Original Article

Effects of cinacalcet on gastrointestinal hormone release in patients with secondary hyperparathyroidism undergoing dialysis

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Abstract

Objective. Our aim has been evaluating the influence of an acute dose of cinacalcet on the gastrointestinal hormonal responses to a test meal in uraemic patients with secondary hyperparathyroidism undergoing peritoneal dialysis (PD) or haemodialysis (HD).

Methods. Twenty patients (11 PD, 9 HD) on cinacalcet treatment (30–120 mg/day) were studied. Twelve patients (1 PD, 11 HD) who never received cinacalcet were studied as control group. Each patient received a test meal with blood samples at 0, 2 and 4 h. At 0 time, patients in the cinacalcet group received their usual oral dose of this calcimimetic. Plasma concentrations of intact parathyroid hormone (PTH), vasoactive intestinal peptide (VIP), ghrelin, substance P, serotonin, cholecystokinin (CCK) and gastrin were quantified at 0, 2 and 4 h.

Results. No significant differences in baseline concentrations of serum VIP, ghrelin, substance P, serotonin, CCK and gastrin were found between controls and cinacalcet-treated patients. In comparison with the control group, cinacalcet administration was followed by a significant decrease in VIP concentration at 4 h and a significant increase in substance P at 4 h. However, the areas under the curves of all studied gut hormones were similar in both groups.

Conclusion. An acute dose of cinacalcet exerts minimal influence on gut hormone responses to a mixed meal in dialysis patients on chronic therapy with this drug. The small but significant differences between control subjects and patients on cinacalcet in VIP and substance P levels at 4 h should be investigated in symptomatic patients.

Keywords: chronic kidney disease; cinacalcet; dialysis; gastrointestinal hormones; secondary hyperparathyroidism

Introduction

Allosteric modulators of the calcium-sensing receptor (calcimimetics) reduce parathyroid hormone (PTH) synthesis and release at parathyroid cells by increasing the receptor sensitivity to circulating calcium [1]. Cinacalcet, a type II calcimimetic agent, has shown to have significant potency in suppressing PTH secretion in primary cultured human parathyroid cells of patients with primary and secondary hyperparathyroidism [2]. Three large phase 3 clinical trials in patients with secondary hyperparathyroidism and under dialysis therapy have shown that chronic therapy with oral cinacalcet is accompanied by a rapid reduction in PTH, calcium and phosphorus levels with a decrease in the calcium–phosphorus product [3,4].

Although treatment with cinacalcet is generally well tolerated, these trials have also shown that gastrointestinal adverse effects occurred in about one-third of patients receiving cinacalcet [3,4]. Nausea was present more often in patients given cinacalcet than in those given placebo in one study (32% versus 19%), as did vomiting (30% versus 16%), these differences being statistically significant [3]. Similar figures have been reported in another large placebo-controlled study in dialysis patients, both for nausea (30% versus 22%) and vomiting (23% versus 12%). Nausea and vomiting were the most common adverse events, seen in 34% and 44%, respectively, of patients in a recently reported long-term study [5].

The mechanisms for cinacalcet-induced nausea and vomiting in patients with chronic kidney disease have not been elucidated. We hypothesized that allosteric modulators of the calcium-sensing receptor might modify the baseline or meal-induced release of some of the gastrointestinal hormones with activity on vomiting centres or gastrointestinal motility. We designed the present pilot study with the aim of evaluating the influence of an acute dose of cinacalcet on the gastrointestinal hormonal responses to a test meal in a group of uraemic patients with secondary hyperparathyroidism who received peritoneal dialysis (PD) or haemodialysis (HD).
We studied the effects of an acute dose of cinacalcet on gastrointestinal hormone responses to a test meal in a group of 20 uraemic patients with secondary hyperparathyroidism and chronic treatment with this calcimimetic drug (cinacalcet). Mean age (mean age, 55.5 ± 5.6 years; mean duration of dialysis, 53.6 ± 14.9 months; 1 on PD, 11 on HD) with secondary hyperparathyroidism defined by PTH concentrations >150 pg/ml. Serum calcium was significantly lower in the cinacalcet group (9.3 ± 0.2 mg/dl) in comparison with the control group (9.7 ± 0.2 mg/dl, P < 0.05). No significant differences between the cinacalcet and control groups were found in plasma PTH concentrations (Table 2).

**Study design**

All patients were ambulatory and were studied as outpatients. Endocrine tests began between 0830 and 0930 h after an overnight fast. Tests were performed in the day between two dialysis sessions in HD patients, and after the morning exchange in PD patients, without infusion of dialysis fluid into the peritoneum during the test. An indwelling catheter was placed in a forearm vein and kept patent with a slow infusion of 0.9% NaCl. Each subject received a test meal consisting on a continental breakfast, i.e. whole milk (200 cc), white bread (60 g), butter (10 g), jam (20 g) and sugar (10 g), with a total energy supply of 469 kcal (protein 11 g, lipids 17 g, carbohydrates 68 g). Blood samples were collected immediately before the starting of the meal (0 time) and then 2 and 4 h after the meal. At 0 time, patients in the cinacalcet group received their usual oral dose of this calcimimetic drug (cinacalcet hydrochloride, Mimpara; Amgen Europe B.V., Breda, The Netherlands). Plasma concentrations of intact PTH, calcium, phosphorus, vasoactive intestinal peptide (VIP), ghrelin, substance P, serotonin, cholecystokinin (CCK) and gastrin were quantified in samples extracted at 0, 2 and 4 h. Blood haemoglobin concentration and serum chemistries were also determined at 0 time.

**Laboratory procedures and hormone assays**

For hormonal determinations, venous blood samples were collected in tubes containing EDTA and Trasylol (5000 KIU Trasylol in 10 ml vacutainer). The samples were cooled in an ice bath immediately. Plasma was separated by refrigerated centrifugation and stored at −30 °C until assayed. Intact PTH was determined by a solid-phase, two-site chemiluminescent enzyme-labelled immunometric assay (Immulite 2500 Intact PTH, Los Angeles, CA, USA). The sensitivity for this assay was 3 pg/ml. Normal values for PTH in our laboratory were 12–60 pg/ml. Maximal intra- and interassay coefficients of variation (CVs) were 5.7% and 8.8%, respectively. Plasma VIP concentrations were determined by using a commercially available radioimmunoassay (EURIA-VIP,
Cinacalcet and gastrointestinal hormones

Table 2. Baseline hormonal concentration in ureamic patients classified according to group, sex, type of dialysis, hypertension and treatment with omeprazol and calcium-containing phosphate binders

<table>
<thead>
<tr>
<th>Group</th>
<th>PTH (pg/ml)</th>
<th>VIP (pmol/l)</th>
<th>Ghrelin (ng/ml)</th>
<th>Substance P (pg/ml)</th>
<th>Serotonin (ng/ml)</th>
<th>CCK (mmol/l)</th>
<th>Gastrin (pg/ml)</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>12</td>
<td>686 ± 113</td>
<td>31.6 ± 2.3</td>
<td>7.13 ± 1.23</td>
<td>6.4 ± 0.9</td>
<td>37.7 ± 6.4</td>
<td>0.42 (0.30–2.92)</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>20</td>
<td>468 ± 63</td>
<td>30.6 ± 2.5</td>
<td>8.02 ± 1.12</td>
<td>6.7 ± 0.3</td>
<td>42.3 ± 5.1</td>
<td>3.65 (0.26–10.9)</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>Male</td>
<td>22</td>
<td>581 ± 80</td>
<td>31.2 ± 2.1</td>
<td>7.36 ± 1.05</td>
<td>6.8 ± 0.3</td>
<td>36.1 ± 4.0</td>
<td>3.63 (0.38–5.97)</td>
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<td>Female</td>
<td>10</td>
<td>680 ± 74</td>
<td>30.6 ± 3.2</td>
<td>8.41 ± 1.33</td>
<td>6.3 ± 0.9</td>
<td>50.4 ± 8.8</td>
<td>0.27 (0.15–1.29)*</td>
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<td>606 ± 84</td>
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<td>7.76 ± 1.07</td>
<td>6.3 ± 0.5</td>
<td>37.8 ± 4.6</td>
<td>0.40 (0.30–3.80)</td>
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<td>11</td>
<td>443 ± 61</td>
<td>25.8 ± 2.6*</td>
<td>7.54 ± 1.35</td>
<td>7.1 ± 0.8</td>
<td>45.9 ± 7.7</td>
<td>4.49 (1.06–16.7)*</td>
</tr>
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<td>16</td>
<td>426 ± 44</td>
<td>31.1 ± 2.1</td>
<td>7.28 ± 1.60</td>
<td>6.4 ± 0.5</td>
<td>47.1 ± 6.1</td>
<td>3.57 (0.34–14.4)</td>
</tr>
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<td>16</td>
<td>674 ± 104*</td>
<td>30.9 ± 2.9</td>
<td>8.09 ± 1.21</td>
<td>6.8 ± 0.5</td>
<td>34.0 ± 4.8</td>
<td>0.37 (0.30–4.25)</td>
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<td>Phosphate binders</td>
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<td>18</td>
<td>486 ± 54</td>
<td>28.6 ± 2.6</td>
<td>7.40 ± 0.80</td>
<td>6.7 ± 0.4</td>
<td>41.8 ± 3.5</td>
<td>2.23 (0.23–5.97)</td>
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<tr>
<td>No</td>
<td>14</td>
<td>631 ± 117</td>
<td>33.9 ± 1.9</td>
<td>8.05 ± 1.63</td>
<td>6.5 ± 0.7</td>
<td>39.0 ± 8.1</td>
<td>0.42 (0.30–4.11)</td>
</tr>
</tbody>
</table>

Data are mean ± SEM for normally distributed data and median (interquartile range) for nonparametric data (CCK and gastrin concentrations). Abbreviations: PTH, parathyroid hormone; VIP, vasoactive intestinal peptide; CCK, cholecystokinin.

*P < 0.05; **P < 0.01.

Euro Diagnostica, Malmo, Sweden). The sensitivity of the VIP assay was 3 pmol/l. Fasting levels in healthy subjects were 3–30 pmol/l. Maximal intra- and interassay CVs were 5.9% and 7.7%, respectively. Serum total ghrelin concentration was measured by using a commercially available RIA (Linco Research, Inc., St Charles, MO, USA) with a sensitivity of 93 pg/ml. Intra- and interassay CVs for ghrelin assay were 4.4% and 16.7%, respectively. Substance P concentrations were determined using a radioimmunoassay (Phoenix Pharmaceuticals Inc., Belmont, CA, USA). Normal fasting levels in our laboratory were 23.6–30.4 pg/ml. Intra- and interassay CVs for this assay were 5.2% and 8.7%, respectively. Plasma serotonin concentration was determined by radioimmunoassay (Labor Diagnostika Nord, Nordhorn, Germany). The sensitivity of this assay was 0.8 pg/ml and the maximal intra- and interassay CVs were 4.7% and 5.6%, respectively. The reference levels for the serotonin assay were 80–450 ng/ml for males and 40–400 ng/ml for females. A radioimmunoassay assay (EURIA-CCK, Euro Diagnostica, Malmo, Sweden) was employed to quantify plasma concentrations of CCK. The sensitivity of this assay was 0.3 pmol/l, and the normal fasting CCK levels in healthy subjects were <1.12 pmol/l. Maximal intra- and interassay CVs were 5.5% and 13.7%, respectively. Gastrin concentrations were measured by using a commercially available radioimmunoassay (Gammalab, Incstar Corp., Stillwater, MN, USA) with a sensitivity of 6 pg/ml. Intra- and interassay CVs for gastrin assay were 4.1% and 6.3%, respectively. Gastrin concentration in healthy subjects was 25–115 pg/ml.

Statistical analysis

The hormonal responses were studied by comparison of the values at 2 h and 4 h with baseline values in each group of patients, and by comparison between groups at each time point. For comparison between groups, we also evaluated the hormonal responses by means of the area under the curves (AUC) and by the changes in hormone concentration from baseline to 2 h (Δ2) and to 4 h (Δ4). The AUC was calculated between 0 and 4 h by a trapezoidal method.

Qualitative variables are expressed as absolute number or percentage. For quantitative variables, results are expressed as mean ± SEM for normally distributed data and as median (interquartile range) for nonparametric data. In figures, nonparametric data have been log transformed. Adjustment to normal distribution was tested by the Kolmogorov test. Comparisons of means between groups were made using the Student t-test for normally distributed data and the Mann–Whitney test for nonparametric data. For ratio comparisons, the chi-square test or Fisher’s exact test was used. The statistical evaluation of the hormone responses after the test meal within each group of subjects (control and cinacalcet) was performed by means of the Friedman analysis of variance by ranks, and the Wilcoxon signed-rank test with the Bonferroni correction was used to determine which pairs of data differed when the Friedman test was significant. A value of P < 0.05 was accepted as statistically significant.

Results

Baseline hormonal concentrations

We found no significant differences in baseline concentrations of serum VIP, ghrelin, substance P, serotonin, CCK and gastrin between control patients and patients who were on chronic cinacalcet therapy (Table 2). The type of dialysis and the treatment with phosphate binders did not affect baseline hormonal concentration. Patients with hypertension showed greater levels of VIP and lower levels of CCK.
than those found in non-hypertensive patients. Treatment with omeprazol was accompanied by an increase in baseline gastrin concentrations and a decrease in PTH levels in comparison with patients who did not take this drug (Table 2).

Responses of PTH, calcium and phosphate

Baseline PTH concentration was similar in the two groups of patients (Table 2). In the cinacalcet group, test meal and cinacalcet administration was followed by a significant decrease in PTH concentration, which reached a minimum of 244.4 ± 45.0 pg/ml (P < 0.001) at 2 h (Figure 1). Significant differences in PTH levels between the two groups of patients were observed at 2 and 4 h (Figure 1). The AUC of PTH levels was significantly lower in the cinacalcet group (1165 ± 167 pg/ml h) in comparison with the control group (2936 ± 438 pg/ml h, Table 3, P < 0.01). In the cinacalcet group, Δ2 and Δ4 for PTH concentration were −181.0 ± 48.1 and −148.5 ± 53.0 pg/ml, respectively. These values were significantly lower than those found in control patients (47.1 ± 49.8 and 99.0 ± 54.3 pg/ml, respectively, P < 0.01).

Administration of a single dose of cinacalcet was followed by a decline in serum calcium that reached the level of 9.1 ± 0.2 mg/dl at 2 h and 9.2 ± 0.2 mg/dl at 4 h. Friedman test showed that these changes were in the limit of significance (P = 0.051). Calcium concentrations at baseline, and 2 and 4 h were significantly higher in control patients in comparison with cinacalcet-treated patients (Figure 1). No changes were observed in serum phosphate in the control group. However, cinacalcet administration was followed by a significant decline in phosphate concentration from 5.5 ± 0.3 mg/dl (baseline) to 5.2 ± 0.3 mg/dl (2 h, P < 0.01) and 5.0 ± 0.3 mg/dl (4 h, P < 0.01).

Gastrointestinal hormone responses

A modest but non-significant decrease in VIP concentrations was found in the cinacalcet group at 4 h (24.7 ± 2.2 pmol/l) in comparison with baseline values (30.6 ± 2.5 pmol/l, N.S.). Control patients exhibited no changes in VIP levels throughout the 4 h of the study. We found a statistically significant difference in the VIP concentration between the two groups at 4 h (P < 0.01, Figure 2). In accordance with this finding, Δ4 for VIP concentrations was −5.5 ± 2.6 pmol/l in the cinacalcet group and 2.2 ± 2.4 pmol/l in the control group, this difference being statistically significant (P < 0.05). However, statistical analysis did not find differences in the AUC of VIP between groups (Table 3, Figure 3).

Meal and cinacalcet administration were followed by a decrease in ghrelin concentrations that reached a minimum of 6.85 ± 0.81 ng/ml at 2 h in the cinacalcet group (P < 0.05, Figure 2). No significant changes in ghrelin levels were observed in control patients. We found no significant differences between groups in ghrelin concentration throughout the test (Figure 2), in ghrelin Δ2 and Δ4 or in the AUC of ghrelin (Table 3, Figure 3).

No significant changes in plasma levels of substance P after the test meal were found in controls or in cinacalcet-treated patients (Figure 2). However, we found that these levels were slightly but significantly higher in the cinacalcet group (7.17 ± 0.30 pg/ml) in comparison with those found in the control group (6.31 ± 0.20 pg/ml, P < 0.05) at 4 h. Δ4 for substance P was 0.46 ± 0.34 pg/ml in the cinacalcet group and −0.06 ± 1.01 pg/ml in the control group; however, this difference was not significant. No differences were found in the AUC of substance P (Table 3, Figure 3).

Plasma serotonin concentration did not exhibit any significant change throughout the test in both cinacalcet-treated patients and control patients (Figure 2). We did not find significant differences between both groups in Δ2, Δ4 and the AUC of serotonin (Table 3, Figure 3).

Test meal was followed by a significant increase in plasma CCK levels in the control group reaching a maximum of 12.7 (1.3–21.1) mmol/l at 2 h (P < 0.05). A parallel increase in CCK concentrations was also found in the cinacalcet group; however, these changes did not reach the level of statistical significance. No differences between groups were found in plasma levels, Δ2, Δ4 or the AUC of CCK (Figures 2 and 3).
Cinacalcet and gastrointestinal hormones

Table 3. Areas under the curves of hormonal responses to a test meal in uraemic patients classified according to group, sex, type of dialysis, hypertension and treatment with omeprazol and calcium-containing phosphate binders

<table>
<thead>
<tr>
<th>Group</th>
<th>PTH (pg/ml h)</th>
<th>VIP (pmol/l h)</th>
<th>Ghrelin (ng/ml h)</th>
<th>Substance P (pg/ml h)</th>
<th>Serotonin (ng/ml h)</th>
<th>CCK (mmol/l h)</th>
<th>Gastrin (pg/ml h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12</td>
<td>2936 ± 438</td>
<td>132.4 ± 6.7</td>
<td>28.23 ± 4.38</td>
<td>26.0 ± 1.4</td>
<td>157 (129–192)</td>
<td>30.1 ± 6.9</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>20</td>
<td>1165 ± 167**</td>
<td>112.8 ± 8.1</td>
<td>28.68 ± 3.52</td>
<td>27.5 ± 1.0</td>
<td>157 (99–214)</td>
<td>45.6 ± 9.0</td>
</tr>
<tr>
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<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
<td>1894 ± 336</td>
<td>120.3 ± 7.6</td>
<td>27.92 ± 3.46</td>
<td>26.8 ± 0.7</td>
<td>145 (94–178)</td>
<td>38.4 ± 7.5</td>
</tr>
<tr>
<td>Female</td>
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<td>1761 ± 342</td>
<td>120.7 ± 8.8</td>
<td>29.81 ± 4.32</td>
<td>27.6 ± 2.1</td>
<td>189 (152–228)</td>
<td>38.5 ± 12.2</td>
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<td>Peritoneal dialysis</td>
<td>12</td>
<td>1697 ± 370</td>
<td>114.0 ± 11.3</td>
<td>31.89 ± 2.95</td>
<td>29.0 ± 1.4</td>
<td>172 (118–270)</td>
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<td>1948 ± 340</td>
<td>124.4 ± 6.3</td>
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<td>2140 ± 349</td>
<td>130.7 ± 5.2</td>
<td>28.53 ± 3.45</td>
<td>25.4 ± 0.8</td>
<td>152 (90–184)</td>
<td>39.8 ± 7.1</td>
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<td>11</td>
<td>1325 ± 253</td>
<td>98.7 ± 11.9**</td>
<td>28.47 ± 4.52</td>
<td>29.4 ± 1.5*</td>
<td>175 (124–288)</td>
<td>39.9 ± 12.8</td>
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<td>2366 ± 483</td>
<td>135.4 ± 6.1*</td>
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<td>26.9 ± 1.0</td>
<td>152 (84–199)</td>
<td>46.3 ± 10.4</td>
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</table>

Data are mean ± SEM for normally distributed data and median (interquartile range) for nonparametric data (serotonin AUC and gastrin AUC). Abbreviations: PTH, parathyroid hormone; VIP, vasoactive intestinal peptide; CCK, cholecystokinin.
*P < 0.05; **P < 0.01.

Plasma concentrations of gastrin did not change in cinacalcet-treated patients, and only minimally increased in control patients (Figure 2). No differences between groups were found when analysing the Δ2, Δ4 and AUC of gastrin (Table 3, Figure 3).

Hormonal responses in HD patients

We analysed hormonal responses in the group of 20 patients on HD (9 cinacalcet-treated patients versus 11 control patients). Changes in plasma hormone concentrations at 2 and 4 h were almost identical to those found in the complete population studied with minimal differences (data not shown). Figure 3 shows the absence of significant differences in the AUC of the gastrointestinal hormones between the control and cinacalcet groups when studying the group of 20 patients on HD in comparison with the whole population of uraemic patients.

We also studied the AUC of gastrointestinal hormones in patients classified according to several variables (Table 3). Sex and type of dialysis did not exert any influence on hormonal responses. Hypertensive patients had higher AUC of VIP and lower AUC of substance P. Lower values of the AUC of VIP were observed in patients treated with phosphate binders. Lastly, treatment with omeprazol was accompanied by an increase in the AUC of gastrin (Table 3).

Discussion

Results of the present study show that baseline concentrations of analysed gastrointestinal hormones were similar in uraemic patients chronically treated by cinacalcet and in patients with a similar degree of secondary hyperparathyroidism who never received this drug. An acute dose of cinacalcet in patients on chronic therapy with this drug exerts minimal influence on gut hormone responses to a mixed meal. We could only detect small but significant differences between control subjects and patients on cinacalcet in VIP and in substance P levels at 4 h.

The use of calcimimetic drugs results in reductions of the risks of parathyroidectomy, fracture and cardiovascular hospitalization in uraemic patients [3–7]. Gastrointestinal complaints in patients receiving cinacalcet are generally mild to moderate but the percentage of patients who have been withdrawn from clinical trials because of nausea, vomiting or other gastrointestinal events is not negligible (5–9%) [3,4]. The calcium-sensing receptor has been identified in the endocrine cells of the stomach, and in small intestinal and colonic mucosal epithelial cells [8]. Thus, there is an interest to elucidate the mechanism involved in these untoward effects. VIP has been shown to induce smooth muscle relaxation, stimulate secretion of water into pancreatic juice and bile and cause inhibition of gastric acid secretion [9]. Patients on calcimimetic therapy showed significant lower VIP concentrations 4 h after the test meal in relation to those found in controls. The meaning of this difference might be in relation to a lower smooth muscle relaxation in patients treated with cinacalcet.

Most circulating ghrelin arises from gastric endocrine cells located in the fundus of the stomach [10,11]. Circulating ghrelin concentrations increase after fasting and decrease with food intake [12,13]. Our cinacalcet-treated patients showed the normal decline in plasma ghrelin levels after a meal, a drop that was not observed in control subjects in our study. The meaning of this difference, if any, remains unclear.

Substance P participates in the regulation of gastrointestinal motility and secretion [14–16]. It also has an emetic action at the central nervous system [17]. Our results of a
Fig. 2. Responses of plasma vasoactive inhibitory peptide (VIP), ghrelin, substance P, serotonin, cholecystokinin (CCK) and gastrin to a test meal in 12 control patients (○) and 20 patients chronically treated with cinacalcet (●). Each point represents the mean ± SEM. Abscissa scale: time (h). Ordinate scale: plasma concentration of corresponding hormone. CCK and gastrin concentrations have been log transformed. *P < 0.05, **P < 0.01 control versus cinacalcet. *P < 0.05 versus baseline concentration (within group).

Discrete elevation of plasma levels of substance P at 4 h in cinacalcet-treated patients seem to suggest that part of the gastrointestinal effects of this calcimimetic might be related to changes in plasma substance P levels.

Activation of 5-HT₃ serotonin receptors has been implicated in acute emesis in patients receiving chemotherapy, and the use of specific 5-HT₃-receptor antagonists has been useful in controlling vomiting [18,19]. Our results indicate that plasma levels of serotonin are not significantly modified by the use of cinacalcet.

CCK is the main hormone responsible for gallbladder contraction and pancreatic enzyme secretion. Main stimuli for CCK secretion are fat and protein ingestion [20]. Recent reports have demonstrated that calcium facilitates fatty acid and protein-induced CCK secretion [21,22]. Furthermore, calcium also participates in the mechanism of action of CCK on gallbladder contraction [23–25] and pancreatic enzyme production [26–28]. Our data suggest that calcimimetics have no relevant role in the release of this hormone.

Expression of the calcium-sensing receptor has been demonstrated in cultured human antral gastrin cells [29,30] and in human gastrinoma cells [31,32]. Oral calcium is a well-known stimulus for gastrin secretion in humans.
Fig. 3. Areas under the curves (AUC) for vasoactive intestinal peptide (VIP), ghrelin, substance P, serotonin, cholecystokinin (CCK) and gastrin, in the two groups of patients (control and cinacalcet) in all studied population (12 patients in the control group, and 20 patients in the cinacalcet group) and in patients on HD (11 patients in the control group and 9 patients in the cinacalcet group). Each column represents the mean ± SEM.

Furthermore, the calcimimetic compound KRN568 increased gastrin release in healthy subjects [36]. However, our results do not show any effect of cinacalcet on gastrin release in dialysis patients.

Among the limitations of this pilot study was the fact that the type of dialysis could not be matched between the control and cinacalcet groups. We could not study the differences between the control and cinacalcet groups in PD patients because of the lack of sufficient number of control subjects in this particular group. However, hormonal responses in HD patients were completely comparable to those obtained in the whole population of studied patients, suggesting that the type of dialysis did not play any relevant role. As we studied patients on chronic therapy with cinacalcet, acute effects of this drug on patients starting therapy might be different from those reported here. Hypertension seems to exert influence in hormone responses. In fact, hypertensive patients exhibited higher baseline levels and AUC of VIP than patients without hypertension. However, we did not find significantly higher levels of VIP in our control group, in spite of the predominance of hypertensive patients in this group. Significant changes in CCK and substance P found in hypertensive patients (Tables 2 and 3) were not found when studying control versus cinacalcet-treated patients. As expected, patients on therapy with omeprazol exhibited higher baseline levels and AUC of gastrin than patients who did not take this proton pump inhibitor. This effect of omeprazol may have been
accounted for by a feedback mechanism on gastrin release by the gastric G-cells [37–40]. A final limitation of this study is not including gastrointestinal symptomatic patients who should specifically be investigated in the near future.

In conclusion, the results of this study show that an acute dose of cinacalcet exerts minimal influence on gut hormone responses to a mixed meal in dialysis patients on chronic therapy with this drug. The small but significant differences between control subjects and patients on cinacalcet in VIP levels and in substance P at 4 h should be investigated in symptomatic patients.

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