

Rapid Communication

The calcimimetic cinacalcet normalizes serum calcium in renal transplant patients with persistent hyperparathyroidism

Anja E. Kruse, Ute Eisenberger, Felix J. Frey and Markus G. Mohaupt

Department of Nephrology and Hypertension, University of Berne, 3010 Berne, Switzerland

Abstract

Background. Treatment of persistent hyperparathyroidism in renal transplant patients resistant to calcium and vitamin D sterols is limited and often requires parathyroidectomy. Given the potential hazards linked to surgery, an alternative approach to manage excess parathyroid hormone (PTH) secretion is needed. Calcimimetics inhibit PTH secretion by modulating the calcium-sensing receptor in the parathyroid. Lowering of the serum calcium concentration with the calcimimetic cinacalcet has previously been demonstrated in patients with primary hyperparathyroidism or with secondary hyperparathyroidism on dialysis. Here we present the first clinical observations of a calcimimetic in patients with persistent hyperparathyroidism.

Methods. A 30 mg dose of cinacalcet was prescribed once daily for 3 months to seven female and seven male stable renal transplant patients, aged 23–65 years, 7 months to 14 years after transplantation, with a serum creatinine ranging from 89 to 229 $\mu\text{mol/l}$ and persistent hyperparathyroidism. Concomitant medication included cyclosporin and low-dose prednisone in all patients.

Results. On cinacalcet, serum calcium decreased and normalized in all but two patients (baseline 2.72 ± 0.03 mmol/l; 1 month 2.42 ± 0.04 mmol/l, $P < 0.001$), whereas serum PTH and phosphate levels did not change significantly. A slight reduction in renal function, as assessed by serum creatinine concentration, was observed at months 2 and 3 ($P < 0.05$). An immunoglobulin-deficient patient developed colitis after 1 week of treatment and cinacalcet was withdrawn. No patient stopped cinacalcet because of other presumed side effects.

Conclusion. Calcimimetics are a promising therapy in renal transplant patients with persistent hyperparathyroidism. Prospective controlled studies must now

be designed focusing on functionally relevant musculoskeletal end-points and allowing the exclusion of negative effects on long-term renal and general outcome of such patients.

Keywords: calcimimetic; cinacalcet; hypercalcaemia; parathormone; persistent hyperparathyroidism; renal transplant

Introduction

Secondary hyperparathyroidism is a common complication of renal failure and end-stage renal disease. Despite normalization of renal function and normal concentrations of 1,25-dihydroxyvitamin D₃ after renal transplantation, elevated parathyroid hormone (PTH) concentrations often persist, leading to markedly increased serum calcium levels, an enhanced fractional excretion of phosphate in the urine and decreased bone mass [1,2]. This condition is due to glandular hyperplasia and autonomous PTH production, in part attributable to monoclonality [3]. In about one-third of the patients, hyperparathyroidism does not completely resolve even after several years of successful renal transplantation [4–6]. In these patients, surgical treatment is often mandatory. In some of these patients, a surgical intervention might be hazardous and therefore a medical treatment would be of interest.

A novel class of compounds called calcimimetics increases the sensitivity of the calcium-sensing receptor of the parathyroid cells to extracellular calcium [7–9]. Recently the oral calcimimetic, cinacalcet HCl, was introduced successfully into clinical practice. Cinacalcet rapidly normalized serum calcium and reduced PTH in patients with primary hyperparathyroidism, an effect persistent through a follow-up 1 year [10,11]. In chronic haemodialysis patients with secondary hyperparathyroidism, this compound reduced plasma PTH concentrations together with a

Correspondence and offprint requests to: Markus G. Mohaupt, MD, Department of Nephrology and Hypertension, University Hospital Berne, Inselspital, Freiburgstrasse, CH-3010 Bern, Switzerland. Email: markus.mohaupt@insel.ch

subsequent decline in plasma calcium and phosphate [12–15]. So far, calcimimetics have not been prescribed to patients after successful renal transplantation. Therefore, we investigated the effect of cinacalcet in stable renal transplant patients with persistent hyperparathyroidism.

Subjects and Methods

Fourteen stable renal transplant patients (seven male, seven female, aged 23–65 years) with persistent hyperparathyroidism, followed for 7 months to 14 years (median 3.5 years) after renal transplantation, were treated with cinacalcet. All patients were followed in our unit. Persistent hyperparathyroidism was defined by increased serum calcium concentrations in the presence of increased PTH levels on dialysis, not normalized 6 months after successful renal transplantation despite normal or increased 1,25-dihydroxyvitamin D₃ levels.

All patients were treated with cyclosporin and doses of prednisone <10 mg/day. In addition, three patients were on azathioprine, five on mycophenolate mofetil and one on sirolimus. Before cinacalcet treatment, PTH levels ranged from 80 to 1295 pg/ml (Figure 1). One patient with a high normal value of 47 pg/ml was also treated because of persistent hypercalcaemia between 2.6 and 2.7 mmol/l in the presence of 1,25-dihydroxyvitamin D₃ levels ranging from 74 to 126 pmol/l.

Patients were given 30 mg of oral cinacalcet once daily. Out-patient visits were scheduled before and 1, 2 and 3 months after therapy was initiated. The following parameters were assessed: creatinine, urea, potassium, calcium, phosphate and PTH (intact) in serum, and cyclosporin trough levels in whole blood; blood pressure; clinical events; and concomitant medication. Repeated measurements of PTH before and 1, 2, 3 and 4 h after intake of cinacalcet were performed in two patients.

Statistical analyses were executed using SYSTAT Version 12.0 (SYSTAT Software, Inc.). Paired Student's *t*-test and the Wilcoxon test for longitudinal non-parametric data were used where applicable. All data given are means \pm SEM if not otherwise indicated.

Results

Effect of cinacalcet on serum PTH, calcium and phosphate

Serum PTH did not change in response to cinacalcet administration. Although the data shown in Figure 1 suggest a decline for the entire population, due to the large inter- and intra-individual variability in response to the calcimimetic, this decline was not statistically significant. In order to better understand this variability, we measured the serum concentrations of PTH before and 1, 2, 3 and 4 h following the intake of cinacalcet in two patients on long-term therapy and observed an acute decline (Figure 2). The trough levels of PTH (concentrations in the morning before the intake of cinacalcet) ranged between 55 and 130 pg/ml in these two patients.

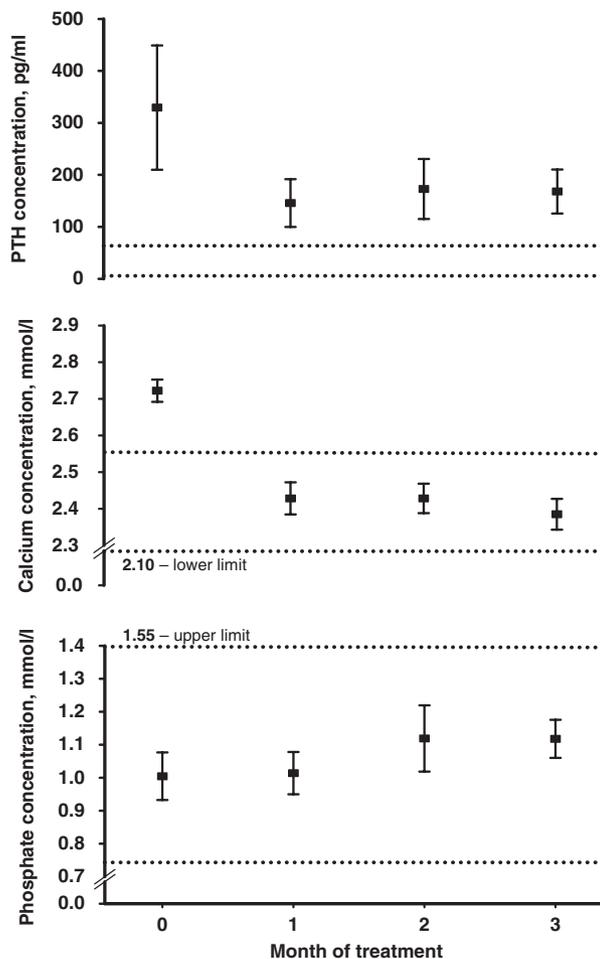


Fig. 1. Serum concentrations of PTH, calcium and phosphate before (month 0) and during treatment (months 1–3) with cinacalcet (mean, SEM). Upper and lower limits of normal ranges are depicted by dotted lines.

Serum total calcium concentrations declined in all subjects after cinacalcet was given and remained stable over the entire period of observation ($P < 0.001$) (Figure 1). In all patients except two, a normalization of serum calcium below 2.55 mmol/l was observed. In one of these two patients, the serum calcium declined from 2.71 to 2.63 mmol/l and in the other from 2.71 to 2.60 mmol/l. Mean serum phosphate concentrations remained unchanged throughout the study period. Before cinacalcet, one patient had hypophosphataemia (0.54 mmol/l), which disappeared with treatment. Two patients experienced a slight hyperphosphataemia between 1.65 and 1.77 mmol/l while on the calcimimetic. The Ca \times P product was not affected by cinacalcet and the highest value observed was 4.27 mmol/l². No consistent changes were detected with respect to the fractional calcium and phosphate excretion and serum alkaline phosphatase levels (results not shown).

Clinical observations

During the treatment period, the immunosuppressive regimen remained unchanged. The whole blood trough

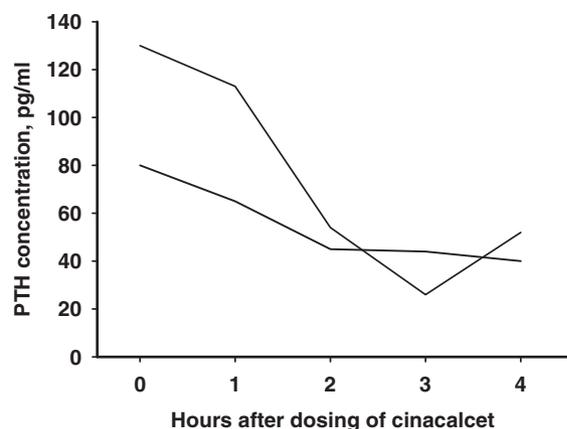


Fig. 2. Serum PTH concentrations before (hour 0) and after dosing of cinacalcet (hours 1–4) in two renal transplant patients on chronic cinacalcet therapy.

concentrations of cyclosporin were not affected by cinacalcet. At baseline, cyclosporin levels ranged from 64 to 177 ng/ml, after 1 month of treatment from 73 to 172 ng/ml, at 2 months from 51 to 131 ng/ml and after 3 months from 80 to 181 ng/ml. With respect to diuretic and antihypertensive therapy, only minor changes occurred. In one patient, 20 mg of furosemide and in another 5 mg of torasemide were withdrawn 2 months after therapy with cinacalcet was initiated. None of the patients was on a calcium supplement. Two patients received 0.5 and 1.75 $\mu\text{g}/\text{week}$ of 1,25-dihydroxyvitamin D_3 for 2 months. Five patients were additionally prescribed 1,25-dihydroxyvitamin D_3 (0.75–1.75 $\mu\text{g}/\text{week}$) at month 2.

Blood pressure remained unchanged during therapy with cinacalcet (results not shown). The glomerular filtration rate, as assessed by serum creatinine concentrations, decreased during the observation period. Serum creatinine concentrations were $140 \pm 15 \mu\text{mol}/\text{l}$ at baseline, $139 \pm 16 \mu\text{mol}/\text{l}$ after 1 month, $153 \pm 17 \mu\text{mol}/\text{l}$ after 2 months and $148 \pm 16 \mu\text{mol}/\text{l}$ after 3 months of treatment ($P < 0.05$ at months 2 and 3).

One patient with a known immunoglobulin deficiency and recurrent intestinal disease developed severe diarrhoea and colitis 1 week after cinacalcet had been prescribed. Cinacalcet was withdrawn and the results from the electrolyte and PTH measurements are not considered for the present analysis. Another patient experienced a myocardial infarction without arrhythmia or complications after 2 months of treatment. The patient received a percutaneous transluminal angioplasty with stent implantation. She continued to take cinacalcet thereafter and the results were included in the present analysis. No patient stopped cinacalcet because of other presumed side effects.

Discussion

Here we present the first clinical observations in stable renal transplant patients with persistent hyperparathyroidism treated with a calcimimetic. These results

demonstrate that a low dose of cinacalcet given once daily significantly reduces the serum calcium concentration. The decline in the PTH concentrations was not significant (Figure 1). This might be attributed first to the small number of subjects investigated, and/or second to the peculiar pharmacokinetics/pharmacodynamics of cinacalcet. Peacock and co-workers recently analysed the pharmacodynamics of cinacalcet in patients with primary hyperparathyroidism at week 24 of chronic prescription of cinacalcet [10]. At 2 h after the morning dose of cinacalcet, they observed a decline of PTH from ~ 80 to 50 pg/ml. At 8 h, the PTH concentrations again reached the pre-dose values. Peacock and co-workers estimated that the area under the plasma concentration–time curve of PTH over each 24 h cycle was reduced by $\sim 20\%$ [10]. A similar rapid and transient response of PTH to the administration of cinacalcet was reported for dialysis patients with secondary hyperparathyroidism [16,17], suggesting an immediate but transient effect of the xenobiotic on PTH release. Thus, if the purpose of cinacalcet prescription was to normalize not only the serum calcium concentration, but also the area under the concentration–time curve of PTH, the drug has to be dosed at least twice a day in renal transplant patients. Given the known beneficial effects of PTH for normal bone formation, it is unknown whether normalization of PTH is a valid potential objective.

In addition to its effect on bone, PTH enhances the urinary excretion of phosphate by regulating the type IIa (Na^{2+})/ P_i co-transporter in the proximal tubule [18]. In line with this effect, we observed a normalization of the phosphate level in the only hypophosphataemic patient and a slight hyperphosphataemia in two patients previously normophosphataemic. With cinacalcet treatment, the serum phosphate concentrations increased by $\sim 10\%$ in patients with primary hyperparathyroidism [10,11], whereas in dialysis patients these concentrations declined by $\sim 8\%$ [13]. The mechanism for the decrease of serum phosphate concentrations in dialysis patients is unknown. Thus, the effect of cinacalcet on serum phosphate levels appears to be complex in patients with kidney diseases and has to be taken into consideration when this drug is prescribed. While hypophosphataemia is a practically relevant issue after renal transplantation and a reduced urinary excretion of phosphate by the calcimimetic might be beneficial, hyperphosphataemia is more relevant in subjects with a reduced glomerular filtration rate. Therefore, special attention has to be paid in the future to the changes of the serum phosphate levels induced by calcimimetics in renal transplant patients with a steadily changing renal function.

In order to protect the bone from the unwarranted effects of high PTH, parathyroidectomy is often considered as a therapeutic option in patients with persistent hyperthyroidism after renal transplantation. Retrospective analyses revealed that such surgical interventions might be associated with a decline in the glomerular filtration rate as assessed by serum

creatinine concentrations. For instance, Rostaing and co-workers observed a significant and persistent increase in serum creatinine levels in eight out of 34 patients after parathyroidectomy, an effect particularly present in those patients presenting with hypertension before surgery [19]. Lee and co-workers followed 22 patients for 1 year after parathyroidectomy and reported a steeper rise in serum creatinine after surgery when compared with the 2 years before the intervention. The effect of parathyroidectomy on the serum calcium concentration was significantly more accentuated in patients exhibiting a worsening of graft function after parathyroidectomy [20]. To the best of our knowledge, it is unknown whether the decline in renal function after surgery was attributable to the intervention itself and/or to the changes of the mineral metabolism induced by the removal of the parathyroid glands. To answer this question, future prospective studies comparing the impact on the serum creatinine concentrations of a calcimimetic with that of parathyroidectomy might be useful. In our group of patients, a slight increase in serum creatinine concentrations could be identified. However, the study duration of 3 months does not allow characterization of the long-term effects of cinacalcet treatment on renal transplant function.

In conclusion, the calcimimetic cinacalcet is a promising alternative to parathyroidectomy in patients with persistent hyperparathyroidism after renal transplantation. To exclude a negative impact of cinacalcet on long-term renal or general outcome of kidney transplant recipients, future studies should focus on the glomerular filtration rate of the allograft and consider functionally relevant musculo-skeletal and therapeutic endpoints.

Conflict of interest statement. None declared.

References

- Lewin E. Involution of the parathyroid glands after renal transplantation. *Curr Opin Nephrol Hypertens* 2003; 12: 363–371
- Torres A, Lorenzo V, Salido E. Calcium metabolism and skeletal problems after transplantation. *J Am Soc Nephrol* 2002; 13: 551–558
- Arnold A, Brown MF, Urena P, Gaz RD, Sarfati E, Drueke TB. Monoclonality of parathyroid tumors in chronic renal failure and in primary parathyroid hyperplasia. *J Clin Invest* 1995; 95: 2047–2053
- Cundy T, Kanis JA, Heynen G, Morris PJ, Oliver DO. Calcium metabolism and hyperparathyroidism after renal transplantation. *Q J Med* 1983; 52: 67–78
- Koch Nogueira PC, David L, Cochat P. Evolution of secondary hyperparathyroidism after renal transplantation. *Pediatr Nephrol* 2000; 14: 342–346
- Torres A, Rodriguez AP, Concepcion MT *et al.* Parathyroid function in long-term renal transplant patients: importance of pre-transplant PTH concentrations. *Nephrol Dial Transplant* 1998; 13 [Suppl 3]: 94–97
- Drueke TB. Modulation and action of the calcium-sensing receptor. *Nephrol Dial Transplant* 2004; 19 [Suppl 5]: V20–V26
- Hammerland LG, Garrett JE, Hung BC, Levinthal C, Nemeth EF. Allosteric activation of the Ca^{2+} receptor expressed in *Xenopus laevis* oocytes by NPS 467 or NPS 568. *Mol Pharmacol* 1998; 53: 1083–1088
- Nemeth EF, Steffey ME, Hammerland LG *et al.* Calcimimetics with potent and selective activity on the parathyroid calcium receptor. *Proc Natl Acad Sci USA* 1998; 95: 4040–4045
- Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005; 90: 135–141
- Shoback DM, Bilezikian JP, Turner SA, McCary LC, Guo MD, Peacock M. The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; 88: 5644–5649
- Antonsen JE, Sherrard DJ, Andress DL. A calcimimetic agent acutely suppresses parathyroid hormone levels in patients with chronic renal failure. Rapid communication. *Kidney Int* 1998; 53: 223–227
- Block GA, Martin KJ, de Francisco AL *et al.* Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004; 350: 1516–1525
- Drueke TB. Treatment of secondary hyperparathyroidism of dialysis patients with calcimimetics as a valuable addition to established therapeutic means. *Pediatr Nephrol* 2005; 20: 399–403
- Lindberg JS, Culleton B, Wong G *et al.* Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. *J Am Soc Nephrol* 2005; 16: 800–807
- Goodman WG, Hladik GA, Turner SA *et al.* The calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. *J Am Soc Nephrol* 2002; 13: 1017–1024
- Quarles LD, Sherrard DJ, Adler S *et al.* The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. *J Am Soc Nephrol* 2003; 14: 575–583
- Murer H, Hernando N, Forster L, Biber J. Molecular mechanisms in proximal tubular and small intestinal phosphate reabsorption (plenary lecture). *Mol Membr Biol* 2001; 18: 3–11
- Rostaing L, Moreau-Gaudry X, Baron E, Cisterne JM, Monrozier-Bernadet P, Durand D. Changes in blood pressure and renal function following subtotal parathyroidectomy in renal transplant patients presenting with persistent hypercalcemic hyperparathyroidism. *Clin Nephrol* 1997; 47: 248–255
- Lee PP, Schiffmann L, Offermann G, Beige J. Effects of parathyroidectomy on renal allograft survival. *Kidney Blood Press Res* 2004; 27: 191–196

Received for publication: 17.3.05

Accepted in revised form: 3.5.05