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Case report

Over-supplementation of vitamin D in two patients with primary hyperparathyroidism

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ABSTRACT

OBJECTIVE: To describe the biochemical effects of an over-supplementation of vitamin D3 in two patients with primary hyperparathyroidism (PHPT). DESIGN: Two patients (A and B) with PHPT took erroneously 2,400,000U (300,000 U/day for 8 days) and 4,500,000U (300,000 U/day for 15 days) of cholecalciferol, respectively. They were followed for 4 months and ionized calcium, creatinine, PTH, 25 hydroxy-vitamin D, 1,25(OH)$_2$D and urinary calcium/creatinine levels were measured. Finally, the patients were operated on and a parathyroid adenoma was removed in both. RESULTS: One week after the last dose of vitamin D, serum ionized calcium (iCa) rose from 1.35 to 1.41 mMol/L (n.r. 1.14-1.31) for patient A, and from 1.43 to 1.62 for patient B, while fasting urinary Calcium/Creatinine (uCa/Cr) augmented from 0.31 to 0.50 mg/mg, and from 0.32 to 0.55, respectively. During the follow-up, the average levels of iCa were 1.37 ± 0.03 and 1.48 ± 0.07 mMol/L, while those of uCa/Cr were 0.29 ± 0.13 and 0.32 ± 0.13, both iCa and uCa/Cr levels returning to baseline values within 4 months. CONCLUSIONS: The unintentional over-supplementation of vitamin D in the two PHPT patients caused a moderate and temporary increase of hypercalcemia and hypercalciuria and was not associated with clinical signs of toxicity.

Key words: Hypercalcemia, Hypercalciuria, Primary hyperparathyroidism, Safety, Toxicity, Vitamin D

INTRODUCTION

Hypovitaminosis D is common in patients with primary hyperparathyroidism (PHPT).[1,2] Some studies suggest that vitamin D deficiency may promote a marked parathyroid cell proliferation in PHPT patients,[3] whilst the maintenance or restoration of vitamin D sufficiency is capable of preventing or reversing this phenomenon.[1-5] The aforementioned considerations have been acknowledged by the recent Guidelines for the Management of Asymptomatic

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Primary Hyperparathyroidism, that recommend the correction of vitamin D deficiency in these patients.[6] Nevertheless, vitamin D supplementation is not prescribed to patients with primary hyperparathyroidism (PHPT) because of the concerns regarding possible exacerbation of hypercalcemia and/or hypercalciuria.[1,7-10] Moreover, the recent review on calcium and vitamin D by the Institute of Medicine raised concerns about the safety of vitamin D supplements.[11] Consequently, data on vitamin D supplementation in PHPT are limited. We report here two patients with PHPT and vitamin D deficiency who erroneously took an over-supplementation of vitamin D3. They were followed for 4 months by evaluating the main biochemical parameters of calcium homeostasis.

CASE REPORT

Two women (patient A aged 53 years, BMI 28, and patient B aged 63 years, BMI 24), referred to our Endocrinology Department for hypercalcemia (patient A: total calcium 10.80 mg/dL, patient B: 11.44), had a diagnosis of PHPT and vitamin D deficiency. According to our experience, in healthy subjects[12] a single oral dose of cholecalciferol 300,000 IU should have been prescribed, but erroneously, the two patients were given 2,400,000 IU (300,000 IU/day for 8 days, patient A) and 4,500,000 IU (300,000 IU/day for 15 days, patient B). The patients were followed for 4 months in our outpatient clinics and gave witnessed informed consent to data collection and examination.

One week after the last dose of vitamin D, serum ionized calcium (iCa) rose from 1.35 to 1.41 mMol/L (n.r. 1.14-1.31) for patient A, and from 1.43 to 1.62 for patient B, while fasting urinary Calcium/Creatinine (uCa/Cr) augmented from 0.31 to 0.50 mg/mg, and from 0.32 to 0.55, respectively (Figure 1). During the follow-up, the average levels (Mean ± SD) of iCa were 1.37 ± 0.03 and 1.48 ± 0.07 mMol/L, while those of uCa/Cr were 0.29 ± 0.13 and 0.32 ± 0.13. Both iCa and uCa/Cr levels returned to baseline values within 4 months.

25-hydroxy-cholecalciferol (25OHD) levels rose quickly and attained values higher than 150 ng/mL during the first month in patient B and during the

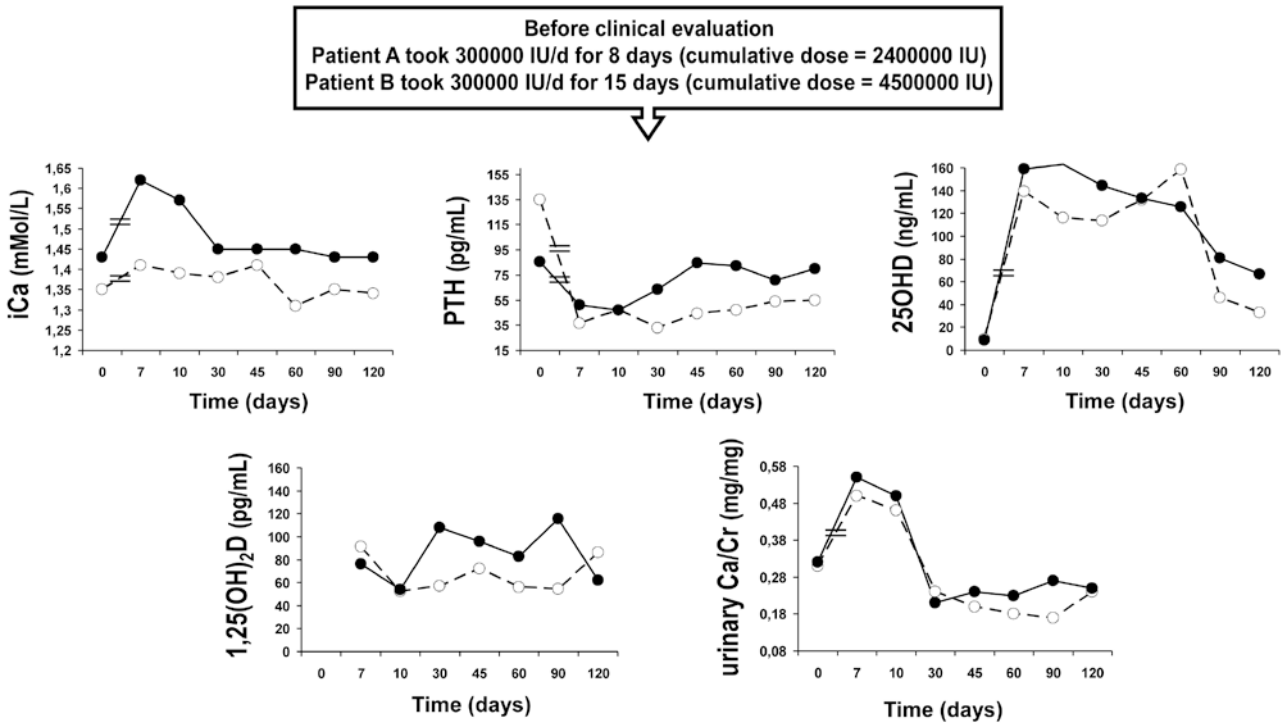

FIGURE 1. Biochemical data of the vitamin D3 over-treatment Variations of the levels of iCa, PTH, 25OHD, 1,25$(OH)_2$D and urinary Ca/Cr during the 4 months after vitamin D loading dose in patient A (○) and B (●).

second month in patient A, reaching ≤70 ng/mL by the end of the observation period (Figure 1). PTH levels, in turn, quickly declined after the vitamin D load and began to rise again from the second month. The changes of PTH and 25(OH)D levels were significantly and negatively correlated (patient A: r = -0.71, p = 0.03; patient B: r = -0.71, p = 0.05), while no significant correlation was found between $1,25(OH)_2D$ variations and changes of PTH or 25OHD levels.

The patients were encouraged to markedly increase their daily water intake (more than 3 litres/day). They did not develop any symptom or clinical sign of hypercalcemia. Serum creatinine levels did not change over time (Mean ± SD, 0.83 ± 0.04 mg/dL for patient A; 0.49 ± 0.04 for patient B) and neither patient developed urolithiasis. After 4 months of vitamin D loading the patients were operated on, because of osteoporosis, and a parathyroid adenoma was removed in both. One year after surgery the patients had not developed any complication and serum, urinary and hormonal data were in the normal range.

DISCUSSION

Despite medical experts' recommendation to maintain serum 25-hydroxyvitamin D levels above 20 ng/mL in PHPT patients,[6] vitamin D supplementation is often avoided in these patients because of fear of exacerbating hypercalcemia and/or hypercalciuria.[1,7-10] Moreover, the recent review on calcium and vitamin D by the Institute of Medicine raised concerns about the safety of vitamin D supplementation.[11]

In normal subjects the threshold for vitamin D toxicity has not been established to date, though 25(OH)D concentration above 150 ng/ml is sometimes associated with hypercalcemia.[13] Several factors have been implicated in individual susceptibility to vitamin D toxicity, among them Vitamin D Binding Protein levels (DBP) and their polymorphic variants,[14] as well as the amount of adipose tissue and, consequently, of fat body mass, which is the storage site of vitamin D in humans.[15] Data on vitamin D supplementation and toxicity as regards PHPT are limited, so that our patients represent an unintentional and interesting clinical model of vitamin D excess in PHPT. Their 25OHD levels above 150 ng/mL induced only a moderate increase of hypercalcemia and hypercalciuria without symptoms of hypercalcemia and/or worsening of the renal function. However, since the most severe effects of excessive doses of vitamin D are manifest during the period of administration and we observed our patients one week after the last dose of vitamin D, we cannot exclude the probability that both serum and urinary calcium levels were higher during vitamin D administration.[15]

The negative correlation we found between 25OHD and PTH levels strongly suggests a vitamin D-dependent mechanism in our patients, a finding which likely could be extrapolated to normal subjects, while it also supports the hypothesis that the local 1α-hydroxylase activity of the parathyroid cells could regulate PTH synthesis and secretion.[16,17]

This case report confirms that PTH secretion may be modulated by vitamin D even in patients with PHPT. The unintentional over-supplementation of vitamin D caused a moderate increase of hypercalcemia and hypercalciuria and was not associated with clinical signs of toxicity. Thus, our cases suggest that there is no concern involved in supplementation for vitamin D deficient PHPT patients.

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