

## Treatment of unresponsive hypoparathyroidism when the oral route administration is not possible: Considering subcutaneous teriparatide



## Tratamiento con PTH subcutánea en el hipoparatiroidismo posquirúrgico de difícil control cuando la vía oral no está disponible

PTH is a polypeptide of 84 amino acids with an active fragment of 34 amino acids in the N-terminal extreme. It is secreted by the parathyroid glands, and it is involved in the regulation of calcium metabolism; its deficiency produces hypocalcemia. Hypoparathyroidism is most commonly caused by radical surgery of the neck or total thyroidectomy; according to different series it affects to 8–12% of the patients temporarily, and 1–2% of the cases permanently.<sup>1</sup> The usual chronic management of hypoparathyroidism is supplementation with calcium and 1,25-OH vitamin D (calcitriol) in variable doses. However, this treatment is sometimes insufficient.

We report the case of a 52-year-old man, with stage IV larynx carcinoma (lung metastases) diagnosed in 2011. Despite radiotherapy and several lines of chemotherapy, he presented slow progression of the neoplastic disease.

In 2014, because of progressive dyspnea, he underwent total palliative laryngectomy, which included total thyroidectomy with extensive resection of surrounding tissues. Histopathological study showed a moderately differentiated squamous cell carcinoma, with lymphatic and vascular invasion, as well as infiltration of adjacent tissues. Postoperatively, he developed a pharyngo-cutaneous fistula, and a nasogastric tube (NGT) was then placed for enteral nutrition, awaiting the closure of the fistula. Levothyroxine replacement, calcium and calcitriol were started through the NGT. However, the patient developed unresponsive postoperative hypocalcaemia, and was thus referred to the Endocrinology Department.

Pre-operative thyroid function and calcemia had always been normal. At the time of our assessment, the patient presented paresthesias. Calcemia reached a nadir of 5.8 mg/dL (normal 8.5–10 mg/dL), with normal albumin serum levels, while serum magnesium was as low as 1.3 mg/dL (normal 1.8–2.6 mg/dL). Serum phosphate was normal. The circulating post-operative PTH was undetectable (<2 pg/mL), and 1,25(OH)<sub>2</sub> D<sub>3</sub> was of 20 pg/mL (18–70 pg/mL).

Conventional treatment of hypoparathyroidism with calcium, magnesium, and calcitriol supplementation was started. We reached high medication doses (calcitriol 4 µg/24 hs, diluted to prevent precipitation in the NGT; calcium 6000 mg/day; and magnesium 1152 mg/day). Nevertheless, magnesium and 1-25-OH vitD levels were persistently low (1.3 mg/dL and 24 pg/mL, respectively). Moreover, the patient had poor digestive tolerance of these large calcium load, and required frequent intravenous infusions of calcium due to hypocalcaemia, which prevented hospital discharge. On the other hand, he developed hypercalciuria, with a calcium/creatinine ratio (24 h urine) of 906 mg/g

(normal 80–210 mg/g), which slightly fell only to 624 mg/g after the addition of thiazides, with no improvement of hypocalcaemia. At this point we decided to start treatment with subcutaneous parathyroid hormone. There are two currently available preparations (intact, 1–84 PTH; and teriparatide or 1–34 PTH). We chose teriparatide due to its availability at our hospital. As its use in hypoparathyroidism is off-label, we requested the patient's consent and the hospital's administration approval. Teriparatide (20 µg/12 h s.c.) was started, and this allowed for a drastic reduction of oral (via NGT) calcium and calcitriol, down to 4000 mg/day and 1.5 µg/day, respectively. Digestive tolerance improved significantly and no further intravenous calcium was required to maintain normocalcaemia, making hospital discharge possible.

After 2 months on teriparatide, the patient developed arthralgia that required opiate analgesia, which caused an intestinal subocclusion. As teriparatide was the suspected cause of arthralgia, it was withdrawn. At that time the fistula had closed, and the NGT was removed. Thus, oral calcium and calcitriol was initiated once the subocclusion resolved. After teriparatide was discontinued, the patient remained normocalcemic under standard doses of oral calcium and calcitriol (1500 mg/day and 0.5 µg/day), and has been well controlled since then. Arthralgias were finally attributed to teriparatide, because they are a frequent adverse effect,<sup>2</sup> and they were completely resolved after withdrawal.

Postoperative hypoparathyroidism is rather common.<sup>1</sup> Conventional treatment with calcium and vitamin D is usually able to maintain serum calcium at the lower limit of normality, thus preventing hypercalciuria. However, this treatment is occasionally not enough due to vitamin D resistance, or to malabsorption, so that alternative treatments such as subcutaneous PTH are needed. In this case, malabsorption was probably related to precipitation of calcium salts in NGT. In fact, to reduce the precipitation, it is advisable to dilute calcitriol before administration through the NGT.

Although hypoparathyroidism is due to PTH deficiency, PTH administration is only approved as an anabolic drug for the treatment of osteoporosis in a fixed dose (20 µg/day of PTH 1–34, or 100 µg/day of PTH 1–84), and for up to 2 years (due to the potential risk of osteosarcoma described in rodents,<sup>3</sup> with much higher doses than those used in humans).

Exceptionally, as in the present case, off-label use of teriparatide is allowed. Recent prospective studies have demonstrated the efficacy and safety of treatment with subcutaneous PTH in hypoparathyroidism of different causes, for up to 4 years.<sup>4</sup> In fact, we have already described treatment of refractory postoperative hypoparathyroidism with teriparatide administered by continuous infusion pump for 5 years.<sup>5</sup>

It has been demonstrated that treatment with PTH 1–84 leads to a significant decrease in calcium supplements of about 37%, and of vitamin D around 45%.<sup>4,6</sup> This is relevant taking into account the poor digestive tolerance and difficult adherence to treatment in patients who require high oral doses of calcium. Furthermore, treatment with teriparatide can decrease urinary calcium, improve bone mineral density at lumbar level, and improve quality of life.<sup>7</sup>

On the other hand, the most common adverse effects of teriparatide are gastrointestinal and musculoskeletal. The estimated incidence of hypercalcaemia is about 1.9% of cases<sup>4</sup> and it is usually easy to correct.

In conclusion, unresponsive hypoparathyroidism is a rare entity that can be controlled effectively by means of subcutaneous PTH, administered either by continuous infusion pump or by multiple injections. As it is an uncommon therapy, there are few security data in the long term, but it could be a therapeutic option to consider in the treatment of some cases of hypoparathyroidism resistant to treatment with calcium and vitamin D. On the other hand, potential side effects such as arthralgias must be taken into account.

### Conflict of interest

The authors declare that they have no conflicts of interest in this research.

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