Persistent Hypercalcemia After Parathyroidectomy in an Adolescent and Effect of Treatment With Cinacalcet HCl

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Background: Hyperparathyroidism is uncommon in adolescence and is more likely to persist after parathyroidectomy than in adults. Cinacalcet HCl is a new calcimimetic that has been used successfully for the treatment of primary and secondary hyperparathyroidism in adults, but its use in adolescents has not been reported.

Case: A 16 year-old male presented with hypercalcemia that had persisted for 1.5 years after parathyroidectomy for primary hyperparathyroidism. Parathyroid hormone (PTH) concentrations were nonsuppressed despite a mean (SD) serum calcium concentration of 2.82 (0.06) mmol/L. Treatment with cinacalcet HCl was initiated and a pharmacodynamic profile was obtained for serum calcium, phosphorus, and PTH. Cinacalcet HCl normalized serum calcium. The changes in PTH were assay dependent.

Issues: We use this case conference to review the evaluation of hypercalcemia in adolescents, examine the changes in relevant laboratory results during treatment with cinacalcet HCl, and discuss differences among assays for PTH.

Conclusions: Interpretation of PTH results in patients treated with cinacalcet HCl requires consideration of the pharmacodynamic effects of the drug and the nature of the PTH assay.

Hypercalcemia is less common in children and adolescents than in adults, and most cases are attributable to primary hyperparathyroidism (1–3). When a diagnosis of primary hyperparathyroidism is established, its etiology is an important guide to therapy. Approximately 85% of cases are due to a single, sporadic parathyroid adenoma, or, less commonly, 2 parathyroid adenomas (4). For a single parathyroid adenoma, parathyroidectomy has a success rate of ≥95% and is recommended for all patients under the age of 50 years. Four-gland parathyroid hyperplasia can be sporadic and is often due to an inherited disorder. Therapy for multigland disease includes 3 and one-half–gland parathyroidectomy with autotransplantation of the remaining parathyroid tissue into the forearm. Four-gland parathyroid hyperplasia is more common in adolescents than adults and recurrent hypercalcemia is especially problematic in this group (5).

Calcimimetic compounds offer a treatment alternative for patients who do not meet the criteria for parathyroidectomy or for whom parathyroidectomy has failed (6, 7). These compounds decrease glandular parathyroid hormone (PTh) secretion by binding the calcium-sensing receptor (CaSR) and decreasing the threshold for activation of the receptor by calcium (8, 9). Cinacalcet HCl is a new calcimimetic agent that has been used successfully for the treatment of primary and secondary hyperparathyroidism in adults (10–12), but its use in adolescents with persistent primary hyperparathyroidism has not been previously reported.

In this case conference, we describe clinical and laboratory findings in an adolescent male with persistent hypercalcemia after subtotal parathyroidectomy. We review the differential diagnosis of hypercalcemia in chil-
children and adolescents and we discuss the differences among PTH assays observed during cinacalcet HCl therapy.

**Case History**

A 16-year-old male presented with persistent hypercalcemia 1.5 years after parathyroidectomy. He initially presented to the emergency department at the age of 10 years after suffering a single nonfebrile seizure. At the time of initial presentation, the patient’s plasma calcium was increased at 3.00 mmol/L (reference interval 2.10–2.50 mmol/L) and plasma phosphorus was decreased at 1.06 mmol/L (1.26–2.26 mmol/L). Urinary calcium was 5.90 mmol/24 h, a value within the reference interval of 0.32–7.91 mmol/L for ages 9–17 years (13). At the time of presentation, the patient’s plasma PTH, measured by use of the Nichols Advantage Intact PTH assay, was 6.40 pmol/L, a value inappropriately high for the patient’s age ≤5.51 pmol/L in patients <17 years (13) and his increased calcium concentration. The findings of hypercalcemia in combination with hypophosphatemia and nonsuppressed PTH led to a diagnosis of primary hyperparathyroidism (14).

The patient’s fractional excretion of calcium was 0.02, providing evidence that familial hypocalciuric hypercalcemia (FHH) was unlikely to be the cause of the hypercalcemia (14, 15). To further explore if the hypercalcemia was due to familial hyperparathyroidism, calcium and phosphorus measurements were obtained from the patient’s parents and were within the appropriate reference intervals. There was no family history of endocrine abnormalities suggestive of multiple endocrine neoplasia (MEN) syndromes, and the patient did not exhibit signs or symptoms of pituitary, pancreatic, adrenal, or thyroid tumors. Electrocardiogram results were normal, and echocardiography revealed no evidence of supravalvular aortic stenosis, mitral valve prolapse, or other cardiac abnormalities seen in Williams syndrome (16).

The patient was asymptomatic for a total of 5 years after the initial event, but mild hypercalcemia and hypophosphatemia persisted (Table 1A, Parathyroidectomy). The bone-specific alkaline phosphatase (obtained at age 13) was 86 U/L, a value within the reference interval [30–405 U/L for ages 11–16 years] (17), suggesting the absence of excessive bone remodeling. Over the course of 5 years, plasma PTH was measured 5 times (approximately once every year) by several different laboratories using 3 different assays for PTH: the Nichols Advantage Intact PTH assay, the Immulite Intact PTH assay, and the Immulite 2000 Intact PTH assay. The patient’s mean PTH concentration remained within the reference interval for the Nichols Intact PTH assay and was above the upper limit of the reference interval for the Immulite and Immulite 2000 Intact PTH assays (Table 1B). The concentrations of PTH measured by all 3 assays were not suppressed, however, in the context of the concurrent hypercalcemia (Table 1A, Parathyroidectomy).

At 15 years of age, the adolescent still had persistent hypercalcemia. He began experiencing manifestations of hypercalcemia, including symptoms of nephrolithiasis,

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**Table 1. Calcium, phosphorus, and PTH before and during a 5-year period after parathyroidectomy.**

<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Preparathyroidectomy (measurements obtained over 5 years)</th>
<th>Postparathyroidectomy (measurements obtained over 1.5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Ca [2.10–2.50 mmol/L]</td>
<td>2.97 (0.08) [n = 10]</td>
<td>2.82 (0.06) [n = 9]</td>
</tr>
<tr>
<td>PO₄ [1.26–2.26 mmol/L]</td>
<td>0.94 (0.2) [n = 7]</td>
<td>0.65 (0.06) [n = 6]</td>
</tr>
<tr>
<td>Urine Calcium [0.32–7.91 mmol/L]</td>
<td>4.91 (2.01) [n = 4]</td>
<td>3.49 [n = 1]</td>
</tr>
<tr>
<td><strong>B.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH Assays</td>
<td>Preparathyroidectomy (measurements obtained over 5 years)</td>
<td></td>
</tr>
<tr>
<td>Nichols Intact PTH [1.06–6.90 pmol/L]</td>
<td>6.41 (0.01) [n = 2]</td>
<td></td>
</tr>
<tr>
<td>Immulite Intact PTH [1.27–7.64 pmol/L]</td>
<td>8.60 [n = 1]</td>
<td></td>
</tr>
<tr>
<td>Immulite 2000 Intact PTH [1.27–6.90 pmol/L]</td>
<td>7.59 (4.73) [n = 2]</td>
<td></td>
</tr>
<tr>
<td><strong>C.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH Assays</td>
<td>Postparathyroidectomy (measurements obtained over 1.5 years)</td>
<td></td>
</tr>
<tr>
<td>Immulite 2000 Intact PTH [1.276.90 pmol/L]</td>
<td></td>
<td>4.24 [n = 1]</td>
</tr>
<tr>
<td>Nichols Biomathtact PTH [0.85–5.31 pmol/L]</td>
<td>4.20 (0.72) [n = 6]</td>
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</table>

A. Calcium and phosphorus were measured in lithium-heparin plasma. The 24-h timed urine specimens were collected in polyethylene containers with 15 mL of 6 mol/L HCl. Calcium and phosphorus concentrations were measured by Arasenazo III dye-binding and acid-molybdate methods, respectively. Pre- and post-parathyroidectomy values represent the mean (SD) of measurements obtained over periods of 5 and 1.5 years, respectively. Reference intervals are shown in brackets. The reference interval for urine calcium is for ages 9–17 years (13). B. Preparathyroidectomy plasma PTH concentrations were measured with the Nichols Advantage Intact PTH assay, the DPC Immulite Intact PTH assay, and the DPC Immulite 2000 Intact PTH assay. Mean (SD) values are shown. C. Postparathyroidectomy plasma PTH was measured by use of the DPC Immulite 2000 Intact PTH assay and the Nichols Advantage Biomathtact PTH assay. The reference interval shown for the Nichols Advantage Biomathtact PTH assay encompasses all seasons; the majority of values were obtained during the winter months, for which the Nichols Biomathtact PTH reference interval is slightly higher [1.27–5.52 pmol/L]. Mean values (SD) are shown.
and was deemed a candidate for parathyroidectomy (18, 19). The baseline intact PTH (Immulite 2000) value obtained 1 week before surgery was 10.92 pmol/L (1.27–6.90 pmol/L) and the calcium value was 3.08 mmol/L. The patient’s preparathyroidectomy intact PTH (Bayer) concentration was 28 pmol/L (0.95–5.70 pmol/L). This value was likely artificially increased due to the atypical PTH surge sometimes seen during manipulation of the parathyroid glands before surgery (20). Surgical exploration identified 4 parathyroid glands; all appeared enlarged and 3 of the glands were subsequently removed. After removal of the 3rd gland, the intact PTH concentrations (Bayer) decreased from 28 pmol/L to 5.26 and 4.84 pmol/L (0.95–5.70 pmol/L) at 25 and 45 min, respectively. Half of the remaining gland was then removed. A search of the remainder of the neck identified no other apparent parathyroid tissue. Pathological evaluation of the resected tissue revealed diffuse hyperplasia of all 4 glands.

Four days after the surgery, the plasma calcium concentration was 2.68 mmol/L and the intact PTH (Immulite 2000) was 4.24 pmol/L (Table 1C). Although the concentration of intact PTH (Immulite 2000) had decreased by ~61% from the initial baseline measurement and was now within the reference interval, the patient continued to exhibit hypercalcemia. The patient remained hypercalcemic for the next 1.5 years (Table 1A, Postparathyroidectomy). The mean biointact PTH remained near the upper end of the reference interval (Table 1C). Although the concentration of PTH appeared to decrease after parathyroidectomy (Table 1, B and 1C), the long-term effect was difficult to ascertain because multiple assay types were used to measure PTH both before and after parathyroidectomy.

At 16 years of age, the patient developed signs and symptoms of hypercalcemia including mild hypertension, abdominal pain, and frequent dysuria (19). Sequencing of exons 2 through 7 of the CaSR was performed to further exclude the possible diagnosis of FHH (21). No associated variations were identified, and the diagnosis remained persistent primary hyperparathyroidism of unknown etiology.

Given the risk of autotransplantation failure, the patient and his parents were reluctant to pursue further surgical debulking and autotransplantation of the remaining parathyroid tissue into the forearm. As an alternative therapeutic approach, treatment with the oral calcimimetic agent cinacalcet HCl was initiated (7) after approval was given by the University of Virginia Institutional Review Board and after the patient and his family gave informed consent. Initial baseline biochemical measurements were obtained before administration of cinacalcet HCl. Calcium was 2.85 mmol/L and biointact PTH (Nichols) was 3.78 pmol/L (0.85–5.31 pmol/L). Cinacalcet HCl was initiated at a dosage of 30 mg/24 h for 4 weeks, after which the patient underwent a follow-up evaluation and pharmacodynamic study which showed that the morning predose calcium value had decreased from 2.85 mmol/L to 2.70 mmol/L. Three assays were used to measure PTH concentrations at multiple time points after the morning dose of cinacalcet HCl: the Bayer Centaur Intact PTH assay, the Nichols Advantage BioIntact PTH assay, and an RIA that uses antibodies specific to the carboxy-terminal domain of PTH (C-PTH) (22–24). The predose concentrations of PTH (t = 0 min) are shown in Fig. 1. PTH, as measured by all 3 assays, reached a nadir at 120–180 min after the morning dose and returned to near baseline values by 300–360 min (Fig. 1). The plasma calcium concentration decreased within 30 min, with a nadir of 2.40 mmol/L at 360 min, then increased to 2.50 mmol/L by 480 min. Phosphorus increased in response to cinacalcet HCl and approached the lower limit of the reference interval by 480 min.

Because the patient’s calcium concentrations began to increase after 360 min (Fig. 1), the dosage of cinacalcet HCl was increased from 30 mg/24 h to 60 mg/24 h (30 mg/12 h). Four weeks after the change in dose, the predose plasma calcium concentration normalized to 2.50 mmol/L (Table 2). The biointact PTH (Nichols) concentration was 4.49 pmol/L, a value similar to the predose value obtained with the 30 mg/24 hr dose (Table 2). The intact PTH (Bayer) concentration decreased by ~18% from the 30 mg/24 h predose value of 7.58 pmol/L to 6.20 pmol/L. The PTH concentration, as measured by the C-PTH RIA, increased by ~25% from the initial predose value of 7.12 pmol/L to 9.54 pmol/L. The patient reported no side effects during therapy except for mild headache.

**Discussion**

This patient’s course prompted discussion of (a) the differential diagnosis of hypercalcemia in adolescents, (b) the emerging use of calcimimetic therapy and its effects on relevant laboratory test results, and (c) the differences among assays for PTH.

**Differential Diagnosis of Hypercalcemia in an Adolescent**

The etiologies of hypercalcemia fall into 2 major categories, parathyroid and nonparathyroid. In children and adolescents, hypercalcemia is most often related to primary hyperparathyroidism (1). Primary hyperparathyroidism is characterized by excessive secretion of PTH from the parathyroid glands. The diagnosis is best confirmed by demonstrating persistent hypercalcemia in the presence of PTH concentrations above the reference interval (25). However, hypercalcemic patients with asymptomatic primary hyperparathyroidism can exhibit PTH values in the high-normal range. In the absence of hyperparathyroidism, PTH is normally low or undetectable in the presence of increased calcium and thus a PTH value within the reference interval is inappropriate in the context of hypercalcemia (14, 19, 25). The identification of primary hyperparathyroidism is particularly important in
children because it is associated with a higher incidence of end-organ damage than in adults (1).

In children, hypercalcemia attributable to hyperparathyroidism must be differentiated from nonparathyroid causes such as malignancy, calcium or vitamin D intoxication, hypophosphatasia, and Williams syndrome. Our patient had normal to high plasma concentrations of PTH rather than low PTH, thus excluding nonparathyroid causes of hypercalcemia. Pathologic evaluation of the excised parathyroid tissue confirmed 4-gland hyperplasia and suggested a form of familial hyperparathyroidism.

Inherited forms of hyperparathyroidism include FHH, MEN syndromes, familial hyperparathyroidism-jaw tumor syndrome, and hereditary isolated primary hyperparathyroidism. In children, inherited forms are more common than in adults and the majority are a result of FHH or MEN-1. The other inherited forms are rare and will not be discussed here. Recurrent hypercalcemia occurs in ~6%–12% of children after parathyroidectomy and is most often associated with familial hyperparathyroidism (1, 2).

FHH is an autosomal dominant disorder associated with heterogeneous loss-of-function variations in the CaSR. Most variations occur in the extracellular domain of the CaSR (exon 2 through the beginning of exon 7) or in the transmembrane region (exon 7) (21, 26). Patients rarely exhibit symptoms of hypercalcemia, and typically have normal or slightly increased PTH in the presence of mild hypercalcemia. A fractional excretion of calcium (\(\text{Ca}_{\text{urine}} \times \frac{\text{Cr}_{\text{serum}}}{\text{Ca}_{\text{serum}} + \text{Cr}_{\text{urine}}}\)) of <0.01 is diagnostic (14). The condition is generally without long-term sequelae and parathyroidectomy is not recommended. Several lines of evidence suggest that a diagnosis of FHH in our patient is unlikely. The fractional excretion of calcium

Table 2. Predose calcium and PTH after treatment for 4 weeks with 30 or 60 mg cinacalcet HCl per day.

<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Cinacalcet HCl</th>
<th>30 mg/24 h × 4 weeks</th>
<th>60 mg/24 h × 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Ca (2.10–2.50 mmol/L)</td>
<td>2.70</td>
<td>2.50</td>
<td></td>
</tr>
<tr>
<td>Bayer Intact PTH (1.49–7.64 pmol/L)</td>
<td>7.58</td>
<td>6.20</td>
<td></td>
</tr>
<tr>
<td>Nichols BioIntact PTH (0.85–5.31 pmol/L)</td>
<td>4.35</td>
<td>4.49</td>
<td></td>
</tr>
<tr>
<td>C-PTH (RIA) (2.31–10.03 pmol/L)</td>
<td>7.12</td>
<td>9.54</td>
<td></td>
</tr>
</tbody>
</table>

The dose of cinacalcet HCl was increased from 30 mg/24 h to 60 mg/24 h (30 mg/12 h) after 4 weeks, and repeat testing was performed 4 weeks later. PTH was measured with the Bayer Centaur Intact PTH assay, the Nichols Advantage BioIntact PTH assay, and the C-PTH RIA. Predose values are shown and were obtained before the morning doses. Values represent single measurements, and the reference intervals are shown in brackets.
calcium was 0.02, no evidence of hypercalcemia was found in samples obtained from the patient’s parents, and DNA sequencing of the CaSR revealed no variations associated with FHH.

The MEN syndromes are autosomal dominant disorders characterized by multiple endocrine tumors (4, 27). MEN-1 is characterized by the development of parathyroid, pituitary, and pancreatic tumors. Parathyroid hyperplasia occurs in 95% of MEN-1 cases and may occur in the first decade of life. MEN-2 is associated with tumors of the thyroid, parathyroid, and adrenal medulla. Parathyroid involvement is much less common in MEN-2 and usually manifests later in life. Thus, MEN-2 is unlikely to be the cause of the parathyroid hyperplasia observed in our pediatric patient. Diagnosis of MEN syndromes is generally based on clinical findings, but demonstration of MEN-associated variations in MEN1 (MEN-1) or RET (MEN-2) by direct DNA sequencing can confirm the diagnosis (4, 28). Our patient exhibited no evidence of additional endocrine features of MEN-1, but in the absence of MEN1 gene analysis we could not exclude this diagnosis as the cause for his multigland hyperparathyroidism. Thus, the diagnosis remained primary hyperparathyroidism of unknown etiology.

**CINACALCET HCL FOR RECURRENT PRIMARY HYPERPARATHYROIDISM IN AN ADOLESCENT**

Several studies have shown that cinacalcet HCl is effective for the treatment of primary and secondary hyperparathyroidism in adults (10–12, 29). Cinacalcet HCl received FDA clearance in March 2004 for the treatment of secondary hyperparathyroidism. The results presented here are consistent with those in previous studies in which cinacalcet HCl therapy normalized calcium concentrations in adults with primary hyperparathyroidism (10, 11). After 4 weeks of cinacalcet HCl therapy in our patient, predose calcium decreased by 0.15 mmol/L. Although cinacalcet HCl did not appear to decrease the steady-state, predose biointact PTH (Nichols; Table 2) compared with the baseline biointact mean value (Table 1C), PTH suppression was observed with all 3 assays shortly after the morning dose (Fig. 1). Our patient exhibited rapid PTH suppression, with maximum suppression occurring 120–180 min after drug administration, a nadir consistent with intact PTH (Nichols) measurements reported in the adult studies (10, 11). In contrast to the maximum mean suppression of 37%–55% reported in these studies, our patient achieved a maximum decrease of >73%–85% of the predose PTH value as measured by both the intact (Bayer) and biointact (Nichols) assays. The difference in the magnitude of the PTH responses in our patient could reflect the presence of interindividual differences in the pharmacodynamic response, the etiology of the hyperparathyroidism (e.g., multigland disease vs parathyroid adenoma), or the amount of hyperfunctioning tissue. A similar study with a larger sample size would be required to evaluate the magnitude of response in the pediatric population.

**EFFECTS OF CINACALCET HCL ON DIFFERENT PTH ASSAYS**

Measurement of PTH has been improved by the development of assays that can distinguish among full-length PTH and various proteolytic products of PTH found in the circulation (30–34). The availability of multiple PTH assays that measure different molecular forms of PTH can lead to confusion for clinicians attempting to follow the long-term progress of their patients.

First-generation PTH assays are RIAs that use antisera specific to epitopes located in the mid- or C-terminal regions of the hormone (34, 35). These assays detect both biologically active, full-length PTH (1–84) and multiple C-terminal PTH fragments (30, 32–34, 36) (Fig. 2). Newer immunometric (sandwich) assays use 2 antibodies directed at different epitopes of the PTH molecule, one in the N-terminal portion and another in the C-terminal region (37). These “intact PTH assays” were thought to specifically detect PTH (1–84), but HPLC analysis suggested the presence of additional large, N-terminal truncated fragments called “non-(1–84)-PTH” (33). C-terminal and non-(1–84)-PTH fragments are often greatly increased in renal failure, leading to the overestimation of PTH (1–84) by 1st generation and intact PTH assays. Detection of these fragments is thought to account for the inability of intact PTH assays to predict renal bone disease in patients with secondary hyperparathyroidism (38). Newer “biointact” (Nichols), “cyclic-AMP activating” (Scantibodies) or “third-generation” PTH assays use antibodies that require the first 4 amino acids of PTH for binding and therefore specifically detect full-length PTH (1–84) but not PTH fragments (39, 40).

By measuring PTH with several different immunoasays that utilize antibodies with different epitopes, we examined the dynamic changes in PTH (1–84) and PTH fragments after modulation of the CaSR by cinacalcet HCl. In our patient, the relationships between pairs of PTH assays did not remain linear during cinacalcet HCl therapy: The ratio of intact (Bayer) to biointact PTH (Nichols) decreased from the predose value of 1.7 to 1.2 at 120 min, then increased to 2.7 by 300 min, and finally decreased toward the baseline by 360 min (Fig. 1, middle panel). The ratio of C-PTH fragments to biointact PTH (Nichols) and the ratio of C-PTH fragments to intact PTH (Bayer) increased from predose values of 1.6 and 0.9, respectively, to 14.6 and 7.3 at 180 min and returned to near baseline values by 300–420 min (Fig. 1, bottom panel).

In contrast to these changing relationships among assays during dynamic testing, steady-state PTH values

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7 Human genes: MEN1, multiple endocrine neoplasia 1; RET, ret proto-oncogene (multiple endocrine neoplasia and medullary thyroid carcinoma 1, Hirschsprung disease).
have been observed in our laboratory to be linearly related for various intact PTH assays such as DPC Immulite Intact vs Nichols Advantage Intact PTH (41) and Bayer Centaur Intact vs DPC Immulite Intact PTH. Furthermore, a linear relationship has also been demonstrated between steady-state PTH values measured by biointact vs intact PTH assays over a large range of PTH concentrations, e.g., Nichols Advantage Intact vs Scantibodies Whole PTH and Nichols Advantage BioIntact (42–45) PTH; Nichols Advantage BioIntact vs Roche intact and DPC Immulite Intact PTH (46). In those studies, biointact PTH concentrations were typically 30%–40% lower than the corresponding intact PTH concentrations. Similarly, at 4 weeks, our patient’s predose, steady-state biointact PTH (Nichols) was 43% lower than his corresponding intact PTH (Bayer). A linear correlation between PTH assays has also been observed in patients receiving cinacalcet HCl. In a recent trial, cinacalcet HCl decreased steady-state PTH concentrations by 54% in patients with secondary hyperparathyroidism, and the relationship between biointact (Nichols) and intact PTH (Nichols) measurements remained linear (47). However, in our kinetic study, modulation of the CaSR influenced the ratio of biointact to intact PTH fragments, an observation particularly apparent at the nadir where the biointact to intact ratio approached 1.0 (Fig. 1, middle panel). The ratio of C-PTH to biointact or intact PTH also did not remain linear, a finding consistent with the ability of C-terminal RIAs to detect fragments with longer half-lives (36). Furthermore, the apparent effect of the change in dose of cinacalcet HCl differed depending on the assay. Although increasing the dose to 60 mg/24 h (30mg/12 h) normalized the concentration of calcium, the concentration of intact PTH (Bayer) decreased, C-PTH (RIA) increased, and biointact PTH (Nichols) did not appear to appreciably change.

Cinacalcet HCl is approved for the treatment of secondary hyperparathyroidism, and an increasing number of studies suggest that cinacalcet HCl is also effective for treatment of primary hyperparathyroidism (10, 11). As calcimimetics are becoming more widely used, an understanding of their effects on laboratory test results is essential for laboratorians and clinicians. Our data show that the pharmacodynamic profile of PTH suppression and recovery in response to calcimimetic therapy differed depending on the type of assay used for measurement of PTH. The PTH response observed after a change in the dose of cinacalcet HCl was also found to be assay dependent. In April of 2006, the Nichols Advantage BioIntact PTH assay was discontinued. However, reagents for other assays that measure full-length PTH are currently available and additional PTH (1–84)-specific assays will likely become available in the near future. Our findings suggest that a baseline, predose PTH value should be obtained each time a new assay is implemented, and the length of time between cinacalcet HCl administration and

\[ \text{Fig. 2. Relationship between PTH assays, PTH assay epitopes and PTH molecular forms detected in circulation.} \]

The upper panel depicts the structure of human PTH and the epitopes detected by various PTH assays. First-generation PTH assays detect full-length PTH (1–84) in addition to PTH fragments. These assays include RIAs that use antisera specific to the amino-terminal (N-RIA), middle (MID-RIA) or carboxyl-terminal (C-RIA) regions of PTH. Second-generation “intact PTH” assays detect full-length PTH (1–84) and non(1–84)-PTH fragments. Third-generation PTH assays (“biointact PTH” in this study) detect only full-length PTH (1–84). The bottom panel depicts PTH molecular forms present in circulation (35, 48–51).
sample collection should remain constant. In addition, the type of assay used to measure PTH should be an important consideration when evaluating PTH concentrations during suppression of the parathyroid gland.

We thank Tjin-Shing Jap, from Taipei Veterans General Hospital for DNA sequencing of the CaSR and Theresa A. Guise for a critical review of an earlier draft of this manuscript. Reagents for the Nichols Advantage Intact PTH Assay were provided by Nichols Institute Diagnostics (San Clemente, CA) who had no input in the design, conduct, or reporting of this Case Conference. No support was received from the manufacturer of cinacalcet HCl.

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