CONTINUOUS 1-34 rhPTH THERAPY IN A GIRL WITH A PTH-GENE DEFECT

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Introduction

Familial isolated hyperparathyroidism (FIH; OMIM 14600) is an inherited disorder characterized by impaired parathyroid hormone (PTH) secretion or function caused by mutations in the calcium-sensing receptor gene (CASR; OMIM 601199), in the PTH gene (PTH; OMIM 168450) or in the GCM2 gene (OMIM 603716). The human PTH gene is located on chromosome 11 and consists of 3 exons. Exon 1 is untranscribed, exon 2 encodes a 25-amino-acid signal peptide and partly the prohormone, while exon 3 encodes the rest of the prohormone (6 amino-acids) and the entire PTH molecule (summing 84 amino-acids). Only a few mutations of the PTH gene have been described so far, only one of them suggesting an autosomal dominant manner of inheritance. FIH is clinically characterized by often severe hypocalcaemic episodes which require urgent intravenous administration of calcium and, after stabilisation of the pressure, a life-long calcium and vitamin D substitution. The main therapeutic challenge is to maintain serum calcium levels and urinary calcium excretion in normal ranges. Teriparatide (rhPTH 1-34) therapy has been proven efficient in decreasing the urinary calcium excretion and, as a result, to lower doses of vitamin D and calcium in patients with FIH. The literature data in children treated with rhPTH are sparse [Table 1].

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study pediatric population</th>
<th>Intervention and starting dose</th>
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</thead>
<tbody>
<tr>
<td>Matarazzo et al. [1]</td>
<td>6 patients 9.8±5.1 yr</td>
<td>PTH 1-34 s.c. 12.5 µg bid</td>
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<tr>
<td>Lingart et al. 2011 [2]</td>
<td>3 patients 8-11yr</td>
<td>PTH 1-34 pump 2.6 µg/kg/day</td>
</tr>
<tr>
<td>Winer et al. 2010 [3]</td>
<td>12 patients 5-14 yr</td>
<td>PTH 1-34 s.c. 0.4 µg/kg/dose</td>
</tr>
<tr>
<td>Winer et al. 2008 [4]</td>
<td>14 patients 4-17 yr</td>
<td>PTH 1-34 s.c. 0.4 µg/kg/dose</td>
</tr>
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</table>

Table 1: Published pediatric studies on therapy with PTH 1-34

Case report

In 2012 we have published a novel mutation of the PTH gene in a female patient, diagnosed at the age of 4 months with hyperparathyroidism [5]. First presentation occurred during an episode of symptomatic hypocalcaemia, with normal 25- and 1,25-Vitamin D serum levels. Treatment with 1,25-cholecalciferol and calcium was started immediately and led to a prompt improvement of the clinical status. Nephrocalcinosis II/III diagnosed at age of 2 years did not deteriorate thereafter. During the following 6 years of medical observation, the patient grew normally and showed stable serum calcium levels. At the age of 9 years the patient presented two episodes of severe hypocalcaemia and high dosages of intravenous calcium were necessary. At this point, a continuous subcutaneous rhPTH therapy was considered.

Treatment protocol

- PTH 1-34 therapy (trade name FORSTEQ) using a pump system (Medtronic Veo®) with a 1.8 ml reservoir
- Initial PTH 1-34 dosage: 0.5 µg/kg/day
- Constant continuous administration, no micropulses
- No additional calcium and vitamin D supplementation
- Normal diet
- Blood analysis and urine probes every 2 hours during the first 24 hours.
- Laboratory parameters: serum calcium and phosphorus, 25- and 1,25-Vitamin D, crosses, amino-terminal type I procollagen propeptide (P1NP) and urinary calcium/creatinine ratio.

Disscussion

- Analysis of rhPTH action in a human model of PTH +/-
- The increase of serum calcium corresponded with a peak crosses, suggesting an initial calcium regulation through bone resorption and not through renal calcium excretion
- Calcium urinary excretion remained elevated in the first 5 months of treatment, and decreased dramatically thereafter
- A reduction of the PTH dosage was not possible in the first 6 months of treatment, remarkably, 5 months after start of therapy the daily dose had to be increased to 0.55 µg/kg/day because of persistent paresis

Follow-up

Evolution of measured parameters during the first 35 hours and during the following 6 months

References

1. Matarazzo et al. [1].
2. Lingart et al. [2].

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