Precocious puberty and unlicensed paediatric drugs for severe hyperparathyroidism

Justine Bacchetta1,2, Ingrid Plotton2,3, Bruno Ranchin1, Thierry Vial4, Marc Nicolino2,5, Yves Morel2,3 and Pierre Cochat1,2

1Service de Néphrologie et Rhumatologie Pédiatriques, Centre de Référence des Maladies Rénales Rares, Hôpital Femme Mère Enfant, Bron, 2Université de Lyon, F-69008, Lyon, 3Service d’Endocrinologie Moléculaire et Maladies Rares, Centre de Biologie Est, Hospices Civils de Lyon, Bron, 4Centre de Pharmacovigilance des Hospices Civils de Lyon, Lyon and 5Service d’Endocrinologie Pédiatrique, Hôpital Femme Mère Enfant, Lyon, France

Correspondence and offprint requests to: Justine Bacchetta; E-mail: justine.bacchetta@chu-lyon.fr

Abstract
Puberty is often delayed in children with chronic kidney disease. A 5-year-old boy suffering from severe chronic kidney disease due to a mutation in the TCF2 gene presented with a clinical precocious peripheral puberty 3 weeks after introducing cinacalcet and 2 months after introducing lanthanum carbonate. A retrospective measurement of serum sexual and adrenal hormones before the introduction of cinacalcet but after the introduction of lanthanum carbonate revealed an asymptomatic biological underlying precocious puberty. With more than 1-year follow-up, the aetiology of this precocious puberty remains unexplained. Cinacalcet can be responsible for hypotestosteronaemia in adults, but no case of precocious puberty has been described in association with cinacalcet so far. Natural lanthanides can activate in vitro the calcium sensor receptor, but there are no clinical data about side effects of lanthanum carbonate on sexual hormones. An unknown phenotype of TCF2 mutation may also be discussed. Monitoring of plasma testosterone in patients receiving unlicensed paediatric drugs for managing hyperparathyroidism and presenting with a change in genitals is therefore recommended.

Keywords: cinacalcet; chronic kidney disease; lanthanum; precocious puberty; TCF2 mutation

Case report
A 5-year-old boy was diagnosed with renal hypodysplasia with a de novo mutation in the TCF2/HNF1ß (transcription factor 2/hepatocyte nuclear factor type 1ß) gene during infancy (renal cysts and diabetes syndrome). Renal function progressively deteriorated, leading to severe CKD (estimated GFR 10 mL/min/1.73 m2).

Hyperparathyroidism progressed despite conventional conservative measures. The first therapeutic step included alphacalcidol, calcium carbonate and sevelamer. Due to an increase of serum calcium without any impact on parathyroid hormone level (PTH, Roche Elecsys® assay, Roche Diagnosis, Mannheim, Germany), calcium carbonate and sevelamer were discontinued. Lanthanum carbonate was then introduced, with a moderate benefit on PTH levels. As PTH remained between 500 and 800 pg/mL despite a good therapeutic and dietary compliance, cinacalcet was introduced at a daily initial dose of 10 mg (corresponding to Day 0 in Figure 1), 2 months after the introduction of lanthanum carbonate was discontinued at the beginning of cinacalcet therapy. Four weeks later, PTH level remained high and cinacalcet was increased to 20 mg, and 1 week later to 30 mg. PTH level remained high but stable, ~500 pg/mL. In the mean time, serum calcium and phosphate levels remained stable leading to cinacalcet discontinuation 50 days after its introduction, because of digestive intolerance (nausea, vomiting and weight loss). Since PTH levels increased again, cinacalcet was reintroduced at a low dose (10 mg/day) 3 weeks after the first stop.

Concomitant treatments were not modified during this period (alphacalcidol, oral iron supplementation and sodium bicarbonate).

The patient was at a prepubertal stage before starting cinacalcet (Tanner stage G1 P1). Pubic hair was first noticed by the mother about 2 weeks after starting cinacalcet and progressively increased together with the onset of numerous erections. The parents complained about this problem about 45 days after the first clinical signs (i.e. 45 days from the first effect of cinacalcet).
1 week after cinacalcet reintroduction). Physical examination revealed symmetric enlargement of both testis and increased length of penis, corresponding to Tanner stage G3 P2.

An adverse effect of cinacalcet was first hypothesized, and cinacalcet was immediately stopped.

Biological data concerning PTH and pubertal follow-up are summarized in Figure 1 and in Table 1. Briefly, serum testosterone was markedly increased since the patient always presented serum values >0.7 nmol/L (normal values for age and gender: 0.28 ± 0.01 nmol/L), with a peak of 9 nmol/L. Serum follicle-stimulating hormone (FSH) was normal whereas serum luteinizing hormone (LH) was slightly increased, fluctuating between 1.1 and 4.1 IU/L (normal values for age and gender: 0.17–0.6 IU/L). Serum estradiol level was normal. Antimullerian hormone (AMH) serum levels were decreased, fluctuating between 68 and 126 pmol/L (normal values for age and gender: >200 pmol/L). Inhibin B serum levels were decreased, fluctuating between 68 and 126 pmol/L (normal values for age and gender: >200 pmol/L). Inhibin B serum levels were decreased, fluctuating between 68 and 126 pmol/L (normal values for age and gender: >200 pmol/L).

Thus, biological data corresponded to a precocious puberty. A central precocious puberty was initially unlikely as serum FSH was normal, despite a slight increase of serum LH level. Two magnetic resonance imagings of the brain and hypothalamic-pituitary axis 2 months and 15 months after the beginning of precocious puberty were normal. An adrenal aetiology of precocious puberty was excluded by normal levels of steroids. Adrenal ultrasound examination was normal. DHAS was increased for age, corresponding to normal pubertal values. Tumour markers (human choriocarcinoma gonadotropin and α fetoprotein) were negative.

A retrospective measurement of serum sexual and adrenal hormones before the introduction of cinacalcet but after the introduction of lanthanum carbonate revealed an asymptomatic increase of serum testosterone, DHAS and LH levels, whereas serum AMH was decreased, suggesting the presence of an underlying asymptomatic precocious puberty before the introduction of cinacalcet (Table 1, Figure 1).

There was also an acceleration of both growth velocity (from 0.5 standard deviation to the mean within 6 months) and skeletal age, as illustrated in Table 1.

About 2–3 weeks after cinacalcet discontinuation, the parents noted a stabilization of pubic hair with a reduction of the frequency of erections. Six months after cinacalcet had been discontinued, biological data progressively normalized and clinical symptoms improved (Tanner stage G2 P2). But 7 months after cinacalcet discontinuation, testosterone levels increased again, in association with an increased serum LH. A secondary central puberty due to the maturation of the hypothalamus/hypophysis axis after testosterone exposure was then hypothesized; a treatment by triptorelin was therefore initiated, leading to an initial escalation of

---

**Table 1. Clinical and biological evolution**

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 28</th>
<th>Day 73</th>
<th>Day 117</th>
<th>Day 240</th>
<th>Day 300</th>
<th>Day 345</th>
<th>Day 390</th>
<th>Day 480</th>
<th>Day 510</th>
<th>Day 540</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinacalcet (mg/day)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronological age (months)</td>
<td>61</td>
<td>70</td>
<td>74</td>
<td>95</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tanner pubertal stage</td>
<td>G1P1</td>
<td>G3P2</td>
<td>G2P2</td>
<td>G2P2</td>
<td>G2P2</td>
<td>35 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular length/volume</td>
<td>Prepubertal</td>
<td>40 mm</td>
<td>30 mm</td>
<td>7 mL</td>
<td>8 mL</td>
<td>35 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penile length (mm)</td>
<td>40</td>
<td>65</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>360</td>
<td>305</td>
<td>627</td>
<td>579</td>
<td>231</td>
<td>137</td>
<td>72</td>
<td>139</td>
<td>240</td>
<td>182</td>
<td>381</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>325</td>
<td>315</td>
<td>325</td>
<td>320</td>
<td>328</td>
<td>381</td>
<td>368</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (nmol/L, (N = 0.28 \pm 0.01))</td>
<td>3.78</td>
<td>5.58</td>
<td>6.1</td>
<td>3.54</td>
<td>0.85</td>
<td>2.2</td>
<td>3.71</td>
<td>3.7</td>
<td>7.99</td>
<td>9</td>
<td>4.6</td>
</tr>
</tbody>
</table>
clinical and biological symptoms, probably secondary to the transient agonist effect (flare-up effect) of triptorelin. After 4 months of triptorelin therapy, testosterone serum levels remained high but stable and clinical symptoms moderately improved.

Discussion

Virilization in young children is uncommon and is associated with androgens, which may be from either endogenous or exogenous source. In this patient, the role of CKD adds an important bias in analysing clinical and biological data, since biological normal values of sexual and adrenal hormones are not well known in advanced paediatric CKD. Moreover, the acceleration of growth velocity despite a low GFR (10 mL/min/1.73 m²) was probably equivalent to a ‘pubertal’ growth acceleration.

An exogenous intoxication with testosterone can be excluded since testis would have had a normal size in that case. Exceptional genetic aetiologies of testotoxicosis were excluded: there was no mutation neither in the LH receptor nor in the GNAS gene, encoding for the α subunit of the protein G.

Cinacalcet is a recent drug without license in children that acts as a calcimimetic agent via an allosteric activation of the calcium sensor receptor (CaR) in the parathyroid gland, inducing conformational changes in the CaR [5]. Recent reports have showed a good tolerance and efficacy in children [6–8]. Initial half-life of cinacalcet is 6 h and terminal half-life is 30–40 h. The equilibrium state is obtained within 7 days. Its biodisponibility ranges from 20–25% (fasting) to 50–80% (during a meal) [9]. Adverse effects mainly include nausea and vomiting (~30% of patients, mainly with high doses), hypersensitivity, rash, seizures, hypocalcaemia and asthenia [9]. Cinacalcet can be responsible for hypotestosteronaemia that has been described both in chimpanzees and in men during the first studies of the molecule. In chimpanzees, hypotestosteronaemia was explained by a delay of maturation in these animals, possibly due to a decreased weight gain; testes were normal on histological examination [9]. In adult male patients, plasma testosterone was found to be decreased 6 months after the beginning of the treatment, with a median decrease of 31% with cinacalcet versus 16% with placebo. Such a biological adverse effect was not associated with any clinical consequences [9]. The pathophysiology of hypotestosteronaemia is currently unknown, but a protein G may be involved, since both CaR and LH-receptor act via such a protein. Long-term studies are ongoing, but results are currently unavailable. To our knowledge, there are no described homologies between the CaR and the LH receptor.

In our patient, the causal relationship between the occurrence of precocious puberty and cinacalcet treatment is likely according to the WHO–UMC system for standardized case causality assessment [10]. The time relationship with precocious puberty observed 2 weeks after the introduction of cinacalcet, the only new drug during the last month, is plausible. Furthermore, biological and clinical abnormalities initially progressively disappeared after stopping cinacalcet. Finally, alternative causes were not found. However, cinacalcet may have destabilized a previously abnormal endocrinological state, since pre-therapeutic serum analysis showed that there was probably an underlying asymptomatic endocrinological dysregulation. In such a hypothesis, the LH receptor could have already been activated. The administration of cinacalcet could have activated both the CaR (that was the therapeutic target) and the LH receptor, thus inducing hypotestosteronaemia and clinical symptoms.

With more than 1-year follow-up, the aetiology of asymptomatic precocious puberty before the introduction of cinacalcet remains unexplained; it could be secondary to lanthanum carbonate, since (1) no obvious aetiology for the precocious puberty was found after complete endocrinological investigations and (2) natural lanthanides can activate in vitro the CaR [11]. However, to our knowledge, there are no clinical data about side effects of lanthanum carbonate on sexual hormones.

An unknown complication of ‘renal cysts and diabetes syndrome’ may also be regarded. This syndrome is due to a mutation in the TCF2 gene. It associates renal abnormalities (i.e. hypoplastic glomerulocystic kidney disease, cys
tic renal dysplasia or solitary functioning kidney), genital malformations (mainly müllerian abnormalities), abnormal liver enzyme levels, pancreas atrophy and maturity-onset diabetes of the youth [12–14]. To our knowledge, only hypospadias (one case report) in association with a TCF2 gene mutation has been described [14]; precocious puberty and testotoxicosis have not been described in this syndrome. Moreover, there was no evidence of other endocrine dysregulation, in particular for glucose, thyroid and adrenal metabolism.

In conclusion, this patient presented with precocious puberty just after the introduction of cinacalcet and 2 months after the introduction of lanthanum carbonate. To our knowledge, it is the first report of a likely iatrogenic precocious puberty with a calcimimetic drug and/or with lanthanum carbonate. Physicians should be aware of this adverse effect: a monitoring of plasma testosterone in patients receiving drugs for hyperparathyroidism and presenting with a change in genitals may be recommended.

Conflict of interest statements. None declared.

References

Optimal treatment of painful bone metastases with Samarium EDTMP in a haemodialysis patient: effectiveness and safety of internal radiotherapy

Saadia Skalli1, Marie-Dominique Desruet1, Jean-Cyril Bourre2, Jean-Pierre Caravel2 and Jean-Philippe Vuillez2

1Pharmacy Department and 2Nuclear Medicine Department, Hospitalo-University Center of Grenoble, Grenoble, France

Correspondence and offprint requests to: Saadia Skalli; E-mail: SSkalli@chu-grenoble.fr

Abstract
One of the current therapeutic approaches in the treatment of osteoblastic bone metastases uses the affinity of Samarium (\(^{153}\)Sm) ethylene-diamine-tetramethylene phosphonic acid (EDTMP) for bone areas of bone turnover. As Samarium EDTMP is a \(\beta\)-emitter, the radiotherapy contributes to osteoblastic bone lesion control over time. To date, the safety and effectiveness of Samarium therapy have not been established in patients with renal impairment. In this first report, we describe our experience of use of Samarium EDTMP in conjunction with bisphosphonates in a haemodialysis patient for treatment of painful bone metastasis. Encouraging results were obtained in achieving pain control. The use of this radioisotope could be more widely applied to treat haemodialysis patients.

Keywords: bone metastases; haemodialysis patient; multiple myeloma; Samarium EDTMP

Case report
A 71-year-old woman treated with maintenance haemodialysis suffered from widespread metastases of breast cancer, requiring opioid analgesics (fentanyl and dextropropoxyphene) that were insufficient to alleviate pain and disability. Her medical history consisted of untreated asthma and hypertension. To relieve her bone pain, the patient underwent \(^{99m}\)Tc-HDP (hydroxy-methylene-diphosphonate) bone scintigraphy using 540 MBq of \(^{99m}\)Tc-HDP. Scan imaging revealed bone metastatic lesions in the spine, pelvic bone, ribs, left shoulder blade, femur and possibly left tibia and skull compatible with metastatic breast cancer (Figure 1). Pain evaluation by visual analogic scale (VAS) was expressed as 7/10, and the recorded motor score was 5/20. This patient received a cure of 15 mg of pamidronic acid and the internal radiotherapy with Samarium EDTMP for improved pain relief.

Two days before Samarium EDTMP therapy, the number of leucocytes was 9.7 \(\times\) 10\(^9\)/L (reference range 4–11 \(\times\) 10\(^9\)/L), haemoglobin 98 g/L (reference range 115–145 g/L) and platelets 240 \(\times\) 10\(^9\)/L (reference range 150–400 \(\times\) 10\(^9\)/L). Considering her renal failure and impaired urinary excretion of Samarium after intravenous administration (35.3% \(\pm\) 13.6%, the first 12 h), subsequent doses were decreased to only 80% of the conventional dose, i.e. 29.6 MBq/kg (0.8 mCi/kg) instead of 37 MBq/kg (1 mCi/kg), 16 h before haemodialysis. Whole body scans were done using a standard gamma camera, 6 h after receiving Samarium EDTMP therapy (Figure 2). Due to the short physical half-life of samarium (46 h), the excreted activity via the residual urine flow and the faeces was collected over 16 h.