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Reduction in requirements of oral calcium and 1-25 dihydroxy vitamin D in patients with post-surgical hypoparathyroidism treated with teriparatide (PTH_{1-34})

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Abstract

The objective of the study is to evaluate the effect of daily administration of recombinant parathyroid hormone (PTH_{1-34}), 20 µg, on serum calcium concentrations (Cas), and the requirements of oral calcium and calcitriol in patients with hypoparathyroidism. It is a prospective, longitudinal study, analytical, with intervention, in patients treated with high doses of calcium (> 7 g/day), with symptoms of hypocalcemia and/or intolerant to treatment. Serum levels of phosphorus (Ps) and Cas, urinary calcium excretion, oral doses of calcitriol and calcium were compared before and after administration of teriparatide, for three months on average, in patients with post-surgical hypoparathyroidism. We studied 16 patients with oral elemental calcium requirements of 22.5 ± 16 g/day of calcitriol 0.79 ± 0.4 µg/day. Cas at baseline was 7.6 ± 1.2 and Ps 5.4 ± 0.76 mg/dl. After administration of teriparatide, Cas was 9.0 ± 0.69 mg/dl (p = 0.007) and Ps of 4.5 ± 0.87 mg/dl (p = 0.003). Doses of calcium and calcitriol showed a statistically significant reduction (p = 0.0001 and 0.001, respectively). We conclude that use of recombinant parathyroid hormone can normalize Cas and Ps, with reduction in oral calcium and calcitriol requirements. (Gac Med Mex. 2016;152:289-94)

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Introduction

Hypoparathyroidism is one of the last classical endocrine deficiencies whose treatment still does not include the administration of the deficient hormone. Usual therapy consists of oral calcium, calcitriol and phosphorus chelating agents at different doses, and its goals are to prevent hypocalcemia symptoms, relieve hyperphosphatemia and maintain serum calcium ($_sCa$) at acceptably low levels in order to prevent hypercalciuria; sometimes, thiazide diuretics are added to attain the latter goal[1,2]. Even when the patient has good adherence to medical indications, important fluctuations occur in the levels of $_sCa$ over time in such a way that long-term treatment can represent a considerable challenge, in part because some patients require high doses of oral calcium, which causes adverse effects. It is usual for a patient to alternate signs and symptoms of hypocalcemia that may even be

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life-threatening, with signs and symptoms secondary to the adverse effects of high doses of oral calcium[13].

This falling behind in hypoparathyroidism treatment with regard to the treatment of the other hormone deficiencies is partly due to the fact that primary hypoparathyroidism is a relatively rare entity; the most common etiology is inadvertent removal or permanent damage of the parathyroid glands in neck surgery. Post-surgical transient hypoparathyroidism is relatively common (6.9 to 46%), but the chronic form, defined as that which remains for at least 6 months, is rarer (0.9 to 1.6%)[4]. The prevalence of post-surgical hypoparathyroidism is estimated at approximately 22 per 100,000 individuals. Autoimmune hypoparathyoidism and the variety that forms part of some genetic syndromes are even rarer.

Since the year 2002, the Food and Drug Administration (FDA) approved the use of parathyroid hormone (PTH) for the treatment of osteoporosis; although its use in hypoparathyoidism is appealing, it was until January 23, 2015 when the FDA approved the use of recombinant PTH (PTH_{1-84}Natpara®) in the treatment of hypoparathyroidism; however, this drug is not available in Mexico, unlike PTH_{1-34} (Forteo®), which has been used since 2002 for the treatment of osteoporosis and is available in Mexico but is not approved by the FDA for the treatment of hypoparathyroidism.

In the past few decades, both observational and randomized controlled studies have published, where PTH_{1-34}[5-10] and intact PTH (PTH_{1-84}) have been employed in the treatment of patients with hypoparathyroidism[11,12].

Based on the difficulties some patients may have to maintain $_sCa$ levels within normal limits at the long-term without experiencing the adverse effects of high doses of oral calcium, the performance of this study, which has the purpose to assess the effect of PTH_{1-34} daily administration on $_sCa$ and $_sP$ levels and on oral calcium and clacitriol requirements in patients with difficult-to-control hypoparathyroidism was decided.

Material and methods

This is an analytical, interventional, prospective, longitudinal study carried out in patients older than 18 years who had been diagnosed with post-surgical hypoparathyroidism, were treated with high doses of calcium (elemental calcium > 7 g/day) and were treatment-intolerant and/or had hypocalcemia symptoms in spite of several adjustments. $_sCa$ and $_sP$ levels, urinary calcium excretion, oral calcium dose and calcitriol dose were compared prior and after PTH_{1-34} administration.

All patients were treated at the Endocrinology Department of the ISSSTE CMN 20 de Noviembre, a national tertiary care center. At the initial visit, after having signed an informed consent form, and being explained the study procedures, the PTH_{1-34} administration technique was explained to them and a subcutaneous dose of 20 mg every 24 h was indicated; simultaneously, the reduction of initial calcium and calcitriol doses was started. Subsequent visits of the patients were every 8 to 10 days and, at each one of them, data on hypocalcemia were inquired (paresthesias, tetany, broncho- or laryngospasm and seizures), oral calcium administration side effects were assessed (epigastric burning sensation, diarrhea, abdominal distension), a well as PTH_{1-34} administration side effects such as nausea, dizziness, headache, orthostatic hypotension or allergic skin reactions. Trousseau and Chvostec signs were searched in all patients at physical examination. $_sCa$ and $_sP$ results were also reviewed. If $_sCa$ levels were higher than 9 mg/dl, calcium doses were reduced by 25%; on the contrary, if $_sCa$ level was lower than 8 mg/dl, the calcium doses were increased by 25%, without the PTH_{1-34} dose being modified. When blood calcium levels reached between 8 and 9 mg/dl, in addition to the levels of $_sCa$ and $_sP$, 24-hour urinary calcium and urinary calcium/creatinine (Ca/Cr) ratio were requested. Patient follow-up was 3 months on average (range, 1 to 8 months) and they had 6.6 visits on average (5 to 8), until $_sCa$ levels and oral calcium and calcitriol doses were stabilized.

This protocol was authorized by the ISSSTE CMN 20 de Noviembre Research and Ethics Committees.

Statistical methods: Descriptive statistics, frequency, average and standard deviation were used. For the comparison of quantitative variables, statistics for dependent groups was used, the Wilcoxon test with an alpha value of 0.05.

Results

A total of 18 patients were included in the study, out of which two were eliminated: a female patient decided to withdraw from the study and another had an adverse reaction to PTH_{1-34}; finally, a 16-patient sample remained.

Of the 16 remaining hypoparathyroidism patients, 15 females and one male, with an average age of 54 ± 12 years were studied. The patients' demographic characteristics are shown in table 1. In all of

Table 1. Demographic characteristics of the patients with postsurgical hypoparathyroidism (average ± SD)

No. of patients	16
Gender (female/male)	15/1
Age (years)	54 ± 12
BMI (kg/m^2)	29.2 ± 5
Time of evolution (years)	10.3 ± 10
TT surgical indication	
Papillary cancer	8
Medullary cancer	2
Multinodular compressive goiter	5
Hashimoto's thyroiditis	1

BMI: body mass index; TT: total thyroidectomy.

them, parathyroidism had been caused by total thyroidectomy. Surgical indication was papillary cancer in 8 patients, medullary cancer in 2, multinodular goiter with compression symptoms in 5 and, in one patient, total thyroidectomy was practiced due to a fine needle aspiration biopsy with a diagnosis of papillary cancer, although definitive histopathological diagnosis was Hashimoto's thyroiditis (Table 1).

Parathyroidism time of evolution was 10 ± 10 years; one male patient had one year of evolution and one female patient 41 years. At the start of the study, all patients required oral calcium high doses, with an average of 22.5 ± 16 g of elemental calcium, in the form of calcium carbonate powder coffee or tablespoons, 1 g calcium carbonate capsules, 500 to 750-mg calcium carbonate tablets or 500-mg glubionate plus calcium carbonate effervescent tablets. The patient with the highest requirements consumed 72 g of elemental calcium, whereas the one who required the least employed 7.8 g. With regard to calcitriol, maximum dose was 1.5 µg and minimum 0.25 µg/day. A single patient was taking hydrochlorothiazide as part of the treatment of systemic arterial hypertension; however, at the start of the study, the treatment was changed, with the thiazide diuretic being discontinued.

The patients entered the study with an average $_sCa$ of 7.6 ± 1.2 mg/dl and 5.4 ± 0.76 mg/dl for phosphorus.

Table 2 shows the results for the initial mineral profile of the group of studied patients, including urinary calcium, the initial average of which was 212 ± 152 mg/dl, and initial elemental calcium requirements.

Before the treatment with PTH_{1-34} was started, 14 of the 16 patients (88%) had clinical signs and symptoms of hypocalcemia almost every day, including paresthesias or positivity to the Chvostek or Trousseau signs.

One-hundred percent of the patients had at least one symptom consistent with hypocalcemia or one side effect to the use of oral calcium; 15 patients (93%) had signs and symptoms consistent with gastritis, 11 (69%) experienced diarrhea, 81%, abdominal distension, 75%, cramps and/or paresthesias, 32% nausea, and one patient constipation. The calcium consumption side effects in the group of studied patients are described in table 3.

PTH_{1-34} initial dose was 20 µg every 24 hours in all patients. In one female patient, final dose was 20 µg every 24 hours and 20 µg every 12 hours every other day; the rest of the patients used one administration (20 µg) per day.

The patients required between 3 and 5 office visits to stabilize the calcium, calcitriol and PTH_{1-34} doses and attain $_sCa$ levels ≥ 8 mg/dl.

Table 2. Baseline mineral profile and elemental calcium baseline requirements

	Average ± SD	Minimum	Maximum
Serum calcium (mg/dl)	7.6 ± 1.2	6.0	9.5
Serum phosphorus (mg/dl)	5.4 ± 0.76	4.1	6.8
Serum magnesium (mg/dl)	1.9 ± 0.14	1.5	2.1
Urinary calcium (mg/24 h)	211 ± 152	39.7	492.8
s Ca/P ratio*	41.9 ± 8.3	27	57
u Ca/Cr ratio†	0.30 ± 0.29	0.03	1.10
Elemental calcium initial dose (g/24 h)	22.53 ± 16.6	7.8	72

*serum
†urinary

Table 3. Calcium oral doses side effects

	Number of patients (%)
Epigastric burning sensation	15/16 (93%)
Diarrhea	11/16 (69%)
Gastric distension	13/16 (81%)
Nausea	5/16 (31%)
Constipation	1/16 (6%)
Cramps and paresthesias	12/16 (75%)

Final $_{s}$Ca, at the moment of study data cutoff, was 9 ± 0.69 mg/dl, with a statistically significant difference (p = 0.007) with regard to initial calcium (7.6 ± 1.2 mg/dl). $_{s}$P at the end of the study was 4.5 ± 0.87 mg/dl, with a statistically significant difference with regard to phosphorus baseline value (p = 0.003). There is no significant difference between urinary calcium values at the beginning and the end of the study (229 ± 121 final vs. 211 ± 152 mg/24 h initial, p = 0.326), or in the urinary Ca/Cr ratio (p = 0.205) or the $_{s}$Ca/$_{s}$P product (p = 0.379) (Table 4).

Elemental calcium final dose was 3.86 ± 2.6 g, which has a statistically significant difference with the initial dose of 22.5 ± 16 g (p = 0.0001). Elemental calcium dose had an average reduction of 18.6 ± 16 g with the use of PTH_{1-34}, which represents a decrease of 78% in calcium requirements.

With regard to calcitriol, final dose was 0.35 µg/day ± 0.18, with a statistically significant difference (p = 0.001) as related to the dose at the start of the study, with an average decrease of 0.43 ± 0.36 µg/day, which represents a reduction of 44.7% with regard to calcitriol initial dose (Table 4).

The reduction of 50% or more in the oral calcium dose was attained in 100% of the patients; 68% of the patients decreased the calcitriol dose by 50% or more, 4 patients (25%) remained on the same dose and one patient reduced the dose by 33% (Table 5).

When symptoms associated with the start of the treatment with PTH_{1-34} were assessed, 50% of the patients (8/16) had no symptoms at all after the medication administration. In the remaining 50%, several symptoms were reported; however, headache was the most common (50%), followed by musculoskeletal pain (43%), tiredness (18.7%) and dizziness and nausea (12.5%). However, these symptoms disappeared in an average of 2 weeks after the administration of PTH_{1-34}. By the end of the study, 100% of the sample denied symptoms associated with the PTH_{1-34} administration.

As for the reduction in calcium ingestion-related signs or symptoms, 50% of the patients referred a complete improvement and the other 50% partial improvement.

Maximum follow-up time was 26 months in one female patient, and the minimum was 6 months.

Discussion

The general purpose of this study was to demonstrate that daily administration of PTH_{1-34} helps to maintain $_{s}$Ca normal concentrations and at the same time reduces oral calcium and calcitriol requirements in patients with difficult-to-control hypoparathyroidism, as defined by considerable variations displayed in calcium requirements and/or persistence of signs and symptoms of hypocalcemia and/or adverse effects associated with high doses of oral calcium.

Table 4. Comparison of the mineral profile and elemental calcium doses at the beginning and the end of the study

	Initial (average ± SD)	Final (average ± SD)	p
Serum calcium (mg/dl)	7.6 ± 1.2	9 ± 0.69	0.007
Serum phosphorus (mg/dl)	5.4 ± 0.76	4.5 ± 0.87	0.003
Urinary calcium (mg/24 h)	211 ± 152	229 ± 121	0.326
Urinary Ca/Cr ratio	0.30 ± 0.29	0.34 ± 0.16	0.205
Plasma calcium/phosphorus product	41.9 ± 8.3	40.4 ± 7.2	0.379
Elemental calcium dose (g)	22.53 ± 16.6	3.86 ± 2.6	0.0001
Calcitriol dose (µg)	0.79 ± 0.4	0.35 ± 0.18	0.001

Wilcoxon test. SD: standard deviation.

Table 5. Percentage of reduction in oral calcium and calcitriol doses for each patient

Patient	Oral calcium dose reduction %	Calcitriol dose reduction %
1	51.3	33
2	100	66
3	98.8	75
4	70	50
5	66.7	66
6	83.4	0
7	62.5	66
8	50	0
9	83	0
10	88.5	0
11	71.8	50
12	98.3	83
13	72.4	50
14	68	66
15	75	50
16	100	66

This work demonstrated that, after PTH_{1-34} administration, $_sCa$ values can be maintained at normal levels, with a concomitant decrease of oral calcium and calcitriol doses, with a statistically significant difference, similar to data that have been reported in previous studies[5-10]; in addition, a decrease and normalization in the levels of $_sP$ was also observed.

Although 24-h urinary calcium normalization and therefore urinary Ca/Cr ratio normalization have also been reported to occur after the use of PTH_{1-34}, we did not find an improvement in these parameters, as in the studies by Sikjaer[12] and Winer et al[7], who found a reduction in 24-h urinary calcium below the upper reference limit in the group treated with PTH_{1-34}, but with no significant difference with the conventionally-treated group.

As for the adverse effects experienced by the patients in our study, they are similar to those described in placebo-controlled trials; in no patient had the treatment to be discontinued due to adverse events and these disappeared in an average of 2 weeks after treatment initiation[5-11].

According to the results of this and other studies, there is no doubt on the usefulness of PTH_{1-34} in the treatment of patients with hypoparathyroidism; however, there is so far no experience enough on its long-term use.

Currently, there are two forms of recombinant PTH available: PTH_{1-84} and PTH_{1-34}. In November 2002, the FDA approved PTH_{1-34} for the treatment of osteoporosis, but its use is limited to 2 years and only for patients at substantial risk for fracture[13]. In January 23, 2015, the FDA approved the use of recombinant PTH_{1-84} (Natpara®) for the treatment of hypoparathyroidism, based on one pharmacological and 4 efficacy and safety studies. The pivotal study for approval was REPLACE, a multi-center trial with 134 patients with a 24-week follow-up; the first study goes back to 1996, when 10 adult patients with hypoparathyroidism were administered PTH_{1-34} for 12 weeks[5]; this pilot study was followed by a 28-week randomized crossover trial comparing once-daily with twice-daily PTH_{1-84} administration; subjects randomized to two daily doses showed less variations in the $_sCa$ levels and normalized urinary calcium[7]. Subsequently, the two-dose regimen was selected for a 3-year randomized trial comparing PTH_{1-34} with calcium and calcitriol in 27 subjects; $_sCa$ levels were similar in both arms, urinary calcium mean was normal in PTH-treated subjects but with no statistically significant difference with the control group; in our study, we also observed no difference between the levels of urinary calcium before and after the treatment with PTH_{1-34}. These results have been replicated both in adults and in children[8-10]. There is still a lack of studies to assess the safety of long-term treatment with PTH, since the longest studies have used it for 4 years; there is the work published in 2009 b KK Winer, where the case of a 20-year old woman on treatment with PTH_{1-34} since the age of 6 years and 2 months is described, concluding that its use can be safe on the long-term, even in children[15]. The safety of PTH_{1-34} has been recently reviewed, with special attention to reports of osteosarcoma in rats, which were administered doses equivalent to 3 to 60-fold the doses in humans for a period equivalent to 75 years in human beings[16,17]. The nearly 12 years of history of PTH in the treatment of osteoporisis do not provide evidence of osteosarcoma being a risk when PTH_{1-34} or PTH_{1-84} are used for 2 years[18,19].

The treatment with oral calcium and vitamin D and/or its metabolites or analogues is the cornerstone of the treatment of hyperparathyroidism, but it is not free of gastrointestinal side effects, or else it is not strange for hypercalcemia and hypercalciuria to occur, with the ensuing risk for nephrolithiasis and nephrocalcinosis. Hyperphosphatemia is also not unusual and can lead to soft tissue and basal ganglia calcification.

The most important difference of our study with regard to others is that it selected exclusively patients with difficult-to-control hypoparathyroidism, who used high doses of calcium and calcitriol and that in spite

of these doses experienced episodes of hypocalcemia, frequently driven by the onset of the adverse effects caused by the high oral calcium doses employed.

The weakness of this study lies in its design, since it is not a placebo-controlled randomized clinical trial, in addition that it has a reduced number of patients, since it included a single center.

PTH_{1-34} is not approved for the treatment of hypoparathyroidism in our country in spite of its potential advantages; in addition to those found in this study, other have been demonstrated, such as the reduction of urinary calcium excretion, decrease in soft tissue calcifications and improved quality of life. The treatment with PTH_{1-34} has also been described as being able to counteract the bone mass increase observed in patients with hypoparathyroidism, with an improvement in bone quality, since bone tissue dynamics can return to that observed in the euparathyroid state[12,20,21].

According to the results of our study, we conclude that PTH_{1-34} can be an adjuvant treatment in the control of patients with difficult-to-control hypoparathyroidism who require high doses of oral calcium, who are intolerant to these doses and/or have difficulty to maintain $_{s}Ca$ stable levels due to the frequent appearance of oral calcium adverse effects. According to our study, PTH_{1-34} recommendable doses can be 20 mg every 24 hours, since the aim is not to substitute the conventional treatment based on oral calcium and calcitriol with this analogue, but only to avoid the side effects associated with the consumption of large amounts of calcium, favor $_{s}Ca$ stabilization and improve the patient's quality of life. A higher dose of PTH_{1-34} is not recommendable since we lack information on long-term side effects, in addition that the cost of the treatment, high as it is with a single dose, would increase substantially, especially in comparison with the usual treatment with calcium and calcitriol, which should be considered the first line of treatment.

The results shown are promising, but the lack of studies on long-term safety and the elevated cost of the drug are parameters that, in our country, must be taken into account in the selection of patients that may benefit from this treatment.

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