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Long-term Treatment of Acromegaly with Lanreotide: Evidence of Increased Serum Parathormone Concentration

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Abstract. The somatostatin analogue lanreotide is effective in reducing growth hormone levels in patients with acromegaly. Acromegaly is characterized by calcium homeostasis alterations. The aim of our study was to evaluate the effects of lanreotide on bone turnover markers in a group of acromegalic patients and to verify a possible increase of intact parathormone (iPTH) levels in a transient or persistent way. Serum GH, IGF-I and serum and urinary markers of bone metabolism were measured before treatment and on months 3 and 24. In short-term treatment (3 months), lanreotide significantly decreased GH, IGF-I, serum calcium, osteocalcin and alkaline phosphatase levels, but increased iPTH level (49 ± 16.7 *vs* pre-treatment 28.3 ± 7.6 ng/L, $p<0.001$). During long-term study (24 months) GH and IGF-I were significantly still low; serum calcium and alkaline phosphatase levels returned to pre-treatment levels. iPTH level was significantly still higher compared with pre-treatment (46.4 ± 9.2 *vs* 28.3 ± 7.6 ng/L, $p<0.05$). No changes were seen in serum albumin, creatinine and vitamin D during short and long term treatment. The changes of most bone markers during lanreotide treatment can be explained by the decrease of GH and IGF-I. The increase of iPTH concentration suggests that lanreotide has ulterior and long-standing actions on calcium homeostasis: intestinal malabsorption of calcium due to the lanreotide could contribute to this "secondary" hyperparathyroidism. The clinical relevance of these long-standing effects needs to be further investigated.

Key words: Acromegaly, Lanreotide, Parathormone, Bone homeostasis

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THE somatostatin analogue lanreotide is a powerful growth hormone (GH) lowering drug in patients with acromegaly. Common early, but mainly transient, side-effects are flatulence, diarrhea and fatty stools, interpreted as signs and symptoms of malabsorption. Calcium homeostasis is regulated by iPTH and by the active form of vitamin D (1,25 $(OH)_2$ vit D) [1].

GH is indispensable for normal bone growth, and could play an active role in adulthood bone turnover [2]. It is known that acromegalic patients show abnormalities in calcium-phosphate metabolism and morphologic skeleton alterations [3]. Pituitary adenectomy corrects many of these biochemical alterations [4, 5]. During octreotide treatment in acromegaly normal levels of calcium, phosphate and 1,25 $(OH)_2$ vit D have been reported [6, 7]. Few authors have reported that long treatment with octreotide significantly corrects some biochemical abnormalities of bone turnover, but they also reported that it induces an increase of iPTH [8, 9] in contrast to pituitary adenectomy [4] and bromocriptine therapy [10].

The aim of our study was to evaluate the effects of lanreotide on bone turnover markers in 35 acromegalic patients and to verify a possible increase of iPTH levels in a transient or persistent way.

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Patients and Methods

In our department we enrolled 35 patients (21 females and 14 males), aged 32–75 years, with clinical signs and symptoms of acromegaly. Informed consent

to participate in the study was obtained from each patient and the study was approved by the local ethical committee. Eight females patients were in menopausal age, but they had not received estrogenic substitutive therapy. Lanreotide was administered subcutaneously two times a month and the dose was adjusted for optimal effect on GH and IGF-I levels. No other therapy for acromegaly was allowed during this study. GH, IGF-I and bone metabolism parameters were determined before treatment and on months 3 and 24. GH was measured by immunoradiometric assay (hGH-CTK IRMA; Sorin Biomedica, Saluggia, Italy; sensitivity of the assay was 0.15 μg/L); IGF-I was tested by radioimmunoassay (RIA, Nichols Institute Diagnostic, San Juan Capistrano, CA, USA; sensitivity of the assay was 0.3 μg/L); serum calcium, phosphate, alkaline phosphatase and albumin were measured using an autoanalyzer method; serum calcium was corrected for albumin concentration. Urinary excretions of calcium, phosphate, hydroxyproline and creatinine were measured with colorimetric methods. Urinary excretions were expressed as ratio with the urinary creatinine (mg/g). We evaluated renal phosphate handling deriving the phosphate threshold concentration (TmP/GFR) from the nomogram by Walton *et al.* [11]. Osteocalcin was tested by immunoradiometric assay (Immutopics Inc., San Clemente, CA, USA.; normal range 11–32 μg/L) and iPTH was measured by radioimmunoassay (Nichols Institute of Diagnostic; normal range 12–53 ng/L). All assays were performed in duplicate. Results are given as the mean ± SEM, if not otherwise stated. Statistical analysis was performed by means of Student's *t*-test for paired data with correction for multiple comparison according to the method of Bonferroni.

Results

Short-term treatment (3 months)

During short-term treatment with lanreotide GH and IGF-I levels significantly decreased, as did serum calcium, osteocalcin and alkaline phosphatase levels. Serum iPTH increased gradually during the whole treatment period and was significantly higher than the basal level. Treatment had no significant effects on serum phospate, albumin and 1,25 $(OH)_2$ vit D levels. Calcium urinary excretion significantly decreased while urinary phosphate excretion increased (171.8 ± 101.9 mg/g *vs* 112.6 ± 98.3 mg/g, $p<0.01$ and 561.7 ± 176.4 mg/g *vs* 658.1 ± 150.8 mg/g, $p<0.05$, respectively). No variation of urinary hydroxyproline excretion was observed (21.2 ± 10.8 mg/g *vs* 19.9 ± 11.1 mg/g, NS). No significant variation of renal threshold phosphate concentration was observed during short-term treatment (3.7 mg/dl *vs* 3.5 mg/dl, NS).

Long-term treatment (24 months)

During long-term treatment, GH and IGF-I values were still significantly low. Mean serum calcium and alkaline phosphatase levels returned to the pre-treatment values, while osteocalcin level was still low.

The mean serum iPTH concentration remained significantly higher compared to pre-treatment. Long-term treatment had no effect on phospate, albumin and 1,25 $(OH)_2$ vit D. No variation of urinary excretion of hydroxyproline was observed (21.2 ± 10.8 mg/g *vs* 20.4 ± 11.2 mg/g, NS). Urinary excretion of calcium significantly decreased and urinary phosphate excretion significantly increased (171.8 ± 101.9 mg/g *vs* 98.6 ± 96.2 mg/g, $p<0.01$ and 561.7 ± 176.4 mg/g *vs* 677.2 ± 102.6 mg/g, $p<0.01$, respectively). Renal threshold phosphate concentration significantly decreased (3.7 mg/dl *vs* 3.3 mg/dl, $p< 0.05$).

Table 1 summarizes the changes in urinary and blood parameters during short and long-term lanreotide treatment.

Discussion

Calcium homeostasis is altered in acromegaly [10]. Serum total calcium level is generally within the upper normal range and hypercalciuria is frequent in acromegalics [12–14]: this is due to the increased intestinal calcium absorption secondary to enhanced renal synthesis of 1,25 $(OH)_2$ vit D [4, 8, 15, 16], although the increased bone resorption may contribute [3]. Furthermore, acromegalic patients show increased renal phosphate reabsorption [17] resulting in serum phosphate levels within or above normal range [18]. Increased serum osteocalcin levels have been found in acromegalics [3, 5, 12, 19–22] as GH, IGF-I and 1,25 $(OH)_2$ vit D stimulate osteocalcin synthesis [23, 24].

A significant decrease in circulating levels of calcium, phosphate and 1,25 $(OH)_2$ vit D have been observed in patients with acromegaly after pituitary

Table 1. Serum and urinary markers of bone metabolism in 35 patients with active acromegaly before lanreotide treatment and on month 3 and 24 (mean ± SEM)

	Range	Pre-treatment	On treatment (3 months)	On treatment (24 months)
GH (μg/L)	<5	23.6 ± 9.8	4.9 ± 2.4*	4 ± 1.3*
IGF-I (μg/L)	<300	876 ± 231.7	238 ± 72.3°	217 ± 58.3*
Calcium (mg/dL)	8.6–10.6	9.9 ± 0.3	9.1 ± 0.2§	9.8 ± 0.2
Osteocalcin (μg/L)	11–32	13.4 ± 4.6	11.5 ± 4.9°	11.1 ± 3.5°
Alkaline phosphatase (U/L)	30–85	92.4 ± 17.4	81.1 ± 21.6°	91.1 ± 11.3
IPTH (ng/L)	7–35	28.3 ± 7.6	49 ± 16.7§	46.4 ± 9.2°
Phosphate (mg/dl)	2.5–4.3	4.3 ± 0.5	4.2 ± 0.6	4.0 ± 0.4
Albumine (g/dl)	3.5–5.0	4.2 ± 0.6	4.1 ± 0.4	4.2 ± 0.3
25Hydroxycholecaliferol (ng/ml)	8–40	30.0 ± 8.4	31.0 ± 7.9	30.0 ± 6.8
1,25Dihydroxycholecalciferol (ng/ml)	15–75	48.0 ± 11.0	46.0 ± 9.2	47.0 ± 8.3
Urinary calcium (mg/g)	—	171.8 ± 101.9	112.6 ± 98.3*	98.0 ± 96.2*
Urinary phosphate (mg/g)	—	561.7 ± 176.4	658.1 ± 150.8°	677.2 ± 102.6*
Urinary hydroxyproline (mg/g)	—	21.2 ± 10.8	19.9 ± 11.1	20.4 ± 11.2
Tm P/GFR (mg/dl)	2.5–4.2	3.7 ± 0.2	3.5 ± 0.1	3.3 ± 0.2°

°$p<0.05$, *$p<0.01$, §$p<0.001$ *vs* pre-treatment

adenectomy [4]. This can be explained by the decrease in GH levels with diminished effects on renal 1α-hydroxylase activity and on renal phosphate reabsorption [4, 5]. In the same way, the significant changes in calcium and phosphate levels in the present study could be explained physiopathologically by the significant decrease of GH and IGF-I secretion due to lanreotide treatment.

Serum levels of iPTH in normocalcemic acromegalic patients are reported to be normal or increased [4, 25]. No significant changes in iPTH levels after pituitary adenectomy have been observed [4]. In contrast, the most striking finding in our study is an early but lasting significant increase of iPTH levels. Legovini and Fredstorp observed the same result with octerotide [8, 9].

Chanson *et al.* reported signs of malabsorption during lanreotide treatment not only as an initial and temporary side-effect, but also during long-term treatment [26]. It may be postulated that calcium intestinal absorption could decrease during long-term lanreotide treatment. This could enhance the calcium lowering effect of decreased GH levels. In our study we found a significant reduction of serum calcium after 3 months of treatment with lanreotide, but not after 24 months. Our data suggest that treatment of acromegaly with lanreotide decreases serum calcium levels enough to trigger an increased iPTH secretion from the parathyroid glands; so this secondary hyperparathyroidism can completely restore the serum levels of calcium as our study reported. Takamoto *et al.* reported a significant decrease of serum 1,25 $(OH)_2$ vit D in acromegalic patients after pituitary adenectomy, and they explained it by the decrease in GH levels with diminished effects on renal 1α-hydroxylase activity and on renal phosphate reabsorbion [4]. Our data show no difference in 1,25 $(OH)_2$ vit D levels before and after lanreotide treatment. We suppose that this could be explained by the secondary increase of iPTH, seen during long-term lanreotide therapy, but not after pituitary adenectomy [4]. In fact iPTH stimulates renal 1α-hydroxylase activity, which may oppose the decreased GH stimulation of this enzyme, resulting in unaltered 1,25 $(OH)_2$ vit D levels, as seen in the present study.

In conclusion the present study shows that lanreotide could revert some abnormalities of bone metabolism in acromegalic patients through reduction of GH and IGF-I secretions, but it may have further effects due to its action on gut, notably a transient reduction of serum calcium and a persistent "secondary" increase of parathormone concentrations. The clinical consequences of this mild hyperparathyroidism need to be clarified, particularly as far as bone density is concerned.

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