Abstract

Introduction: Therapy with vitamin D3 analogs suppress the parathyroid hormone (PTH) secretion in chronic kidney disease (CKD) patients suffering from secondary hyperparathyroidism (sHPT). The concurrent administration of calcium-containing phosphate binders further increases the likelihood of developing hypercalcemia. Calcimimetics, such as cinacalcet, lower PTH level while limiting the risks of hyperphosphatemia and/or hypercalcemia. In adults, clinical experience with calcimimetics has shown significant reductions in PTH levels in cases with sHPT, but the clinical experience in children with CKD is limited.

Case series: We report here the effect of short term use of cinacalcet on sHPT in two children on regular hemodialysis for CKD stage 5. Both children had very high PTH level which failed to be controlled with vitamin D3 and phosphate binders. We started cinacalcet therapy at a dose of 30 mg/day for both of them for duration of eight weeks. The first case was an 11 year-old male, his iPTH level decreased by 26% at four weeks after initiation of therapy and decreased by 39% at eight weeks. The second case was a 13 year-old female, her iPTH level decreased by 25% at four weeks after therapy and by 40% at eight weeks. There were no drug related side effects in both cases. Serum calcium and phosphorus levels remained stable in both patients.

Conclusion: Cinacalcet can be effectively used in the treatment of sHPT in children in the short term, with minimal changes in the serum levels of calcium and phosphorus.

Keywords: Children; Cinacalcet; Hemodialysis; hyperparathyroidism

Introduction

Therapy with an analog of 1,25 vitamin D3 and maintenance of low serum phosphorous levels, via dietary restriction of phosphorous intake and use of phosphate binders, suppress the PTH secretion by the parathyroid glands. This modality of therapy is used to treat secondary hyperparathyroidism (sHPT) in patients with chronic kidney disease (CKD) [1]. The concurrent administration of calcium-containing phosphate binding agents further increases the likelihood of developing hypercalcemia [2]. Accordingly, therapeutic strategies that lower parathyroid hormone (PTH) while limiting the risks of hyperphosphatemia and/or hypercalcemia, such as calcimimetics, are of considerable interest [3].

Cinacalcet (Sensipar/Mimpara®, Amgen, USA), a type II calcimimetic, allosterically increases the sensitivity of the calcium-sensing receptor, lowering the threshold for activation of parathyroid gland, and thereby decreasing secretion of parathyroid hormone (PTH) [4]. Studies have demonstrated its ability to lower PTH without significantly increasing serum calcium, phosphorus, and thus the calcium-phosphorus product [5].

We report here the effect of short term use of cinacalcet on sHPT in two children on regular hemodialysis for end stage kidney disease (ESKD).

Cases Series

Both patients were on hemodialysis, using Fresenius 2008K machines and hollow fiber polysulfone dialyzers (Fresenius, Bad Homburg, Germany), using standard dialysate solution.

The routine dialysis prescription was as follows: three sessions per week, three hours per session and blood
Case 1
A male aged 11 years was on regular hemodialysis for 3.5 years, for ESRD due to sickle cell nephropathy. He had persistently high iPTH for the previous year though his serum calcium and phosphorus levels were within the accepted ranges. We initiated cinacalcet (Mimpara, Amgen, USA) at a dose of 30 mg/day and followed his serum calcium, phosphorus and iPTH at four weeks and eight weeks of therapy. The results showed iPTH reduction by 26% at four weeks and by 39.4% at eight weeks. Serum calcium was slightly decreased after four weeks of therapy, accordingly we increased the dose of calcium carbonate and decreased the dose of intravenous paricalcitol according to guidelines for iPTH > 800 pg/mL [6]. After this modification, serum calcium returned to near normal level. Serum phosphorus showed almost no change during this treatment (Table-1).

Case 2
A female aged 13.5 year on regular hemodialysis for ESRD due to chronic interstitial nephritis for the previous 2.6 year. She also had high iPTH level that failed to be controlled with phosphate binders and intravenous paricalcitol. We initiated cinacalcet at a dose of 30 mg/day and followed her serum calcium, phosphorus and iPTH levels at four and eight weeks of therapy. At four weeks, iPTH decreased by 25.3% and by 40.1% at eight weeks with almost no effect on both serum calcium and phosphorus levels (Table-2).

Discussion
Secondary hyperparathyroidism, a high-turnover bone disease (HTBD), is manifested by elevated parathyroid hormone (PTH) levels. Control of HTBD may be achieved by maintaining low serum phosphorous levels and administering vitamin D therapy, although some patients continue to exhibit high PTH levels [7]. Clinical studies have shown significant reduction in PTH levels, decrease in the size of the hyperplastic parathyroid gland, avoidance of vascular calcification with minimal changes in serum calcium and phosphate level with the use of calcimimetics. The clinical experience with the use of calcimimetic in children with chronic renal disease is extremely limited. This is primarily due to concerns regarding bone growth, because of localization of calcimimetics in chondrocytes [8] and the fact that activation of the calcium-sensing receptors in the growth plate induces longitudinal bone growth [9, 10]. The effect of cinacalcet on mineral homeostasis is less clear in pediatric CKD patients than adults; perhaps as a result of active skeletal growth and the consequent influx and efflux of these minerals from bones [11]. The data regarding its use in children is mainly dependent on clinical experience. The cases presented here were two children with sHPT for which conventional therapy with active vitamin D and phosphate binders failed to achieve acceptable iPTH level. Both achieved significant reduction in iPTH levels without adversely affecting calcium and phosphorus levels. Silverstein and co-workers have described similar

Table 1: Serum levels of iPTH, calcium and phosphorus before and after initiating cinacalcet in case 1

<table>
<thead>
<tr>
<th></th>
<th>-8 weeks of cinacalcet</th>
<th>-4 weeks of cinacalcet</th>
<th>At the start of cinacalcet</th>
<th>+4 weeks of cinacalcet</th>
<th>+8 weeks of cinacalcet</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH (pg/ml)</td>
<td>796.8</td>
<td>853.6</td>
<td>901</td>
<td>666.3</td>
<td>546</td>
</tr>
<tr>
<td>Serum Calcium (mg/dl)</td>
<td>8.8</td>
<td>8.6</td>
<td>9.1</td>
<td>8.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>6.3</td>
<td>5.2</td>
<td>5.9</td>
<td>5.7</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Table 2: Serum levels of iPTH, calcium and phosphorus levels before and after initiating cinacalcet in case 2

<table>
<thead>
<tr>
<th></th>
<th>-8 weeks of cinacalcet</th>
<th>-4 weeks of cinacalcet</th>
<th>At the start of cinacalcet</th>
<th>+4 weeks of cinacalcet</th>
<th>+8 weeks of cinacalcet</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH (pg/ml)</td>
<td>1067</td>
<td>1192</td>
<td>1230</td>
<td>918.3</td>
<td>733</td>
</tr>
<tr>
<td>Serum Calcium (mg/dl)</td>
<td>9.3</td>
<td>8.8</td>
<td>8.7</td>
<td>8.9</td>
<td>8.1</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>6.7</td>
<td>4.4</td>
<td>6.6</td>
<td>6.1</td>
<td>5.2</td>
</tr>
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</table>
Cinacalcet use in children

results in nine pediatric patients with a mean age of 14.5 ± 1.0 years [7]. After three months of cinacalcet therapy, there was a 60% decline in parathyroid hormone levels. Muscheites and colleagues have also shown that cinacalcet was efficacious in the treatment of poorly controlled and vitamin D unresponsive shPTH in seven patients on renal replacement therapy with a mean age of 17 years (range 1.1-19). In these patients cinacalcet was given for four weeks at a dose of 0.25 mg/kg per day. There was a significant reduction in parathyroid hormone levels by approximately 74% [12]. Other studies used cinacalcet for longer duration, up to 3 years, as Platt and her colleagues who reported six cases with at least 86% reduction in serum iPTH [10].

Conclusion
We conclude that the short-term use of cinacalcet can be effective on reducing shPTH with minimal changes in the serum levels of calcium and phosphorus.

References


