, and magnesium did not differ between PTH (1-34) treatment schedules and did not change as compared with baseline values. In a subsequent open-label study, 12 children aged 5-14 years with HypoPT were randomized to three years of treatment with either PTH (1-34) administrated twice-a-day or conventional treatment with calcitriol plus calcium [35]. Similar to the findings in adults, treatment with PTH (1-34) maintained plasma calcium, phosphate and magnesium concentrations at levels comparable to conventional treatment. Renal 24h calcium, phosphate and magnesium excretion did not differ across time or by treatment group.

Due to the different pharmacokinetic and –dynamic characteristics of PTH (1-34) and intact PTH (1-84) (Tabel 2), the two drugs may cause a differential response in patients with HypoPT. However, so far clinical experiences with intact PTH (1-84) in HypoPT are limited as only results from one cohort study are available [9]. In this study, PTH (1-84) was administrated for two years to 30 adult patients with HypoPT of different etiologies including postsurgical (n=15), idiopathic (n=11), autoimmune (n=1), DiGeorge (n=2) and autosomal dominant (n=1) HypoPT. In the studies on effects of treatment with PTH (1-34), the dose of PTH (1-34) was adjusted in order to obtain normocalcemia without needs for concomitant treatment with active vitamin D metabolites. In contrast, in the cohort study, PTH (1-84) was administrated as an add-one therapy in a fixed dose of 100 μg administrated as a subcutaneous injection in the thigh every other day and the daily dose of calcitriol and calcium was down-titrated if plasma calcium levels, as measured 48h after last dose of intact PTH, were above the pre-treatment level. Accordingly, the need for oral calcium and calcitriol decreased significantly from 3.030±2.325 to 1.661±1.267g/day and from 0.68±0.5 to 0.40±0.5 μg/day, respectively. Seven patients ended up with no need for active vitamin D. During treatment with intact PTH, plasma calcium levels were maintained in the lower half of the normal range and did not differ from baseline values from month 9 and forward. The 24h-renal calcium excretion was significantly increased at month 3, but unchanged compared with baseline at subsequent measurements. Moreover, plasma phosphate and magnesium levels decreased slightly but significantly during the two years of treatment.

In summary, in 5 randomized studies in adults and children PTH (1-34) therapy has been shown to maintain plasma calcium concentrations at an acceptable level thereby fully abolishing the needs for treatment with active vitamin D analogues [9-13, 35]. Apparently, administration of PTH (1-34) twice a day controls plasma calcium levels better than once-a-day-administration. Treatment with intact PTH (1-84) has been investigated lees extensively, but administration of intact PTH (1-84) every second day has been shown to decrease the doses of calcitriol and calcium needed to maintain normocalcemia. Urinary calcium levels are often markedly increased in patients with HypoPT on conventional therapy. As PTH increases renal tubular calcium reabsorption, a decrease in renal calcium excretion is to be expected in response to PTH-RT. However, discrepant results have been reported on whether urinary calcium is reduced in response to PTH, with most studies showing no significant effect [9;12;13]. A physiological explanation for this could be that the PTH treatment facilitates renal $1\alpha,25(OH)_2D$ production and thereby intestinal calcium absorption. Furthermore, PTH treatment may increase bone remodeling leading to a transient loss of bone mineral. Both mechanisms will tend to increase the renal output of calcium. Furthermore, the relative few participants included in the trials have limited the statistical power to detect significant changes, and the primary focus of the studies has been maintenance of

normocalcemia, whereas a reduction in urinary calcium has been considered as a secondary end-point. In some studies, plasma phosphate and magnesium levels have been reported to decrease in response to PTH-RT, but overall no consistent effects have been reported on phosphate- and magnesium-homeostasis in response to treatment. Most of the patients included in published studies have had acquired or idiopathic HypoPT, whereas only a few have had ADH due to an activating mutation in the CaSR. However, as underlined by the 14 weeks study by Winer et al. [12], in which 6 patients with ADH were included such patients are atypical and should be treated with extraordinary caution due to their tendency to develop hypocalcaemia.

Bone metabolism in hypoparathyreoidism

Due to the lack of PTH, HypoPT is a state of low bone turnover. In a few studies, histomorphometric analyses on transcortical iliac crest bone biopsies have been performed [36-38], showing that despite normal plasma calcium levels, conventional treatment with vitamin D and calcium is not able to maintain a normal bone turnover. Compared with 13 age- and gender matched healthy controls, Langdahl et al [36] found a significantly decreased activation frequency with a prolonged quiescent period in 12 vitamin D treated patients with HypoPT (10 treated with 1α-hydroxylated vitamin D and 2 with calciferol oil). Compared with the controls, the patients had a significant reduced total resorption rate and final resorption depth, and a prolonged resorption period. Indices of bone formation were reduced as well, but to a lesser extent than those of bone resorption causing an overall tendency toward a positive bone balance [36]. In accordance with these findings, a recent study by Rubin et al [37] showed a decreased bone resorption- and formation-rate in a group of 33 1α-hydroxylated vitamin D treated patients with HypoPT as compared with 33 age- and sex-matched control subjects. Patients with HypoPT had a larger cancellous bone volume with an increased trabecular- and cortical-width. The duration of the disease correlated positively with both trabecular- and cortical-width. In a subsequent analysis of the biopsies using high-resolution microcomputed tomography (μCT), Rubin et al [39] showed that patients with HypoPT (n=25) compared with matched controls had a significantly greater bone surface density, trabecular thickness, trabecular number, and connectivity density. Additionally, HypoPT was associated with a greater cancellous bone volume, whereas trabecular separation and estimation of the plate-rod characteristic were significantly lower, indicating a more plate-like trabecular structure [39].

In accordance with the histomorphometric- and μCT findings, areal bone mineral density (aBMD) as assessed by dual energy X-ray absorptiometry (DXA) is increased [40-42] whereas bone turnover as assessed by measurements of biochemical markers of bone turnover (BTM) is decreased [37;41-44] in HypoPT. In several cross-sectional studies, an increased aBMD has been found at the lumbar spine and/or the proximal femur [40-42;45-47] and in cohort studies, decreased bone loss rates have been found in patients with HypoPT [42]. However, at the distal forearm and femoral midshaft, variable results have been reported as only some [42;46;47], but not all [40;45] studies have shown an increased BMD compared with matched controls. Fujiyama et al [42] found an increased BMD at the ultradistal forearm which contains predominantly trabecular bone, whereas BMD did not differ from matched controls at the 10% and 33% distal ends, which contain predominantly cortical bone. Similarly, using peripheral quantitative computed tomography (pQCT), Chen et al [47] found an increased trabecular volumetric BMD (vBMD) at the forearm, whereas cortical vBMD was similar to healthy age- and sex-matched controls. These findings are in agreement with the findings

by Chan et al [41] showing that the increase in aBMD is relatively greater at the lumbar spine (rich in trabecular bone) than at the femoral neck (rich in cortical bone). Accordingly, it seems that the increased bone mass in HypoPT is mainly due to an increase in cancellous bone, with a preservation of cortical bone.

Effects of PTH-RT on bone turnover

In all studies in which patients with HypoPT have received replacement therapy with PTH, bone turnover has increased in response to treatments, as assessed by measurements of biochemical bone turn-over markers (BTM). In the short-term studies by Winer et al [10;11;13], treatment of adults and children with PTH(1-34) caused a significant increase in bone formation markers (osteocalcin and alkaline phosphatase) compared with conventional treatment with calcitriol, whereas levels of bone resorption markers (24h urine deoxypyridinoline and pyridinoline) increased only non-significantly in response to treatment. However, compared with conventional treatment, urinary levels of deoxypyridinoline and pyridinoline increased significantly in response to 3 years of treatment with PTH (1-34) [12]. In this study, formative as well as resorptive BTM increased gradually in response to PTH treatment with a peak following 2 to 2.5 years of treatment. However, at year three (end of study), BTM decreased compared with values at year 2.5, which may indicate that PTH treatment is needed for a long time period before bone turnover starts to normalize. Similarly, in children treated with PTH (1-34) markers of bone formation and resorption were increased throughout the three years of treatment compared with conventional treatment, although a tendency towards decreased levels of markers of bone resorption was observed from year two to three [35]. Only few data are available on effects of treatment with PTH (1-84) on markers of bone turnover. In an uncontrolled dose-finding pilot study including five patients with HypoPT, six-months of treatment with PTH (1-84) increased levels of bone formation markers (plasma propeptide of type 1 procollagen and bone specific alkaline phosphate) and resorption markers (plasma ß-C-telopeptide and Tartrate-resistant acid phosphatase) considerably compared with baseline levels [9]. The rise in BTM was more pronounced if PTH (1-84) was administrated daily compared with administration every second or third day. During two years of treatment with 100 μg of PTH (1-84) administrated every second day, levels of alkaline phosphatase were increased compared with baseline values, but did not exceed the upper limit of the reference interval [9].

Effects of PTH-RT on bone mineral density

In three studies, the long term (two to three years) effects of PTH-RT on aBMD have been investigated [9;12;35;37]. In two randomized studies the effects of three years of PTH-RT on aBMD were compared to conventional treatment in adults [9;12;37] and children [35]. In adults as well as in children, PTH (1-34) did not cause significant changes in aBMD compared with conventional treatment at the lumbar spine, femoral neck, total femur, or whole body. However, at the distal one-third of the radius, PTH (1-34) treatment resulted in a downward trend in aBMD in children [35] as well as in adults [9;12;37]. In adults, although groups did not differ significantly, aBMD increased in both groups during the three years of study, with a significant trend effect in the PTH (1-34) group [12]. Similar to the finding on effects of PTH (1-34), aBMD at the distal radius decreased significantly compared with baseline during two years of treatment with PTH (1-84) [9;37]. However, in contrast to the findings from studies with PTH (1-34), Rubin et al.

[9;37] reported a significantly increased lumbar spine aBMD with no changes in aBMD at the femoral neck in response to two years of treatment with PTH (1-84). So far, PTH-RT with PTH(1-34) and PTH(1-84) has not been compared head-to-head and therefore it is unknown whether the different results are due to differences in pharmacological effects of the two drugs or solely reflects *by chance* findings which in part may be due to the relatively small number of patients included (Table 1).

In a case report, Theman et al [53] have reported data on a 20 year old female with ADH treated with PTH (1-34) twice a day for 13.5 years. Apparently, this is the longest follow-up report on the effects of PTH-RT. In accordance with the findings from the above mentioned trials, longitudinal growth was normal as compared with her healthy twin sister, indicating no harmful effects on growth of long term PTH-RT in growing ADH children. Moreover, in accordance with the findings in groups of patients treated with PTH-RT, aBMD at the lumbar spine, femoral neck, and whole body increased to above normal, whereas aBMD at the distal radius decreased to below normal. In a transcortical iliac crest bone biopsy obtained at the age of 19 years, cancellous bone volume was elevated due to an increase in trabecular numbers but not trabecular width.

Overall, HypoPT is a state with increased bone mass which mainly is due to an increase in cancellous bone, with a preservation of cortical bone. Similar to patients with osteoporosis, PTH-RT in patients with HypoPT seems to exert bone anabolic effects on trabecular bone, causing a further increase in aBMD at sites rich in cancellous bone, whereas the effects seems to be slightly less positive or neutral at sites rich in cortical bone, except for the forearm. Similar to patients with osteoporosis, PTH treatment decreased aBMD at the radius [22]. In patients with osteoporosis, the decrease was present at the shaft of the radius, rich in cortical bone, but not at the ultradistal site, rich in trabecular bone [22]. In patients with osteoporosis, effects of treatment with PTH (1-34) have been assessed by the use of pQCT scans at the 15% distal radius sites, showing an improve bone geometry [48;49]. Compared with placebo, treatment did not affect total or cortical bone density, but increased total bone mineral content (BMC) and total as well as cortical bone area, which was due to an increased periosteal and endocortical circumferences despite an unchanged cortical thickness. In terms of biomechanical properties, the net results of the increased periosteal mineral apposition and increased endocortical bone resorption were higher axial and polar cross-sectional moments of inertia with increased bone strength [48;49]. Accordingly, assessments of treatment effects by aBMD do not seem to reflect cortical bone changes in an appropriate manner. If similar changes in bone geometry apply to patients with HypoPT on PTH-RT, the decrease in aBMD at the forearm does probably not reflect a decreased biomechanical competence.

Effects of PTH substitution therapy on quality of life

Despite plasma calcium levels within the accepted therapeutic range, HypoPT is associated with a decreased quality of life (QoL) due to symptoms such as anxiety, phobic anxiety and their physical equivalents [7;8]. So far, effects of PTH-RT on indices of QoL have not been evaluated systematically, but Winer et al [12] reported that several patients in the PTH (1-34) treatment arm described an improved QoL, less fatigue and greater endurance in contrast to the calcitriol arm [12]. Whether this is due to a better regulated (i.e. more physiological) calcium homeostasis during PTH-RT or due to a direct effect of PTH on the neuromuscular system needs further evaluation, as well as the potential effects of PTH-RT on indices of QoL needs to be studied further.

Adverse effects

During initiation of PTH (1-34) therapy, episodes of hypercalcemia occur more frequently until the dose has been titrated. Winer et al. [10] reported hypercalcaemia in 9.5% of the blood samples in the PTH (1-34) arm with a peak around 10 days after initiation of treatment compared with 2.9 % in the calcitriol arm. During the three years of treatment with PTH (1-34), Winer et al. [12] found no significantly difference in overall number of reported adverse events compared with placebo. However, seven patients in the PTH (1-34) arm complained of mild intermittent lower extremity pain, consistent with bone pain compared to three patients in the calcitriol arm [12].

In the study by Rubin et al [9], no serious adverse events occurred during two years of treatment with PTH (1-84), although transient mild hypercalcaemia occurred sporadically during the study in about 4% of all blood samples. The highest plasma total calcium level measured was 3.2 mmol/l. Incidences of hypercalcemia were not closely related to time and dose. However, as blood was collected 48h following last injection, more studies are needed on diurnal changes in plasma calcium levels, as a temporal relationship exist between plasma calcium levels and time of drug administration [10;11;13].

In the assessment of unwanted and beneficial effects of PTH-RT, it is important to compare these effects with effects of conventional treatment. Treatment with active vitamin D analogues may cause vitamin D intoxication, which it is very unpleasant for the patient and threatens renal function. As the plasma half-life of active vitamin D analogues is much longer than the half life of PTH, hypercalcaemia due to intoxication will last for a longer period if caused by active vitamin D compared with PTH. Furthermore, vitamin D intoxication tends to increase plasma phosphate whereas PTH has the opposite effect.

In growing rats, treatment with a very high dose of PTH (1-34) was found to increase the risk of osteosarcoma [53;54]. Thus, there have been concerns on whether similar adverse effects may apply to humans during long term treatment [55]. However, until now more than 400.000 patients with osteoporosis have received treatment with either PTH (1-34) or PTH (1-84) and within this population there have only been reported two cases of osteosarcoma [54]. Nevertheless, there is a need for further assessment of potential long-term risks, as PTH only is administrated for a maximum of two-years in the treatment of osteoporosis.

Overall, risk of fracture in patients with HypoPT is unknown. Due to an increased aBMD at most measurement sites, a decreased risk of fracture may be expected. However, in the group of patients with HypoPT (n=30) included in the study by Rubin et al [9;37], 24% reported a prior fracture, which may indicate that risk of fracture is not as low as may be predicted from the aBMD values. This may be due the fact that a very low bone turnover may impair the process of repairing microdamage and cause accumulation of hyper-mature bone. Theoretically, this may lead to bone that is stiffer than tough and thus more likely to fracture, similar to the findings in patients on long term treatment with bisphosphonates [50]. Effects of HypoPT on bone strength may differ according to the relative distribution of trabecular and cortical bone at different sites. In a cohort study on 33 postmenopausal patients who had a total thyroidectomy due to a thyroid carcinoma, the incidence of radiographic spinal deformities was significantly lower in the 13 subjects who developed HypoPT following thyroidectomy compared with the incidence in the 20 women who retained a normal parathyroid function [42]. Accordingly, it is possible that sites rich in cortical bone may be more hampered by low bone

remodeling, than sites rich in trabecular bone. Large epidemiological studies are warranted in order to assess whether risk of fracture is increased compared with the background population, as well as long term follow up during PTH-RT is needed in terms of fracture risk assessment.

Perspectives

In addition to assessment of long term effects of PTH-RT, further studies should investigate how to optimize administration of PTH. In osteoporosis, a peak in PTH concentration is warranted in order to obtain a bone anabolic effect. In contrast, a steady level within the reference range of plasma PTH is desirable in the treatment of HypoPT. This has been underlined by the findings by Winer et al [11;13], showing that twice-a-day-administration of PTH (1-34) caused a more physiological regulation of plasma calcium levels than administration of a higher dose once-a-day. Moreover, studied subjects reported that they preferred to inject themselves twice-a-day rather than once-a-day; indicating that maintaining plasma calcium levels at a steady level and the persistence of circulating PTH during all 24 hours is of importance to patients. However, more studies are necessary to demonstrate that exogenous PTH to patients with HypoPT is superior to treatment with active vitamin D metabolites with respect to QoL, physical performance and risk of complications.

A patch has been develop by which PTH (1-34) can be administrated transdermal, causing a rapid rise in plasma PTH concentrations similar to the peak occurring in response to s.c. injections [51]. Further studies should investigate whether slow-release patches can be developed in order to deliver a continuous low amount of PTH throughout the day to patients with HypoPT. Multipulse subcutaneous infusion of teriparatide with a MiniMed pump [56] and a Pulsatile-release of parathyroid hormone from an implantable delivery system [57] have also been investigated.

Following neck surgery, severe hypocalcemia may develop if the parathyroid glands are damaged, necessitating intravenous calcium infusions. In a case-report [48], s.c. administration of PTH to a patient with severe post-surgical hypoparathyroid hypocalcemia abolished the needs for calcium infusions. Further studies should try to determine whether PTH treatment is a feasible option as rescue treatment in severe post-surgical hypoparathyroid hypocalcemia.

Conclusion

PTH-RT is fully capable to maintain plasma calcium within the physiological normal range and may possess potential advantages compared with conventional therapy in terms of a reduced renal calcium excretion and an improved QoL. Moreover, the very low bone turnover normally present during conventional treatment is increased in response to PTH-RT. A normalisation of bone remodelling might enable repairing of micro cracks, and thereby increase bone strength. Despite an increased bone turnover, aBMD does not seem to decrease in response to PTH-RP. Similar to patients with osteoporosis on treatment with PTH, PTH-RT seems to exert bone anabolic effects in patients with HypoPT thereby increasing bone mass. Further studies should aim to confirm these potential advantageous effects of PTH-RT as well as long term beneficial and adverse effects of treatment should be determined, Moreover, there is a need for studies on how PTH is best administrated in order to obtain a steady level with plasma calcium concentrations within the normal range. Finally, we should know more about the epidemiology of HypoPT and the clinical consequences of the disease and its treatment.

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