The Calcimimetic Agent AMG 073 Lowers Plasma Parathyroid Hormone Levels in Hemodialysis Patients with Secondary Hyperparathyroidism

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Abstract. Treatment with vitamin D sterols can lower plasma parathyroid hormone (PTH) in many patients with secondary hyperparathyroidism due to end-stage renal disease, but hypercalcemia, hyperphosphatemia, or both often develop during treatment. As such, alternative therapeutic approaches to managing excess PTH secretion are needed. Calcimimetic agents directly inhibit PTH secretion by activating the calcium-sensing receptor in the parathyroid glands, but clinical experience with them is limited. Fifty-two hemodialysis patients with secondary hyperparathyroidism were given single orally administered doses of the calcimimetic agent AMG 073 ranging from 5 to 100 mg, or placebo. Plasma PTH levels decreased 2 h after 25-, 50-, 75-, or 100-mg doses, falling by a maximum of 43 ± 29%, 40 ± 36%, 54 ± 28%, or 55 ± 39%, respectively. Plasma PTH levels decreased in all patients given doses of ≥25 mg but did not change in those who received placebo. In patients treated with daily doses of 25 or 50 mg of AMG 073 for 8 d, plasma PTH levels declined for the first 3 to 4 d and remained below baseline values after 8 d of treatment. Serum calcium concentrations also decreased by 5 to 10% from pretreatment levels in patients given 50 mg of AMG 073 for 8 d, but values were unchanged in those who received lower doses. Serum phosphorus levels and values for the calcium-phosphorus ion product both decreased after treatment with AMG 073. Thus, 8 d of treatment with AMG 073 effectively lowers plasma PTH levels and improves several disturbances in mineral metabolism that have been associated with soft tissue and vascular calcification and with adverse cardiovascular outcomes in patients with end-stage renal disease.

Treatment with vitamin D sterols such as calcitriol, paricalcitol, or doxercalciferol effectively lowers plasma parathyroid hormone (PTH) levels in many patients with secondary hyperparathyroidism due to end-stage renal disease (ESRD) (1–5). Serum calcium and phosphorus concentrations often rise, however, during vitamin D therapy, and episodes of hypercalcemia, hyperphosphatemia, or both frequently limit the doses that can be given safely (6,7). Because hypercalcemia and hyperphosphatemia can aggravate soft tissue and vascular calcification and may contribute to the development of cardiovascular disease in those undergoing regular dialysis (8–10), considerable interest exists in identifying alternative strategies for controlling excess PTH secretion in such patients.

Calcimimetic agents are small organic compounds that act as allosteric activators of the calcium-sensing receptor in the parathyroid glands and other tissues (11,12). They lower the threshold for calcium-sensing receptor activation by extracellular calcium ions, thereby diminishing parathyroid hormone (PTH) secretion. By targeting directly the molecular mechanism that modulates calcium-regulated PTH release from the parathyroid cell, calcimimetic compounds provide a novel approach to managing excess PTH secretion in several clinical disorders, including secondary hyperparathyroidism due to chronic renal failure (13).

Previous short-term studies have shown that orally administered doses of the calcimimetic agent R-568 lower plasma PTH levels in hemodialysis patients with secondary hyperparathyroidism (14,15). The bioavailability of R-568 is limited, however, and the pharmacokinetics of the drug vary considerably among patients (15). As such, the effect of treatment with R-568 on plasma PTH levels, and in particular on serum calcium concentrations, is heterogeneous (15). To address these issues, another phenylalkylamine, known as AMG 073, with calcimimetic properties similar to those of R-568 has been developed. The bioavailability of AMG 073 after oral administration is greater and it exhibits a more consistent pharmacokinetic profile than R-568 (Amgen Inc., unpublished data).
The current preliminary study was undertaken to characterize the effect of various single orally administered doses of AMG 073 on plasma PTH levels and on serum calcium concentrations in adult hemodialysis patients with secondary hyperparathyroidism. The biochemical response to different doses of AMG 073 given once daily for 8 consecutive days was also evaluated.

Materials and Methods

Study Population

Patients were eligible for study if they were 18 yr of age or older, medically stable, and had been treated for at least 3 mo with thrice-weekly hemodialysis. Potential study participants were evaluated during a 21-d screening interval immediately preceding their initial dose of AMG 073. To assure that the biochemical data used for determining eligibility accurately reflected steady-state conditions in each study candidate, no adjustments to the doses of vitamin D sterols, calcium supplements, or phosphate-binding agents, or to the concentration of calcium in hemodialysis solutions were permitted during the screening period.

All study candidates had biochemical evidence of secondary hyperparathyroidism, as judged by the results of two plasma PTH determinations obtained at least 1 wk apart and within 21 d of the initial dose of AMG 073 that were between 250 and 1500 pg/ml. Additional inclusion criteria were serum total calcium values of ≥9.0 mg/dl after correcting for serum albumin concentrations, serum phosphorus levels of ≥2.5 mg/dl, and serum aluminum levels <40 μg/L. Study participants were also required to have a hemoglobin level ≥10 g/dl or a blood hematocrit ≥30%, a chest radiograph within the past 6 mo showing no evidence of active parenchymal disease, and a body mass index between 15 and 40 kg/m².

Women of childbearing age were excluded from study unless they had previously been rendered sterile surgically for other medical reasons. Patients were ineligible for study if the serum levels of hepatic transaminases or bilirubin were more that twice the upper limit of normal. Additional exclusion criteria included a history of seizures within the past 12 mo, malignancy within the past 5 yr, hyperthyroidism, myocardial infarction within the previous 6 mo, a cardiac ventricular rhythm disturbance requiring active treatment, a gastrointestinal disorder that could affect the absorption of drugs given orally, or granulomatous diseases that could cause hypercalcemia.

Study Design

The study was conducted in two phases, a single-dose phase and a multiple-dose phase, each of which was completed as a randomized, double-blinded, placebo-controlled, multicenter clinical trial. All study procedures were reviewed and approved by the institutional review boards at each study site, and written informed consent was obtained from each participant.

Single-Dose Phase

The first phase of the study was undertaken to assess the biochemical response to single orally administered doses of AMG 073 or placebo. Participants were initially randomized to treatment with either placebo or 5 mg of AMG 073. Subsequent assessments that used incrementally larger doses of AMG 073 were performed only after the clinical and biochemical results for the preceding dosage cohort had been reviewed by a safety advisory committee. For the single-dose phase of the study, patients were randomly assigned to treatment with 5 mg (n = 8), 10 mg (n = 8), 25 mg (n = 6), 50 mg (n = 6), 75 mg (n = 6), or 100 mg (n = 6) of AMG 073 or placebo (n = 12). Ninety-eight patients were screened as potential study participants, and 52 of these were entered onto the trial. The mean age of patients who participated in the single dose phase of the study was 48 ± 14 yr (range, 19 to 75 yr).

Doses of AMG 073 were given orally within 3 h after completing regularly scheduled hemodialysis treatments. Patients were admitted to the hospital for 3 d beginning immediately after hemodialysis for the administration of the study drug and for safety monitoring procedures. At admission, study participants underwent a physical examination, and blood was drawn for a complete blood count and for various baseline, or pretreatment, biochemical determinations. These included measurements of serum total calcium and phosphorus levels and plasma PTH concentrations.

Additional blood samples were obtained 30 min and 1, 2, 4, 8, 12, 24, 48, and 72 h after the administration of AMG 073. Calcium concentrations in serum and PTH levels in plasma were determined for each sample. Subsequent hemodialysis sessions after test doses of AMG 073 were continued according to the patient’s regular schedule of treatment.

Multiple-Dose Phase

For the multidose phase of the trial, study participants were randomly assigned to receive single daily orally administered doses of 10 mg (n = 8), 25 mg (n = 6), or 50 mg (n = 9) of AMG 073 or placebo (n = 7) for 8 d. Follow-up evaluations were performed on days 11 and 15 of the study (3 and 7 d, respectively) after the last dose of AMG 073 or placebo. Patients who participated in the single-dose phase of the study were eligible to enroll in the 8-d multidose trial after an interval of 4 wk. Twenty-seven of the 30 patients who entered the multiple-dose phase of the study had previously received single orally administered doses of AMG 073; 3 had not. The mean age of participants in the multiple-dose phase of the trial was 46 ± 16 yr (range, 19 to 77 yr).

Because the effect of repeated daily doses of AMG 073 on serum calcium concentrations was unknown when the study was started, participants were randomized initially to treatment with placebo or the lowest dose of AMG 073: 10 mg. A safety monitoring committee reviewed the clinical and biochemical results for the 10-mg dosage cohort before patients were assigned to treatment with the next larger dose of AMG 073 (25 mg). Similarly, results from the 25-mg dosage cohort were reviewed before patients were randomized to treatment with 50 mg of AMG 073 or placebo.

Initial doses of AMG 073 on the first day of study were given within 3 h after completing regularly scheduled hemodialysis procedures and after patients had been admitted to the hospital. Subsequent doses for the remaining 8 d of treatment were given at the same time of day. Study participants were monitored in hospital for the duration of treatment. All doses of AMG 073 on days corresponding to regularly scheduled dialysis sessions were given after hemodialysis.

On the first and eighth day of treatment, blood samples were obtained immediately before and 0.5, 1, 2, 4, 8, 12, and 24 h after doses of AMG 073 for subsequent determinations of serum total calcium and plasma PTH levels. Blood specimens for plasma PTH and serum calcium measurements were collected just before dosing on each day of treatment, and serum phosphorus levels were measured on the first, fourth, and eighth day of treatment. Additional blood samples were obtained 4 and 12 h after each dose of AMG 073 to monitor serum calcium concentrations for safety purposes. For all days on which AMG 073 was given, baseline, or predose, blood samples for
biochemical measurements were obtained just before drug administration. Blood samples for posttreatment biochemical determinations on study day 11 and 15 were obtained at the same time of day. Hemodialysis was continued throughout the study by means of previously established individualized treatment regimens. All dialysis parameters, including the concentration of calcium in dialysate, were kept constant throughout the study.

Three patients who were originally assigned to treatment with daily doses of 50 mg of AMG 073 had their dose reduced to 25 mg on the second or third day of study. In 2 patients, doses were reduced because serum total calcium concentrations transiently fell below 8.0 mg/dl; the dose was reduced in a third patient because of nausea that occurred together with a serum calcium concentration of 8.2 mg/dl. None of these patients experienced symptoms of hypocalcemia, and all successfully completed 8 d of treatment with AMG 073 at the lower dose of 25 mg/d.

**Laboratory Determinations**

Serum electrolyte concentrations and the serum levels of total calcium, phosphorus, aspartate aminotransferase, and alanine aminotransferase were measured with a Hitachi 747-200 autoanalyzer (15). Hemoglobin levels were measured by automated methods as described previously, and hematocrit values were determined by centrifugation (15). Plasma PTH levels were measured with a double-antibody immunoradiometric assay (Allegro PTH; Nichols Institute Diagnostics, San Juan Capistrano, CA) (16). Serum calcium concentrations were corrected for variations in plasma albumin levels, and corrected values are reported.

**Statistical Analyses**

All results are expressed as mean ± 1 SD. For the single-dose phase of the study, the maximum percentage decrease in plasma PTH levels from predose values among groups was compared by ANOVA (17). For the multiple-dose phase of the study, ANOVA was again used to compare the percentage change from baseline values in plasma PTH levels on the eighth day of treatment among treatment groups (17). For all statistical tests, P < 0.05 was considered significant.

**Results**

**Response to Single Doses of AMG 073**

Baseline, or pretreatment, plasma PTH levels did not differ among patients given placebo or various doses of AMG 073. Serum calcium and phosphorus levels also did not differ among groups (Table 1). The mean age of patients, the duration of treatment with dialysis before study, the proportion of diabetic subjects, the percentage of patients who had previously been treated with vitamin D sterols, and the number who had previously undergone parathyroidectomy did not differ among those given placebo or various doses of AMG 073 (data not shown).

Plasma PTH levels decreased from pretreatment values within a few hours in patients given single orally administered doses of 25, 50, 75, or 100 mg of AMG 073. In contrast, values remained unchanged in those given either 5- or 10-mg doses of AMG 073 (data not shown) or placebo (Figure 1). The greatest percentage reductions in PTH concentrations were seen 2 to 4 h after drug administration, and values differed significantly among treatment groups (P < 0.0001 by ANOVA). Maximum decreases were 57 ± 24%, 59 ± 16%, 59 ± 23%, and 72 ± 11% in patients given 25, 50, 75, or 100 mg of AMG 073, respectively. Plasma PTH levels remained below pretreatment values for 24 h in patients who received 25-, 50-, or 100-mg doses of AMG 073 but returned to predose levels after 8 h in those who received 75-mg doses.

The decrease in plasma PTH levels after single doses of AMG 073, expressed either in absolute concentration units or as a percentage of pretreatment values, was unrelated to the predose level of either calcium or PTH. Plasma PTH levels declined in all subjects given doses ranging from 25 to 100 mg

**Table 1. Baseline biochemical data for patients provided single orally administered doses of AMG 073 or placebo**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Plasma PTH (pg/ml)</th>
<th>Serum Calcium (mg/dl)</th>
<th>Serum Phosphorus (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo  (n = 12)</td>
<td>599 ± 362</td>
<td>9.9 ± 0.5</td>
<td>6.5 ± 1.8</td>
</tr>
<tr>
<td>5 (n = 8)</td>
<td>566 ± 281</td>
<td>10.4 ± 0.8</td>
<td>6.9 ± 1.8</td>
</tr>
<tr>
<td>10 (n = 8)</td>
<td>473 ± 284</td>
<td>10.2 ± 0.7</td>
<td>5.7 ± 1.3</td>
</tr>
<tr>
<td>25 (n = 6)</td>
<td>752 ± 580</td>
<td>9.7 ± 1.0</td>
<td>5.1 ± 1.3</td>
</tr>
<tr>
<td>50 (n = 6)</td>
<td>490 ± 340</td>
<td>9.7 ± 1.9</td>
<td>6.5 ± 1.6</td>
</tr>
<tr>
<td>75 (n = 6)</td>
<td>696 ± 482</td>
<td>10.1 ± 0.9</td>
<td>5.8 ± 1.7</td>
</tr>
<tr>
<td>100 (n = 6)</td>
<td>919 ± 479</td>
<td>9.5 ± 0.9</td>
<td>6.0 ± 1.6</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SD. PTH, parathyroid hormone.

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**Figure 1.** Graph illustrating plasma parathyroid hormone (PTH) levels, expressed as a percentage of predose values, during the first 24 h after single orally administered doses of 25, 50, 75, or 100 mg of AMG 073 in hemodialysis patients with secondary hyperparathyroidism. Error bars have been omitted for clarity.
of AMG 073, regardless of the biochemical severity of secondary hyperparathyroidism as judged by baseline, or pretreatment, plasma PTH values. For example, baseline plasma PTH levels ranged from 402 to 1801 pg/ml in patients given 100-mg doses of AMG 073 (Figure 2A), but values decreased by a similar percentage in each patient during the first 24 h after drug administration (Figure 2B).

Serum total calcium concentrations declined modestly in patients given 75- or 100-mg doses of AMG 073 but did not change in those who received smaller doses (Figure 3). Serum calcium concentrations reached their lowest levels 8 to 12 h after 75- and 100-mg doses of AMG 073 and remained below pretreatment values for 24 h. Serum calcium levels returned to, and did not differ from, predose values 48 h after 75- or 100-mg doses of AMG 073. None of the patients given single doses of AMG 073 or placebo developed signs or symptoms of hypocalcemia. The maximum decrease in serum total calcium concentrations averaged 1.0 ± 0.7 mg/dl and 0.9 ± 0.4 mg/dl in patients given 75 or 100 mg of AMG 073, respectively.

Response to Daily Orally Administered Doses of AMG 073 for 8 Days

Plasma PTH levels before dosing on the first day of study did not differ among patients assigned to 8 d of treatment with 10, 25, or 50 mg of AMG 073 or placebo (Table 2). Similarly, there were no differences among groups in baseline serum calcium or phosphorus concentrations. Three patients who were initially given 50-mg doses of AMG 073 had their dose reduced to 25 mg because nausea developed in one and serum calcium concentrations fell transiently below 8.0 mg/dl in 2 others. These 3 patients are hereafter designated as the 50/25-mg group. Baseline serum calcium and phosphorus concentrations and basal plasma PTH levels were no different in this subset of patients than in the other three groups. Overall, the mean age of patients, the duration of treatment with dialysis, the proportion of patients with diabetes, the percentage of patients who had previously been treated with vitamin D, and the number who had undergone parathyroidectomy did not differ among the 10-, 25-, 50-, and 50/25-mg dosage cohorts (data not shown).

Plasma PTH levels on the first day of treatment declined substantially from baseline values after 25- or 50-mg doses of AMG 073 but did not change after 10-mg doses. As such, the results were similar to those seen after single orally administered doses. The largest decreases in plasma PTH occurred 2 h after drug administration, averaging 39.6 ± 33.1% and 44.5 ± 30.8% in patients who received 25- or 50-mg doses of AMG 073, respectively. Plasma PTH levels rose gradually thereafter.

Table 2. Baseline biochemical results for patients provided daily orally administered doses of 10, 25, 50, or 50/25 mg of AMG 073 or placebo for 8 d

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Plasma PTH (pg/ml)</th>
<th>Serum Calcium (mg/dl)</th>
<th>Serum Phosphorus (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 7)</td>
<td>767 ± 457</td>
<td>9.7 ± 0.5</td>
<td>5.9 ± 1.9</td>
</tr>
<tr>
<td>10 (n = 8)</td>
<td>553 ± 370</td>
<td>10.2 ± 1.2</td>
<td>7.0 ± 1.8</td>
</tr>
<tr>
<td>25 (n = 6)</td>
<td>527 ± 239</td>
<td>9.6 ± 0.5</td>
<td>6.7 ± 2.1</td>
</tr>
<tr>
<td>50 (n = 6)</td>
<td>824 ± 694</td>
<td>9.5 ± 0.7</td>
<td>5.0 ± 1.1</td>
</tr>
<tr>
<td>50/25 (n = 3)</td>
<td>578 ± 234</td>
<td>9.9 ± 1.0</td>
<td>6.8 ± 0.9</td>
</tr>
</tbody>
</table>

*Doses were reduced from 50 to 25 mg during the first several days of treatment. Values are expressed as mean ± SD. PTH, parathyroid hormone.*
toward pretreatment values but remained below baseline levels for 24 h in patients given 25- or 50-mg doses of AMG 073. Similar percentage reductions in plasma PTH levels were seen on the eighth day of treatment. Values fell from 401 ± 238 to 233 ± 84 pg/ml, or by 42%, 4 h after 25-mg doses and from 663 ± 624 to 455 ± 481 pg/ml, or by 32%, 4 h after 50-mg doses of AMG 073. In contrast to these findings, plasma PTH levels did not change on the eighth day of treatment in patients given placebo or 10-mg doses of AMG 073.

Plasma PTH levels, measured in plasma samples obtained immediately before each dose and 24 h after the dose, decreased during the first 3 to 4 d of treatment in patients who received daily doses of 25 or 50 mg of AMG 073 for 8 d (Figure 4). Values also decreased in the 50/25-mg group despite early downward adjustments to the dose. In contrast, plasma PTH values remained unchanged in patients given placebo or 10-mg doses of AMG 073 for 8 d. The decrease in plasma PTH levels from baseline values on the eighth day of treatment averaged 28 ± 17% in the 25-mg group, 27 ± 34% in the 50-mg group, and 34 ± 39% in the 50/25-mg group. Collectively, the percentage change in plasma PTH levels for these three treatment groups differed from that seen in patients given placebo (P = 0.05 by ANOVA).

Serum calcium concentrations remained unchanged in patients given placebo or 10-mg doses of AMG 073 for 8 d but were somewhat lower after the last day of treatment in the 25-mg dosage cohort (Figure 5). Values were 5 to 10% below baseline levels during the fifth through the eighth day of treatment in patients given 50-mg doses. Serum calcium concentrations were also lower on the second day of treatment in the 50/25-mg group but rose on the third day, after the dose of AMG 073 was reduced. Serum calcium concentrations were again lower, however, from the fourth through the eighth day of treatment, despite earlier dosage reductions (Figure 5).

Episodes of hypocalcemia during treatment with AMG 073 were transient, and they occurred 30 min to 12 h after drug administration. For the 23 patients given various doses of AMG 073 for 8 d, baseline, or predose, serum calcium levels were <8.0 mg/dl on 3 occasions. One occurred on the fifth day of treatment and another on the seventh day of treatment in 2 different patients from the 50-mg dosage cohort; the third occurred on the fifth day of treatment in a patient in the 50/25-mg group.

Serum phosphorus concentrations after 8 d of treatment were lower than baseline values in all 4 groups of patients given AMG 073 but did not change in those given placebo (Figure 6). Values for the calcium-phosphorus ion product in serum were also lower than baseline levels after 8 d of treatment with AMG 073 but did not differ from baseline values in patients given placebo (Figure 6).
substantially lower than those determined 12 to 24 h later. Levels of AMG 073. Plasma PTH concentrations were 50 to 70% lower than predose values 2 to 4 h after 25- or 50-mg doses, levels of AMG 073. Plasma PTH levels decreased by 30 to 40% within the first few days of treatment and remained below baseline values for 8 d, plasma PTH levels declined by 40 to 60% after 2 h. The magnitude of the response was largely dose dependent. The lowest dose of AMG 073 that consistently lowered plasma PTH levels was 25 mg, whereas larger percentage reductions in plasma PTH levels were achieved with doses of 75 and 100 mg. Plasma PTH levels decreased in all patients who received doses between 25 and 100 mg, regardless of the biochemical severity of secondary hyperparathyroidism.

All patients successfully completed 8 d of treatment with AMG 073 or placebo, and all were followed for an additional 7 d after treatment was ended. None of the patients experienced signs or symptoms of hypocalcemia. The frequency of side effects ascribed to treatment did not differ among patients given various doses of AMG 073 or placebo. The most commonly reported events both in placebo- and in AMG 073-treated patients were nausea, vomiting, headache, and hypertension before regularly scheduled dialysis sessions.

Discussion

The results of the study presented here indicate that treatment with the calcimimetic AMG 073 effectively lowers plasma PTH levels in patients with secondary hyperparathyroidism due to ESRD. After single orally administered doses ranging from 25 to 100 mg, plasma PTH levels declined by 40 to 60% after 2 h. The magnitude of the response was largely dose dependent. The lowest dose of AMG 073 that consistently lowered plasma PTH levels was 25 mg, whereas larger percentage reductions in plasma PTH levels were achieved with doses of 75 and 100 mg. Plasma PTH levels decreased in all patients who received doses between 25 and 100 mg, regardless of the biochemical severity of secondary hyperparathyroidism.

For patients given daily doses of 25 or 50 mg of AMG 073 for 8 d, plasma PTH levels decreased by 30 to 40% within the first few days of treatment and remained below baseline values when assessed by use of results obtained immediately before each daily dose—that is, 24 h after the preceding dose. Substantially greater reductions in plasma PTH levels were evident, however, on the first and eighth day of treatment when measurements were performed in plasma samples obtained more frequently during the 24 h immediately after daily doses of AMG 073. Plasma PTH concentrations were 50 to 70% below predose values 2 to 4 h after 25- or 50-mg doses, levels substantially lower than those determined 12 to 24 h later.

Thus, predose plasma PTH measurements understate the effectiveness of daily doses of AMG 073 in reducing plasma PTH levels throughout the day in patients with secondary hyperparathyroidism due to ESRD. Serum calcium concentrations declined modestly during 8 d of treatment with daily orally administered doses of 25 or 50 mg of AMG 073, but none of the patients developed signs or symptoms of hypocalcemia. It is of particular interest that serum phosphorus levels fell by 20 to 30%. Values for the calcium-phosphorus ion product in serum also decreased, primarily as a result of reductions in serum phosphorus levels. Such findings indicate that repeated daily doses of AMG 073 not only reduce the biochemical severity of secondary hyperparathyroidism in patients undergoing regular hemodialysis, but also favorably affect several abnormalities in mineral metabolism that have been implicated as contributors to vascular and soft tissue calcification and to cardiovascular mortality in patients with ESRD (8,18). Longer-term studies will be required, however, to determine whether similar changes in serum phosphorus levels and in values for the calcium-phosphorus ion product in serum can be achieved during sustained treatment with AMG 073.

The mechanism responsible for the decreases in serum calcium and phosphorus concentrations during treatment with AMG 073 and other calcimimetic compounds remains uncertain. Reductions in serum calcium levels have been a consistent finding after the administration of sufficiently large doses of calcimimetic agents to subtotally nephrectomized rats (19–21), and serum calcium concentrations declined in some adult hemodialysis patients with secondary hyperparathyroidism who were given fixed daily doses of the calcimimetic compound R-568 for 15 d (15). Because plasma PTH levels fall abruptly after the administration of calcimimetic agents, calcium and phosphorus efflux from bone into plasma may decrease substantially, leading to reductions in the serum levels of both calcium and phosphorus within a few hours. This mechanism probably accounts for the reductions in serum calcium and phosphorus concentrations that occur after surgical parathyroidectomy, a clinical condition known as the “hungry bone syndrome.” Alternatively, the activation of calcium-sensing receptor in bone or other tissues could theoretically account for rapid changes in serum calcium and phosphorus levels after the administration of calcimimetic agents (22,23). To date, little information is available that addresses this issue directly.

Additional studies are needed to clarify the role of concurrent therapy with either vitamin D sterols or orally administered calcium supplements as a means of offsetting the effect of calcimimetic agents to lower serum calcium concentrations. The proportion of patients who might require such interventions remains uncertain, and the role of alternative dosing regimens that could attenuate the calcium-lowering effect of calcimimetic compounds has yet to be fully evaluated. Calcimimetic compounds might be particularly valuable, however, in treating patients with secondary hyperparathyroidism whose serum calcium levels are already marginally or overtly elevated.
and in whom vitamin D therapy frequently raises serum calcium and phosphorus concentrations further.

The current management of secondary hyperparathyroidism due to chronic renal failure relies predominantly on the use of orally administered calcium supplements and the oral or intravenous administration of vitamin D sterols to control excess PTH secretion (24). Both interventions act directly on parathyroid cells to diminish pre--PTH gene transcription and lead indirectly to decreases in PTH secretion (24). Treatment with vitamin D often increases serum phosphorus levels and values for the calcium-phosphorus product in hemodialysis patients with secondary hyperparathyroidism. Nevertheless, calcimimetic compounds represent a novel approach for controlling excess PTH secretion in patients with chronic renal failure, alternative strategies for controlling excess PTH secretion in such patients are of considerable interest (25).

Several new vitamin D sterols have become available for the treatment of secondary hyperparathyroidism in patients with ESRD (24). These include 19-nor-1,25-dihydroxyvitamin D2, or paricalcitol, and 1α-hydroxyvitamin D3, or doxercalciferol (3–5). Both have been shown to effectively lower plasma PTH levels in hemodialysis patients with secondary hyperparathyroidism, and serum calcium and phosphorus levels change little or rise modestly during the 12 to 16 wk of treatment. Serum calcium and phosphorus concentrations do not decline, however, even when plasma PTH levels fall in those who respond favorably to treatment with vitamin D sterols, whereas serum calcium and phosphorus levels decreased during treatment with AMG 073. Differences in the mechanism of action between calcimimetic agents and vitamin D sterols probably account for the disparate biochemical responses to these two distinct classes of therapeutic agents (24).

In summary, repeated daily orally administered doses of the calcimimetic agent AMG 073 effectively reduce plasma PTH levels, decrease serum phosphorus concentrations, and lower the calcium-phosphorus ion product in hemodialysis patients with secondary hyperparathyroidism. Calcimimetic compounds represents a novel approach for controlling excess PTH secretion in patients with chronic renal failure, and their use may favorably affect several potentially deleterious abnormalities in mineral metabolism in patients with ESRD. Additional studies will be required to establish the safety and long-term benefits of calcimimetic therapy in patients with secondary hyperparathyroidism. Nevertheless, calcimimetic compounds provide an effective therapeutic intervention to control excess PTH secretion with potentially beneficial effects on mineral metabolism in patients with ESRD.

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References


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See related editorial, “Manipulating the Calcium Receptor,” on pages 1124–1125.

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