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# Calcimimetic agents: Review and perspectives

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**Calcimimetic agents: Review and perspectives.**

*Background.* Recognition of the role of the extracellular calcium-sensing receptor (CaR) in mineral metabolism has greatly improved our understanding of calcium homeostasis. The activation of this receptor by small changes in the extracellular ionized calcium ($_{ec}(Ca^{2+})$) regulates PTH, calcitonin secretion, urinary calcium excretion, and, ultimately, bone turnover.

*Methods.* The cloning of the CaR and the discovery of mutations that make the receptor less or more sensitive to calcium have allowed a better understanding of several hereditary disorders characterized by either hyperparathyroidism or hypoparathyroidism. The CaR, able to amplify the sensitivity of the CaR to $Ca^{++}$ and suppress PTH levels with a resulting decrease in blood $Ca^{++}$, became an ideal target for the development of compounds, the calcimimetics. Experience with the calcimimetic R-568 in patients with primary and secondary hyperparathyroidism and parathyroid carcinoma are summarized.

*Results.* The first clinical studies with the first-generation calcimimetic agents have demonstrated their efficacy in lowering plasma intact PTH concentration in uremic patients with secondary hyperparathyroidism. However, the low bioavailability of these first calcimimetics predicts a difficult clinical utilization. The second-generation calcimimetic, AMG 073, having a better pharmacokinetic profile, appears to be effective and safe for the treatment of secondary hyperparathyroidism, suppressing PTH levels while simultaneously reducing serum phosphorus levels and the calcium x phosphorus product.

*Conclusion.* The advantage of controlling PTH secretion without the complications related to hypercalcemia, hyperphosphatemia, and increased calcium x phosphorus product is very promising.

More than a century after its identification, secondary hyperparathyroidism remains a problem in more than one third of patients with chronic renal insufficiency [1–3]. Despite the use of new vitamin D analogs and new calcium-free, aluminum-free phosphate binders, many patients with secondary hyperparathyroidism are not controlled due to vitamin D–associated hypercalcemia and hyperphosphatemia, or parathyroid gland resistance. Three percent to 5% of patients require a total or subtotal surgical parathyroidectomy every year as a result of treatment failure or severe clinical complications [4]. Parathyroid surgery is associated with major risks related to anesthesia, pre- and post-surgical complications, induction of permanent hypoparathyroidism, or recurrence of the secondary hyperparathyroidism. The hypoparathyroid state is associated with low bone remodeling, adynamic bone disease, increased serum calcium and phosphorus product, vascular calcifications, and the devastating lesions of calciphylaxis [5–7]. Thus, the ideal treatment would be a drug that could efficiently, safely, and cyclically suppress the secretion of parathyroid hormone (PTH) without interfering with the calcium and phosphorus intestinal absorption.

**Key words:** calcium-sensing receptor, calcimimetics, secondary hyperparathyroidism, hypocalcemia, parathyroid hormone, renal osteodystrophy, review.



## Parathyroid cell calcium-sensing receptor

During the last 25 years, scientists have been interested in demonstrating that the secretion of PTH is mainly regulated by a membrane receptor on the parathyroid cells which is capable of responding to small variations in the extracellular ionized calcium ($_{ec}(Ca^{2+})$) concentration. It was only in 1993 that Brown et al [8] cloned the parathyroid cell calcium-sensing receptor (CaR). This is a 121-kD protein with three main structural domains, a long extracellular N-terminal domain, seven membrane-spanning helices, and a hydrophobic intracellular C-terminus characteristic of G-protein coupled receptors. The CaR belongs to the type III family of structurally unique G protein-coupled receptors, which includes other CaRs, metabotropic glutamate receptors (mGluR1-8), putative pheromone receptors expressed in the rodent vomeronasal organ (V2Rs), three sweet taste receptors (T1R1-3), and $GABA_B$ receptors [9]. The parathyroid and kidney CaRs are 1081 and 1079 amino acid long proteins, respectively. The CaR can be considered a low-affinity receptor, responding to relatively high concentration of $_{ec}(Ca^{2+})$, over one mmol/L. The limited selectivity of the receptor is responsible for its activation by numerous divalent or trivalent cations in addition to calcium, such as magnesium, gadolinium, aluminum, and lanthanum, and by other polycationic compounds such as neomycin, spermine, and numerous amino acids [10, 11]. The activation

of the CaR by any one of these agonists results in the stimulation of the Gi protein, phospholipase C, inositide trisphosphate cascade, the mobilization of intracellular calcium, and the activation of protein kinase C (PKC). Its activation also inhibits the adenylcyclase signaling pathway and protein kinase A (PKA) [8, 12]. Modifications in these signal transduction pathways result in the inhibition of PTH secretion.

The physiologic relevance of the cloned CaR in determining the level at which circulating $_{ec}Ca^{2+}$ is set has been established by the identification of several inherited diseases due to inactivation or activation mutations in the parathyroid CaR gene, namely familial hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and familial hypercalciuric hypocalcemia [12–14].

## Calcimimetic agents

After discovery of the CaR there was interest in the development of compounds with the capacity of modulating the function of the receptor, thus providing another tool for the medical treatment of both primary and secondary hyperparathyroidism (Table 1) [10, 15–17]. The first compounds were called "type I calcimimetics" because they mimicked the effects of $_{ec}Ca^{2+}$. The second compounds were called "type II calcimimetics" because they changed the structural conformation of the CaR and stereo-selectively increased its sensitivity to $_{ec}Ca^{2+}$. Type II calcimimetics lose their effect in the absence of $_{ec}Ca^{2+}$ and do not really mimic the effect of $_{ec}Ca^{2+}$; therefore, naming them calcimimetics is probably inappropriate and they should be called "positive allosteric modulators of CaR." The third compounds have been called "calcilytics" because they inhibit CaR function and stimulate PTH secretion [10, 17]. It has been suggested by site-directed mutagenesis studies that the mode of action of the type II calcimimetics agents may reside in its binding to the seventh transmembrane domain of the CaR [18]. Several calcimimetic agents have already been developed: first-generation compounds, including NPS R-567, NPS S-567, NPS R-568, NPS S-568, and KRN-568, and a second-generation compound, AMG 073.

**Table 1.** Agonists and antagonists of the calcium receptors

| | Agonists | |
|---|---|---|
| Type I calcimimetics | Positive charges | $EC_{50}$ |
| Inorganic cations | | |
| Calcium | 2 | 1.2 mmol |
| Magnesium | 2 | 5.2 mmol |
| Lanthanum | 3 | 33 μm |
| Gadolinium | 3 | 20 μm |
| Aluminum | 3 | 4 mmol |
| Barium | 2 | — |
| Cadmium | 2 | — |
| Nickel | 2 | — |
| Cobalt | 2 | — |
| Iron | 2 | — |
| Lead | 2 | 0.1 mmol |
| Polyamines | | |
| Spermine | 3 | 150 μm |
| Spermidine | 4 | 2.0 mmol |
| Pentaethylenehexamine | 6 | 500 μm |
| Hexacyclin | 6 | 21 μm |
| Aminosides | | |
| Streptomycin | 3 | 600 μm |
| Bekanamycin | 5 | 200 μm |
| Gentamycin | 5 | 150 μm |
| Neomycin | 6 | 30 μm |
| Polybasic amino acids and other peptides | | |
| Protamine | 21 | 75 μm |
| Polylysine (38 kD) | 55 | 3 nmol |
| Polyarginine (100 kD) | 640 | 4 nmol |
| Type II calcimimetics | | |
| NPS R-467 | 1 | 4.8 μm |
| NPS S-467 | 1 | 70 μm |
| NPS R-568 | 1 | 0.6 μm |
| NPS S-568 | 1 | 9.8 μm |
| AMG 073 | — | 2.8 μm |
| KRN568 | — | (Cmax) 6.5 ng/mL |
| Others | | |
| Thimerosal (merthiolate) | — | — |
| | Antagonists | |
| Calcilytics | | |
| NPS 2143 | — | — |

## Action of calcimimetic agents in vitro and in animals

The calcimimetic agents suppress the secretion of PTH in a dose-dependent manner in cultured parathyroid cells and in healthy animals. In animals, oral NPS R-568 provokes a rapid dose-dependent ($ED_{50}$, 1.1 ± 0.7 mg/kg) decrease in serum PTH and calcium concentrations. At a dose of 3.3 mg/kg, the maximum effect on PTH levels is reached 15 minutes after administration. At doses ranging from 10 to 100 mg/kg, hypocalcemia is almost immediate, lasting for more than 24 hours. Studies performed in rats submitted to bilateral nephrectomy and parathyroidectomy suggest that the striking hypocalcemia might be due to the abolition of PTH secretion with a decrease in bone turnover, and not to the stimulation of the renal CaR [19, 20].

Six heterogeneous studies in uremic animals with secondary hyperparathyroidism have been published (Table 2). In these studies, NPS R-568 at doses ranging from 1.5 to 15 mg/kg/day reduced the proliferation rate of parathyroid cells by 50%, stopped the progression of parathyroid gland hyperplasia, and corrected the histologic signs of high bone turnover [19, 21–25].

## Clinical use of calcimimetic agents

Calcimimetic agents have been tested in subjects with normal renal function [26, 27]. In one study, 18 postmenopausal women were randomized into two groups; one group received increasing doses of oral NPS R-568 (10 to 400 mg/day), and the other group was treated with placebo. The levels of intact PTH decreased by 34% from baseline values 30 to 120 minutes after the dose of

**Table 2.** Calcimimetics in animals with uremic secondary hyperparathyroidism

| Reference | Type of CRF | Dose of calcimimetic | Duration of treatment | Main results |
|---|---|---|---|---|
| Wada et al [21] | Nx. 5/6th | 1.5–15 mg/kg/b.i.d. (gavage) | 4 days | 50% reduction in the proliferation rate of parathyroid cells |
| Fox et al [19] | Nx. 5/6th | 5–10 mg/kg/q.i.d. (gavage) | 6 hours | 82 to 94% reduction in serum PTH levels |
| Wada et al [22] | Renal arterial ligation | 30–100 μmol/kg/q.i.d. (gavage) | 54 days | 50% reduction in serum PTH levels |
| | | 20 μmol/kg/q.i.d. (subcutaneous) | 54 days | Normalization of serum PTH levels |
| Chin et al [23] | Nx. 5/6th | 10–30 μmol/kg/q.i.d. (gavage) 20 μmol/kg/q.i.d. (subcutaneous) | 8 weeks | Stop the progression of secondary hyperparathyroidism |
| Wada et al [24] | Nx. 5/6th | 3–30 mg/kg/q.i.d. (gavage) | 30 days | Correction of histologic signs of secondary hyperparathyroidism |
| Ischii et al [25] | Adriamycin | 10 mg/kg/q.i.d. (gavage) | 8 weeks | Restoration of trabecular bone volume; 14% increase in bone mineral density |
| | Renal arterial ligation | 4.5 mg/kg/q.i.d. (subcutaneous) | 8 weeks | No bone effect |

Nx. is nephrectomy.

10 mg, and decreased by 74% after 400 mg of NPS R-568. The duration of PTH suppression was also dose-dependent and lasted approximately 12 hours. Serum PTH levels decreased even in the presence of a steady decline in plasma calcium concentration [27].

The NPS R-568 was also tested in patients with primary hyperparathyroidism. Twenty postmenopausal women were enrolled and randomized into two groups; one group received a unique dose of NPS R-568 (from 4 to 160 mg), and the other group received a placebo [28]. The minimal effective dose of NPS R-568 was 20 mg, resulting in a 26% suppression of the intact PTH levels. With doses of 80 and 160 mg, serum PTH fell by 42% and 51%, respectively. The lowest serum intact PTH levels were observed two hours after the administration of either 80 or 160 mg of NPS R-568, and they returned to the initial baseline values four and eight hours after the administration of 80 and 160 mg, respectively. Serum ionized calcium decreased slightly from 1.35 to 1.30 mmol/L four hours after the dose of 160 mg. Similarly, the urinary excretion of calcium increased by a factor of 2.3 only two hours after the administration of 160 mg of NPS R-568 and returned to baseline values eight hours later.

The calcimimetic agent, R-568, was given to a patient with inoperable parathyroid carcinoma who presented with hypercalcemia (blood $Ca^{++}$ 1.96 mmol/L), high PTH levels (1128 pg/mL), and altered mental status; hypercalcemia failed to respond to intravenous saline and furosemide, several doses of intravenous pamidronate, and salmon calcitonin over 18 days [29]. The calcimimetic was initiated at 200 mg/day and subsequently increased to 400 mg/day. The patient's symptoms improved after three days of R-568 treatment and the patient was discharged home after 28 days of treatment with a blood $Ca^{++}$ of 1.53 mmol/L and a PTH level of 357 pg/mL. Treatment with the calcimimetic was continued and the dose was titrated up to 600 mg/day; this treatment maintained the total serum calcium between 2.75 to 3.0 mmol/L, despite the progressive increase in PTH levels from 2000 to 3500 pg/mL. This PTH increase was believed to occur due to progression of the parathyroid carcinoma. The patient remained very active, traveled extensively, and had no side effects over a follow-up of more than 600 days. In addition, all measures of cardiac, renal, hepatic, hematologic, and pancreatic function remained stable throughout the period of treatment. Although such observations were made only in one patient, the data showed that R-568 could be given safely over a prolonged period of time.

Two complete reports were published regarding the use of NPS R-568 in dialysis patients with secondary hyperparathyroidism. The first study [30] was a small, two-day study in seven patients with mild hyperparathyroidism. Doses of 40 or 80 mg caused PTH levels to fall by more than 30% after the first dose in 5 of 7 patients, and more than 60% after the second dose in 6 of 7 patients. With doses of 120 and 200 mg, PTH was reduced by more than 60% after the first dose in 6 of 7 patients. After 24 hours, the pretreatment PTH level was still 50% lower than the initial basal value; nonetheless, PTH fell 50% or more after the second dose in 6 of 7 patients. Blood $Ca^{++}$ was not significantly changed after the low dose, but fell significantly after the high dose. Serum calcitonin levels doubled four hours after the high doses and returned to baseline 48 hours later. The second study [16] was performed in 21 hemodialysis patients with moderate secondary hyperparathyroidism (PTH between 300 and 1200 pg/mL). They were randomized into two groups: 5 patients received a placebo and 16 patients received an oral dose of 100 mg per day of NPS R-568 for 15 days. In the treated group, the serum level of PTH fell by 66%, 78%, and 70% after one, two, and four hours, respectively, and remained significantly lower than the basal values during the next 24 hours. Despite lower ionized calcium concentrations, predose intact PTH levels decreased progressively over the first nine days of treatment with R-568. Levels remained below pretreatment levels for the duration of the study, in contrast with the placebo treated group. Serum total and blood

ionized calcium levels decreased from pretreatment levels in patients given R-568, whereas values were unchanged in those given a placebo. Blood ionized calcium levels fell below 1.0 mmol/L in seven of 16 patients receiving R-568; five patients withdrew from the study after developing symptoms of hypocalcemia, while three patients completed treatment after the R-568 dose was reduced. An interesting point of this study is the pharmacokinetic data of NPS R-568. After a single dose, its maximal plasma concentration was obtained after a variable lapse of time, ranging from 1 to 24 hours. The peak plasma concentration, often observed between 2.5 and 4.4 hours, greatly differed from one patient to another (from 0.42 to 42.2 ng/mL). The bioavailability of NPS R-568 appears to be very low (<1%), which suggests that manipulation of this first-generation calcimimetic would be difficult.

Due to the pharmacokinetic profile and interactions with other drugs, the development of R-568 was discontinued and a second-generation calcimimetic agent, AMG 073, developed. In the initial clinical trials, AMG 073 showed the potential to treat hemodialysis patients with secondary hyperparathyroidism with promising results.

A randomized, double-blind, placebo-controlled, multicenter study was conducted in hemodialysis patients with secondary hyperparathyroidism and six sequential single doses were administered (5, 10, 25, 50, 75, and 100 mg of AMG 073 or placebo) [31]. Doses of 25, 50, 75, and 100 mg caused a dose-dependent decrease in plasma intact PTH with a maximum suppression observed between two and four hours after administration, followed by a slow recovery of the intact PTH during the subsequent hours but remaining below the baseline values after 24 hours. Single doses of 75 and 100 mg of AMG 073 reduced serum calcium by 8.3% and 9.4%, respectively. Following these results daily, fixed doses of 10, 25, and 50 mg of AMG 073 were administered for eight consecutive days in hemodialysis patients with plasma intact iPTH ≥250 pg/mL and ≤1500 pg/mL [31]. Doses of 25 and 50 mg were associated with decreases in iPTH concentrations. The 50 mg dose was associated with a decrease in mean serum calcium levels. On day eight, serum phosphorus levels and the calcium x phosphorus product were reduced from baseline levels in all treatment groups receiving AMG 073.

The efficacy and safety of AMG 073 was shown in a double-blind, placebo-controlled, 18-week study with dose titration during the first 12 weeks using daily doses of 10, 20, 30, 40, and 50 mg AMG 073 or placebo (abstract; Lindberg et al, *J Am Soc Nephrol* 11:578A, 2000). Because of the good safety profile observed in the previous study, doses of AMG 073 were titrated up to 100 mg per day in another study (abstract; Quarles et al, *J Am Soc Nephrol* 12:773A, 2001). Seventy-one hemodialysis patients were evaluated. The baseline intact PTH value was 625 ± 310 pg/mL (mean ± SE) for the 36 patients treated with AMG 073 and 582 ± 421 pg/mL for the placebo-treated patients. The intact PTH levels decreased by 32.5% from the baseline during the maintenance phase in the AMG 073 group and increased by 3.0% in the placebo-treated patients. In the AMG 073 group the calcium x phosphorus product at the end of the maintenance period was decreased by 7.9% from the baseline value, compared to an increase of 11.0% in the placebo-treated group. The serum phosphorus was also reduced by 2.6% in the AMG 073 treated patients and the mean serum calcium level was reduced by 4.6% from baseline, although the absolute serum calcium level remained within the normal range.

The potential of the second-generation calcimimetic for treatment of secondary hyperparathyroidism in hemodialysis patients has been shown in the combined results of three, 12-week, randomized, double-blind, placebo-controlled, dose titration trials (abstract; Drueke et al, *J Am Soc Nephrol* 12:764A, 2001). Two hundred and fifteen hemodialysis patients (141 AMG 073 treated and 74 placebo treated) with serum intact PTH levels ≥300 pg/mL, calcium levels between 8.8 mg/dL and 11.0 mg/dL, and a calcium x phosphorus product less than 70, were evaluated. AMG-073 was titrated up to 50 mg/day in two studies, and 100 mg/day in one study, based upon PTH levels and safety profile. Mean serum PTH levels was reduced by 20% to 33% in the AMG 073 group and increased by 16% in the placebo group. Eighty-three percent of AMG 073 patients had a reduction in serum PTH levels of more than 30% at the end of 12 weeks. Mean serum calcium x phosphorus product decreased by 8% in the AMG 073 group and increased by 14% in the placebo group. No major side effects were reported.

Another randomized, placebo-controlled, double-blind, 12-week trial evaluated AMG 073 at doses up to 180 mg in 82 hemodialysis patients (abstract; Block et al, *J Am Soc Nephrol* 13:572A, 2002). These patients had PTH levels ≥300 pg/mL, despite standard therapy with phosphate binders and vitamin D. The mean PTH levels decreased by 47% from baseline in the active drug group, and the target PTH level was achieved in 54% of the patients not controlled on current therapy. Percent of reductions in calcium and phosphorus product in patients receiving AMG 073 were of similar magnitude to that observed in previous studies. The incidence of adverse events was similar in the two treatment groups.

## CONCLUSION

After the cloning of the CaR and the development of positive allosteric modulators of CaR, the medical treatment of several hyperfunctioning and/or hypofunctioning parathyroid glands states seems to be devoted

**Table 3.** Potential medical uses of calcium receptor modulators

| |
|---|
| Parathyroids |
| Inherited parathyroid disorders |
| Primary hyperparathyroidism |
| Secondary hyperparathyroidism |
| Parathyroid carcinomatosis |
| Surgical parathyroidectomy failure |
| Ectopic parathyroid gland localization |
| Parathyromatosis |
| Parathyroid surgery refusal |
| Surgical contraindications |
| Cardiovascular |
| Arterial hypertension |
| Calciphylaxis |
| Renal |
| Diuretic |
| Slow progressive chronic renal failure |

to a radical change (Table 3). The results obtained with the first-generation calcimimetics showed that it is possible to safely prevent and slow down primary and secondary hyperparathyroidism. However, the weak bioavailability and the intra-individual variability of the catabolism of these compounds prevent their clinical development. The results obtained with AMG 073 are very encouraging. No major side effects have been observed thus far, except for transient episodes of hypocalcemia during the dose titration phases. These hypocalcemic episodes predict the necessity for close monitoring of serum calcium levels during the first weeks of treatment with AMG 073. The association with calcium-containing binders and vitamin D compounds can have a role in the prevention of hypocalcemia. The effect of the calcimimetics on serum phosphate levels and serum calcium and phosphorus product suggests that vitamin D compounds and calcium-containing phosphate binder use will be facilitated. Many patients treated with second-generation calcimimetic agents were already being treated with phosphate binders and vitamin D sterols; this represents a group of patients that had poorly controlled secondary hyperparathyroidism, despite such therapy. Furthermore, despite the lower serum calcium levels observed with calcimimetic treatment, there was a consistent suppression of PTH levels favoring the impressive potency of these compounds. However, it will be necessary to pay attention to other bone and mineral metabolism disorders that could be induced by these compounds, as well. The possibility of inducing an adynamic bone disease or another low bone remodeling lesion because of an excessive PTH inhibition appears to be small; however, only long-term, ongoing studies of bone histology will definitely answer this question. Of interest is the transient and intermittent decline in PTH secretion observed with calcimimetics that may have an anabolic bone effect, leading to a stabilization or gain in bone mineral density.

Calcimimetic agents are powerful compounds that may be very useful for the treatment of primary and secondary hyperparathyroidism, parathyroid carcinoma, and probably a few other rare disorders, such as parathyromatosis and calciphylaxis.

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