

SHORT-TERM INHIBITION OF PARATHYROID HORMONE SECRETION BY A CALCIUM-RECEPTOR AGONIST IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

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ABSTRACT

Background Surgery is the usual therapy for patients with primary hyperparathyroidism. We investigated the ability of a calcimimetic drug that inhibits parathyroid hormone secretion in vitro to decrease serum parathyroid hormone and calcium concentrations in patients with this disorder.

Methods We performed a randomized, placebo-controlled study of single oral doses of 4 to 160 mg of the calcium-receptor agonist drug R-568 in 20 postmenopausal women with mild primary hyperparathyroidism. At base line, the mean (\pm SE) serum calcium concentration was 10.7 ± 0.2 mg per deciliter (2.67 ± 0.05 mmol per liter). Serum parathyroid hormone and calcium were measured repeatedly after each dose, and safety was assessed.

Results Administration of R-568 resulted in a dose-dependent inhibition of parathyroid hormone secretion. The mean serum parathyroid hormone concentration, which was 77 ± 11 pg per milliliter (18.8 ± 2.7 pmol per liter; normal range, 16 to 65 pg per milliliter [3.9 to 15.9 pmol per liter]) at base line, fell by 26 ± 8 percent after 20 mg of R-568 ($P=0.03$), by 42 ± 7 percent after 80 mg ($P=0.01$), and by 51 ± 5 percent after 160 mg ($P=0.005$). Serum ionized calcium concentrations fell only after the 160-mg dose, with the decrease closely following the decrease in the serum parathyroid hormone concentration.

Conclusions The calcimimetic drug R-568 reduces serum parathyroid hormone and ionized calcium concentrations in postmenopausal women with primary hyperparathyroidism. (N Engl J Med 1997;337:1506-10.)

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MOST patients with primary hyperparathyroidism in the United States are asymptomatic.¹⁻³ Although the usual treatment for this disorder is surgical removal of the abnormal parathyroid gland or glands, the need for surgery has been questioned because of the absence of symptoms and absence of progression of the disorder.⁴⁻⁷ At this time, however, there are no alternatives to surgery that can reduce both serum parathyroid hormone and serum calcium concentrations in these patients. An effective medical therapy would provide an option not only for asymptomatic patients but also for those in whom parathyroid surgery is contraindicated because of intercurrent med-

ical conditions, those with previously unsuccessful surgery, and those who decline surgery.⁸

The search for a medical therapy for primary hyperparathyroidism has been stimulated in part by the discovery of a calcium-sensing receptor on parathyroid cells that regulates the synthesis and secretion of parathyroid hormone.⁹⁻¹¹ When activated by increased extracellular calcium, the calcium-sensing receptor signals the cell by means of a G-protein transducing pathway to raise the intracellular calcium concentration, which inhibits the secretion of parathyroid hormone. Molecules that mimic the effect of extracellular calcium could also activate this receptor and inhibit parathyroid-cell function.^{12,13} The phenylalkylamine (*R*)-*N*-(3-methoxy- α -phenylethyl)-3-(2-chlorophenyl)-1-propylamine, or R-568, is one such calcimimetic compound. In vitro and in animals it increases cytoplasmic calcium and decreases parathyroid hormone secretion.¹³⁻¹⁵ In this study we investigated the ability of single oral doses of this compound (supplied by NPS Pharmaceuticals, Salt Lake City) to inhibit parathyroid hormone secretion and lower serum calcium concentrations in postmenopausal women with primary hyperparathyroidism.

METHODS

Patients and Study Design

We studied 20 postmenopausal women with primary hyperparathyroidism (mean age, 62 years; range, 47 to 73). Their mean (\pm SE) serum calcium concentration was 10.7 ± 0.2 mg per deciliter (2.67 ± 0.05 mmol per liter; normal range, 8.4 to 10.2 mg per deciliter [2.10 to 2.53 mmol per liter]), and their mean parathyroid hormone concentration was 77 ± 11 pg per milliliter (18.8 ± 2.7 pmol per liter; normal range, 16 to 65 pg per milliliter [3.9 to 15.9 pmol per liter]). These women were selected from a cohort with primary hyperparathyroidism who are being followed with no intervention because they did not meet the guidelines of the National Institutes of Health for parathyroidectomy,⁴ had refused surgery, or had undergone unsuccessful surgery. All the women gave written, informed consent for the study, which had been approved by the institutional review boards of Columbia-Presbyterian Medical Center and Henry Ford Hospital.

The study was a randomized, within-group, double-blind, pla-

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cebo-controlled trial performed in Detroit and New York. In Detroit, eight women received placebo and then two different doses of R-568 (4 mg, 10 mg, or 20 mg in ascending order). In New York, 12 women received placebo and two different doses of R-568 (20 mg, 80 mg, or 160 mg, also in ascending order). Thus, each woman was studied three times, receiving drug twice and placebo once, with a minimum of two weeks between studies. Thirty-nine of 40 doses of drug and 18 of 20 doses of placebo were administered. One woman did not receive the first (4-mg) dose of drug, and two women did not receive placebo. The clinical and biochemical characteristics of the women studied at each site were similar. The results presented for placebo and the 20-mg dose represent the combined data for women studied at both sites.

The women were admitted to the clinical research center the evening before drug administration. Base-line measurements were obtained 60 minutes before and at the time of drug administration the next morning. Serum parathyroid hormone and ionized calcium were measured at these times and 30 minutes and 1, 2, 4, 8, 12, 24, and 36 hours after drug administration. Urine was collected for calcium measurement for two hours before drug administration and at two- or four-hour intervals for eight hours after administration. The urinary calcium data were normalized for creatinine excretion. The patients did not eat until six hours after drug administration, but they were allowed to drink as much water as they wished. Monitoring for safety included measurements of vital signs, tests for Trousseau's and Chvostek's signs, routine laboratory tests, and electrocardiography.

Biochemical Analyses

Serum ionized calcium was measured by Nova CRT8 Analyzer (Nova Biomedical, Waltham, Mass.; manufacturer's reference range, 4.6 to 5.4 mg per deciliter [1.15 to 1.35 mmol per liter]), with identical machines standardized and calibrated at the two sites. Serum total calcium, phosphorus, urea nitrogen, and creatinine were measured by automated techniques, and urinary calcium was measured by atomic-absorption spectrophotometry. Serum parathyroid hormone was measured by a single laboratory using a modification of the N-tactR PTH immunoradiometric technique (Incstar, Stillwater, Minn.; normal range, 16 to 65 pg per milliliter [3.9 to 15.9 pmol per liter]; limit of detection, 4.2 pg per milliliter [1.0 pmol per liter]). All samples from each woman were analyzed at the same time in each assay, with the exception of serum ionized calcium, which had to be assayed immediately.

Statistical Analysis

Comparisons between groups of women were made with the use of Student's unpaired *t*-tests, and estimates of change over time with repeated-measures analysis of variance. At each drug dose, the response was compared with that after the administration of placebo in the same woman. All statistical tests were two-sided. Base-line values for serum parathyroid hormone and ionized calcium were calculated as the mean of the determinations made one hour before and at the time of drug administration.

RESULTS

Serum parathyroid hormone concentrations decreased significantly after the 20-, 80-, and 160-mg doses of R-568, but not after the 4- and 10-mg doses (Fig. 1). Two hours after the administration of R-568, the mean serum parathyroid hormone concentration had fallen 26 percent, from 77 ± 11 to 57 ± 10 pg per milliliter (18.8 ± 2.7 to 13.9 ± 2.4 pmol per liter), after the 20-mg dose ($P = 0.03$); 42 percent, from 79 ± 22 to 46 ± 7 pg per milliliter (19.3 ± 5.4 to 11.2 ± 4.1 pmol per liter), after the 80-mg dose ($P = 0.01$); and 51 percent, from 65 ± 12 to 32 ± 10 pg per milliliter (15.9 ± 2.9 to 7.8 ± 2.4

pmol per liter), after the 160-mg dose ($P = 0.005$). The nadir values were measured one hour after the 20-mg dose and two hours after the 80- and 160-mg doses, and the values returned to base line by eight hours after administration of the drug. The mean serum parathyroid hormone concentration had decreased slightly one hour after the 10-mg dose (from 84 ± 15 to 69 ± 10 pg per milliliter [20.9 ± 3.7 to 16.8 ± 2.4 pmol per liter], $P = 0.96$). There was no significant change in serum parathyroid hormone after the 4-mg dose or placebo. The mean maximal decreases in serum parathyroid hormone were 28 ± 5 percent after 20 mg of R-568; 42 ± 7 percent after 80 mg; and 56 ± 6 percent after 160 mg.

Serum ionized calcium concentrations decreased slightly after 80 mg of R-568, and the decrease was statistically significant after 160 mg of the drug (Fig. 1). The maximal reduction occurred four hours after administration, with a 4 percent decrease in the mean serum ionized calcium concentration, from 5.4 ± 0.12 to 5.2 ± 0.08 mg per deciliter (1.35 ± 0.03 to 1.30 ± 0.02 mmol per liter, $P = 0.03$). Serum phosphorus and creatinine concentrations did not change after drug administration.

The mean urinary calcium excretion increased by a factor of 2.3 between two and four hours after the administration of 160 mg of R-568, increasing from 269 ± 49 mg per gram of creatinine at base line to 626 ± 68 mg per gram (from 0.8 ± 0.1 to 1.8 ± 0.2 mmol per millimole of creatinine, $P = 0.005$) (Fig. 2). This increase was transient; urinary calcium excretion four to eight hours after drug administration was only slightly higher than at base line. The increase occurred after the decrease in the serum parathyroid hormone concentration; the nadir value in serum parathyroid hormone was measured two hours after drug administration, and urinary calcium excretion was highest during the subsequent two-hour period. The maximal changes in urinary and serum calcium occurred simultaneously. Urinary calcium excretion, like serum ionized calcium concentrations, did not change after lower doses of R-568. All doses of the drug were well tolerated by the women.

DISCUSSION

The results of this study demonstrate that R-568, a calcimimetic drug, inhibits the secretion of parathyroid hormone in postmenopausal women with mild primary hyperparathyroidism. These preliminary data suggest the possibility that a drug of this type may become a useful alternative to parathyroidectomy in patients with primary hyperparathyroidism.

Surgery is the mainstay of therapy for primary hyperparathyroidism,^{16,17} and nonsurgical options are limited.¹⁸ Oral phosphate can lead to potentially dangerous metastatic calcification.¹⁹⁻²² Estrogen therapy has been used with some success in postmenopausal women with mild primary hyperparathyroidism. It

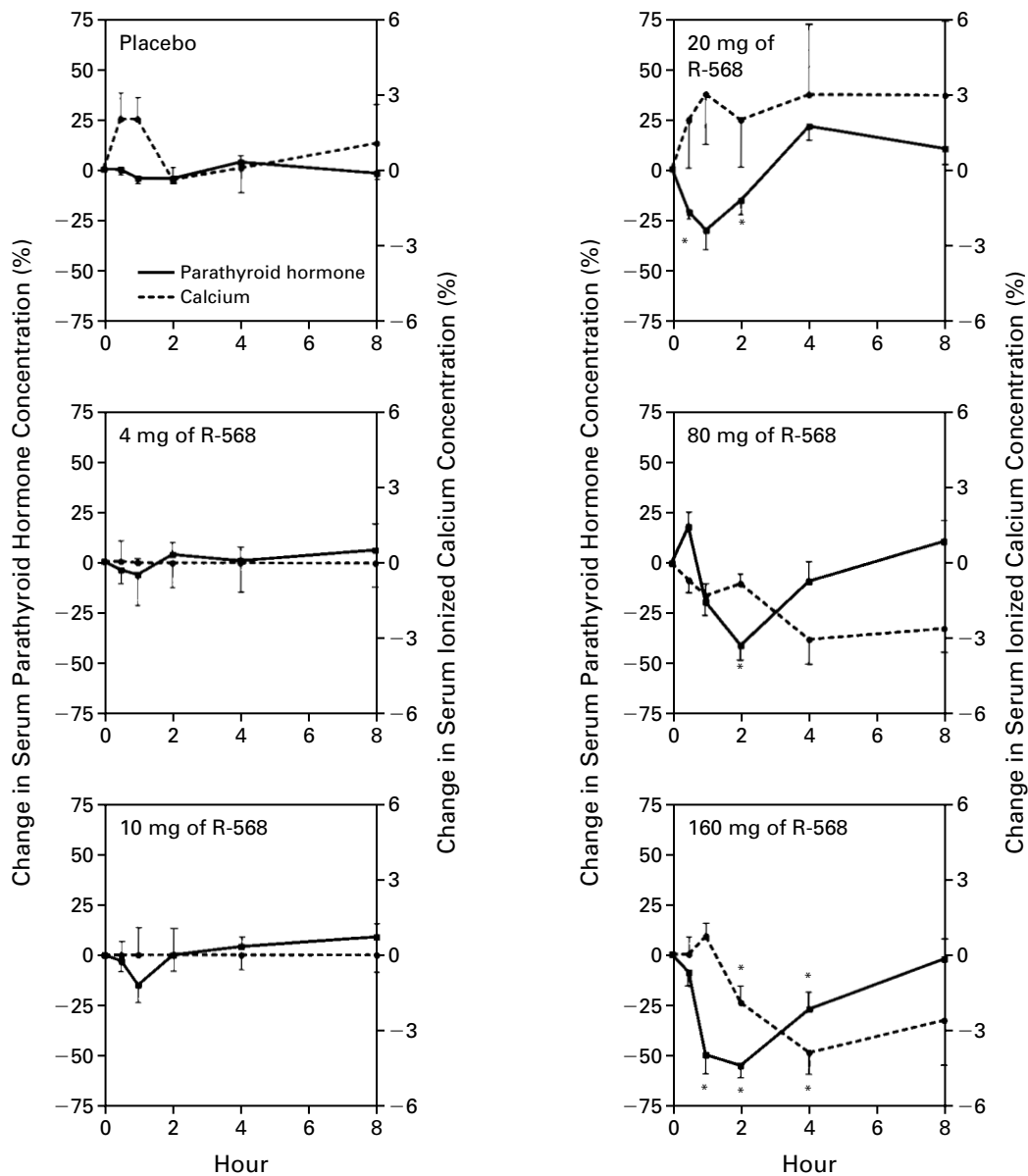


Figure 1. Mean (\pm SE) Changes in Serum Parathyroid Hormone and Serum Ionized Calcium Concentrations after the Administration of the Calcimimetic Drug R-568 in Postmenopausal Women with Primary Hyperparathyroidism.

Eighteen women received placebo, 4 received the 4-mg dose of R-568, 6 received the 10-mg dose, 13 received the 20-mg dose, 8 received the 80-mg dose, and 8 received the 160-mg dose. The asterisks indicate $P < 0.05$ for the comparison with placebo.

leads to a small reduction in serum calcium concentrations, with no change in serum parathyroid hormone or phosphorus concentrations.²³⁻²⁵ Bisphosphonates, by virtue of their ability to inhibit bone resorption, might be expected to have a calcium-lowering effect in patients with primary hyperparathyroidism. However, etidronate is not effective, and other bisphosphonates (e.g., clodronate and pamidronate) have only a transient effect.²⁶⁻²⁹ There are

very few data on other, newer bisphosphonates in this disease.

None of these drugs decrease the fundamental abnormality in primary hyperparathyroidism — namely, hypersecretion of parathyroid hormone. Recent efforts to reduce parathyroid hormone secretion are based on the molecular mechanism by which the parathyroid cell senses perturbations in extracellular calcium. The G-protein-coupled calcium-sensing

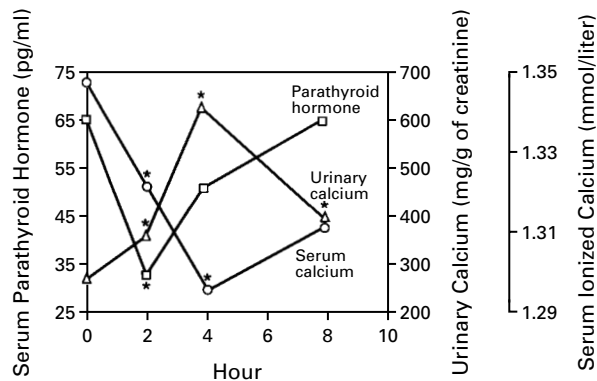


Figure 2. Time Course of the Change in Mean Urinary Calcium Excretion after the Administration of 160 mg of R-568 in Eight Postmenopausal Women with Primary Hyperparathyroidism.

The mean serum parathyroid hormone and ionized calcium concentrations are also shown. The asterisks indicate $P < 0.05$ for the comparison with placebo. To convert values for serum parathyroid hormone to picomoles per liter, multiply by 0.244. To convert values for urinary calcium to millimoles per millimole of creatinine, multiply by 0.0003.

receptor and its ligand, ionic calcium, are central to this mechanism. In the early 1990s, in parallel with the cloning of the calcium-sensing receptor,^{10,11} compounds were identified that could activate this receptor. One such compound, the phenylalkylamine used in this study, was found to increase cytoplasmic calcium and decrease parathyroid hormone secretion in vitro.¹⁵ It was also found to inhibit parathyroid hormone secretion and decrease serum calcium concentrations in rats and in normal postmenopausal women.^{14,30} In vitro this drug inhibited parathyroid hormone secretion from adenomatous and hyperplastic parathyroid cells.¹³

Building on these preclinical and early clinical data, we administered the calcium-receptor agonist R-568 to patients with primary hyperparathyroidism. It had the desired effect of decreasing both serum parathyroid hormone and calcium concentrations. The kinetics of the hypocalcemic response suggest that the decrease in serum calcium concentrations was due to the decrease in serum parathyroid hormone concentrations. The increase in urinary calcium excretion began after the suppression of parathyroid hormone secretion and at the same time as the decline in serum calcium, suggesting that the hypercalciuric response was caused by the inhibition of parathyroid hormone secretion. Loss of the hypocalciuric action of parathyroid hormone would be expected to accompany the acute inhibition of hormone secretion. However, a direct effect of this drug on the kidney, leading to altered tubular reabsorption of calcium, cannot be ruled out. Finally, in single doses, R-568 was well tolerated.

Our results provide proof of principle, demonstrat-

ing that a calcimimetic drug can inhibit parathyroid hormone secretion in patients with primary hyperparathyroidism. The results suggest that a medical approach to primary hyperparathyroidism is a feasible therapeutic goal.

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