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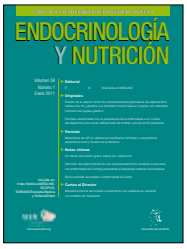

ORIGINAL ARTICLE

Low-dose cinacalcet reduces serum calcium in patients with primary hyperparathyroidism not eligible for surgery

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KEYWORDS
Cinacalcet;
Calcimimetics;
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Abstract Our experience with low-dose cinacalcet to normalize serum calcium in patients with primary hyperparathyroidism (PHPT) not eligible for surgery is reported. The impact of this drug on various parameters of calcium-phosphorus metabolism and its tolerability profile were analyzed.

Seventeen patients diagnosed with PHPT who had hypercalcemia and also met one or more of the inclusion criteria of high risk of parathyroidectomy, persistent/recurrent PHPT after previous parathyroid surgery, or refusal of surgery were recruited.

The starting cinacalcet dose was 30 or 60 mg/day, and dosage was adjusted based on the degree of calcemia reduction and drug tolerability.

A decrease in serum calcium levels was already evident in the first post-treatment test. Appropriate dose adjustment was performed when required, and normal serum calcium levels were achieved in a majority of patients and remained stable during follow-up.

Parathyroid hormone levels decreased but were not normalized in most patients. Urine calcium levels decreased, while serum phosphate and alkaline phosphatase levels increased. Cinacalcet tolerability was usually good at the doses used. The most common adverse effects included weakness, dizziness, and asthenia, but led to treatment withdrawal in only one patient.

It was concluded that low-dose cinacalcet effectively decreases serum calcium levels, normalizes calcium levels in a majority of patients with PHPT not eligible for surgical treatment, and has a good tolerability profile.

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PALABRAS CLAVE
Cinacalcet;
Calciomiméticos;
Hiperparatiroidismo primario

Dosis bajas de cinacalcet reducen el calcio sérico en pacientes con hiperparatiroidismo primario no subsidiario de tratamiento quirúrgico

Resumen Presentamos nuestra experiencia con cinacalcet a dosis bajas, en pacientes con hiperparatiroidismo primario (HPTP) no subsidiario de tratamiento quirúrgico con el objetivo principal de normalizar la calcemia. Analizamos el impacto del fármaco sobre diversos parámetros del metabolismo calcio-fósforo y su perfil de tolerancia.

Reclutamos un total de 17 pacientes diagnosticados de HPTP que presentaban hipercalcemia y que reunían además alguno de los siguientes criterios de inclusión: riesgo elevado para paratiroidectomía, HPTP persistente/recurrente tras cirugía paratiroidea previa o rechazo del paciente a la intervención quirúrgica.

La dosis inicial de cinacalcet fue de 30 o 60 mg/día, la cual se ajustó en función del grado de reducción de la calcemia y la tolerancia al fármaco.

Observamos una reducción del calcio sérico que ya resultaba evidente en el primer control postratamiento. Tras el ajuste pertinente de dosis cuando fue preciso, se consiguió normalizar la calcemia en una mayoría de los pacientes, la cual se mantuvo estable a lo largo del seguimiento.

La PTH se redujo, aunque no se normalizó en la mayor parte de los pacientes. La calciuria descendió mientras que la fosforemia y la fosfatasa alcalina sérica aumentaron.

La tolerancia a cinacalcet fue buena en general a las dosis utilizadas. Los efectos secundarios más frecuentes fueron debilidad, mareos y astenia, y solamente en un paciente motivaron la suspensión del tratamiento.

Concluimos que cinacalcet a dosis bajas reduce la calcemia de forma eficaz y consigue una normalización de la misma en una mayoría de pacientes con HPTP no subsidiarios de tratamiento quirúrgico con un buen perfil de tolerancia al fármaco.

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disease caused by a primary disorder in one of several parathyroid glands which is characterized by inadequate secretion of parathyroid hormone (PTH), with a resultant impairment in calcium homeostasis whose main characteristic is hypercalcemia.

The pathophysiological impact of PHPT is mainly seen in the skeleton and kidney, but other body systems, such as the cardiovascular system, are also affected by excess PTH and hypercalcemia[1].

The clinical spectrum of the disease has greatly varied in recent years, and asymptomatic forms currently predominate. Significant advances have also been made in the diagnostic approach to PHPT, especially as regards presurgical and intraoperative localization procedures, which have allowed for a more selective surgical approach.

Significant innovations have also been made in the drug treatment of PHPT. In asymptomatic patients who did not meet surgical criteria[2] and in those with persistent or recurrent disease after one or several unsuccessful attempts at surgery, the therapeutic approach used to be limited in most instances to attempts to minimize bone resorption with bisphosphonates, but without acting upon the essential pathophysiological changes, hypercalcemia and increased PTH levels.

The advent of calcimimetic drugs has contributed to a change in this situation. These drugs are allosteric modulators of the calcium-sensing receptor (CaSR) which activate the receptor by mimicking the action of extracellular calcium on the receptor. They thus inhibit PTH secretion, PTH gene transcription, and the proliferation of parathyroid cells.

Cinacalcet is a calcimimetic agent previously used for the treatment of secondary hyperparathyroidism and parathyroid carcinoma which was recently approved in Spain for patients with PHPT who have serum calcium levels meeting surgery criteria but in whom parathyroidectomy is not clinically appropriate or is contraindicated[4,5].

This study reports our experience with low-dose cinacalcet (30-60 mg/day) in patients with PHPT not eligible for surgery and analyzes the impact of the drug on various parameters of calcium-phosphorus metabolism.

Materials and methods

Subjects

Seventeen patients diagnosed with PHPT who had hypercalcemia were recruited. Serum calcium levels were higher than 11 mg/dL in all but two patients, who had values of 10.7 and 10.8 mg/dL respectively in the pre-treatment tests, although they had shown levels higher than 11 mg/dL in previous controls. Patients also met one or more of the following inclusion criteria: high risk of parathyroidectomy, persistent/recurrent PHPT following prior parathyroid surgery, or refusal of surgery. Exclusion criteria included chronic renal failure with creatinine clearance < 50 mL/min, vitamin D deficiency not normalized with replacement therapy, and diagnosis or suspicion of other causes of

secondary hyperparathyroidism or familial hypocalciuric hypercalcemia.

Study design

A prospective, open label, single arm study was conducted. Patients were recruited between April 2009 and July 2010. Clinical and biochemical characteristics were analyzed at baseline and during study follow-up after cinacalcet administration. Patients with an associated vitamin D deficiency (15 patients, 88%) were given alfacalcidol supplements (Hidroferol®; 266 µg every 1-2 weeks) before the baseline biochemical tests, and supplementation to achieve vitamin D levels higher than 30 ng/mL was continued during the study. Treatment with bisphosphonates was continued in patients who were taking them, but was not prescribed for patients who were not taking them.

After a baseline clinical and laboratory assessment, patients received cinacalcet 30 mg once or twice daily. There was no definite criterion for the use of one or the other dose. Generally, the patients initially recruited into the study received 60 mg/day in accordance with the dosage recommended in the prescription information. During the study, there was a trend in favour of a starting dose of 30 mg/day, except in the presence of significant hypercalcemia.

Patients were monitored by clinical visits and biochemical controls every three months. At each visit, cinacalcet dose was titrated in order to achieve serum calcium levels < 10.5 mg/dL and to avoid clinical or biochemical hypocalcemia. Adverse effects attributable to cinacalcet were monitored, and drug dose was reduced if clinical intolerance occurred. Treatment was discontinued if no symptom resolution or improvement was seen.

BMD data are not provided because of the limited number of studies available at the time of reporting these results.

Biochemical parameters

Samples for plasma chemistry were taken between 8 and 9 AM after an overnight fast of at least 10 hours. Samples for urinary tests were collected by patients in the 24 hours prior to blood collection.

Serum levels of calcium, phosphorus, creatinine, and alkaline phosphatase were measured using standard methods together with other general chemistry parameters (Elecsys-Roche autoanalyzer). Intact PTH (iPTH) and 25-hydroxyvitamin D were measured using an electrochemiluminescence assay (Elecsys-Roche Diagnostics. Intra-assay and inter-assay coefficients of variation, 1.5%-1.6% and 1.1%-1.2% respectively for iPTH, and 5.6%-5.7% and 3.5%-4.9% respectively for 25-hydroxyvitamin D). Glomerular filtration rate was estimated using the equation of the Modification of Diet in Renal Disease (MDRD) study.

Statistics

A descriptive statistical study was performed to assess demographic and clinical patient characteristics and to analyze the responses of the different biochemical parameters to cinacalcet. Variables are reported using number of patients (n), mean ± standard deviation, median, and ranges (minimum-maximum) for continuous variables, and frequencies (%) for non-continuous variables. Data were analyzed using non-parametric statistical tests for repeated samples (Wilcoxon). The comparative analysis after 12 and 15 months of follow-up is not included because of the poor reliability of its results due to the paucity of the data available. SPSS version 16.0 software was used for statistical analysis. For all results, a value of $p < 0.05$ was considered statistically significant.

Table 1 Baseline demographic and clinical characteristics

Patients (n)	17
Age (years)	73 ± 15 (38-89)
Sex (female/male)	13 (76%)/4 (24%)
Follow-up time (months)	9.4 ± 6.4 (3-16)
Prior parathyroid surgery	4 (24%)
Renal stones	9 (53%)
Vitamin D deficiency	15 (88.2%)
99mTc-MIBI (6-methoxy-isobutyl-isonitrile) scan	14
Single focal uptake	5
Dual focal uptake	1
Multifocal uptake	1
Ectopic uptake	1
Negative	6

Age: mean ± SD (range); sex: n (%); follow-up time: mean ± SD (range); prior parathyroid surgery: n, (%); kidney stones: n (%); vitamin D deficiency (< 20 ng/mL): n (%); MIBI: n.

Results

Baseline demographic and biochemical characteristics of the sample

Demographic characteristics including age, sex, history of parathyroidectomy, kidney stones, bone densitometry study in three areas, and nuclear medicine localization procedures using 99mTc-tetrofosmin were recorded before treatment. Four patients (24%) had persistent PHPT after the failure of prior parathyroidectomy (Table 1).

Patients were followed up for a mean of 9.4 ± 6.4 months.

Biochemical parameters of patients measured at baseline included calcium levels in serum and a 24-hour urine sample, calcium/creatinine ratio, plasma phosphorus, alkaline phosphatase, iPTH, and vitamin D (25-hydrowyvitamina D), and are summarized in Table 2.

Cinacalcet dosage and adjustment

Thirteen (76%) of the 17 patients started with a dose of 30 mg/day, while the remaining four patients (23%) received a total daily dose of 60 mg in two divided doses. In three of

Table 2 Baseline biochemical characteristics

		Normal range
Plasma calcium (mg/dL)	11.5 ± 0.6	8.1-10.5
Plasma phosphorus (mg/dL)	2.6 ± 0.4	2.7-5.2
Urinary calcium (mg/24 h)	270 ± 111	80-250
Calcium/creatinine (mg/mg)	0.35 ± 0.15	0.06-0.20
Alkaline phosphatase (U/L)	72 ± 24	35-104
iPTH (pg/mL)	144 (99-182)	15-65
Vitamin D (ng/mL)	31 ± 15	30-75

Plasma calcium: mean ± SD; plasma phosphorus: mean ± SD; urinary calcium: mean ± SD; calcium/creatinine: mean ± SD; alkaline phosphatase: mean ± SD; iPTH: median (25th-75th percentile); vitamin D: n (%).

the patients initially treated with 30 mg/day, cinacalcet dose had to be increased because the therapeutic goals for serum calcium (< 10.5 mg/dL) had not been achieved. One of the patients initially treated with 60 mg/day had to have the dose reduced to 30 mg/day because calcium levels of 8.2 mg/dL with no associated symptoms of hypocalcemia were found.

Treatment was discontinued in three patients during the study. One of these, initially treated with 30 mg/day, discontinued treatment due to a subsequent change in therapeutic approach and underwent successful surgery. Two patients from the group initially treated with 60 mg/day withdrew from the study, one due to poor cinacalcet compliance and the other because of persistent side effects despite downtitration of the drug.

At the time of writing, following these dose adjustments, 10 patients (71.4%) were continuing on a 30 mg/day dose of cinacalcet, while four (28.6%) were still receiving 60 mg/day (Fig. 1).

Biochemical response

Serum calcium levels

All patients had hypercalcemia at study start, with mean calcium levels of 11.5 ± 0.6 mg/dL. After three months of cinacalcet treatment, serum calcium levels had decreased by a mean of 10.1 ± 0.9 mg/dL, ($p < 0.001$). In subsequent laboratory tests, and after titration of cinacalcet dose, patients continued to have serum calcium levels within the normal range in our laboratory (8.1-10.5 mg/dL) (Fig. 2A).

In the overall group of 17 patients, including those who discontinued treatment, the maximum decrease in calcium levels seen with cinacalcet as compared to pretreatment values was 1.6 mg/dL ($p < 0.001$) (Table 3).

Serum calcium levels decreased by > 1.5 mg/dL in nine (52.9%) of the 17 patients, by 1.1-1.5 mg/dL in four patients (23.5%), by 0.5-1.0 mg/dL in three patients (17.6%), and by ≤ 0.5 mg/dL in one patient (5.8%) (Table 4).

Seven patients received 60 mg/day of cinacalcet during the study, four patients as the initial dose and three patients after a dose increase. Excluding from the analysis the two patients in whom inadequate drug use was shown (n = 5), mean reduction of serum calcium levels depending on cinacalcet dose was 1.7 mg/dL in this group. Calcium levels decreased >1.5 mg/dL in three patients and 1.1-1.5 mg/dL in two patients.

A total of 14 patients were treated with 30 mg/day of cinacalcet. Thirteen of these patients received this dose

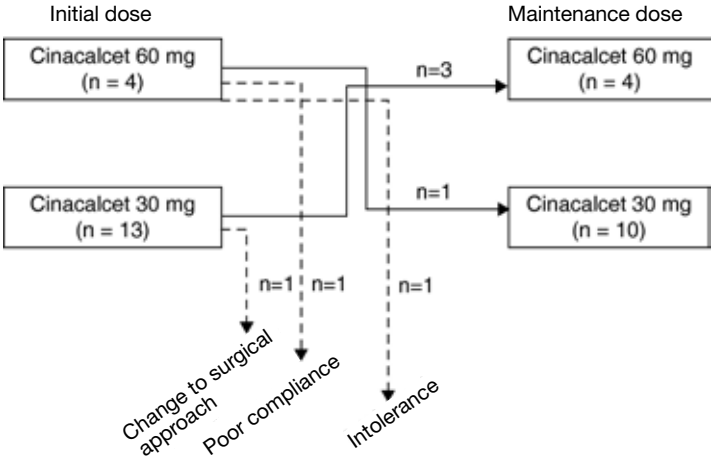

Figure 1 Cinacalcet dosage and adjustment.
Thirteen patients initially received one dose of 30 mg/day, and four patients 60 mg/day in two divided doses. In three of the patients initially treated with 30 mg/day, cinacalcet dose had to be increased because the therapeutic goals for serum calcium (< 10.5 mg/dL) were not achieved. In one of the patients, initially treated with 60 mg/day, the dose had to be reduced to 30 mg/day due to asymptomatic hypocalcemia. One patient initially treated with 30 mg/day discontinued treatment because of reconsideration of surgery. Two patients in the group initially treated with 60 mg/day withdrew from the study due to poor compliance with cinacalcet and side effects respectively. After dose adjustment, 10 patients were continuing to receive 30 mg/day, while four patients were still receiving 60 mg/day.

Table 3 Overall maximum biochemical response

Biochemical parameters	Pre-treatment	Post-treatment	Difference (%)	p
Plasma calcium (mg/dL)	11.5 ± 0.6	9.9 ± 0.9	−1.6 (−14%)	< 0.001
iPTH (pg/mL)	144 (99-182)	119 (86-167)	−25 (−17%)	< 0.01
Plasma phosphorus (mg/dL)	2.6 ± 0.4	2.9 ± 0.6	+0.3 (+11%)	< 0.05
Urinary calcium (mg/24 h)	270 ± 111	204 ± 106	−66 (−24%)	< 0.05
Calcium/creatinine (mg/mg)	0.35 ± 0.1	0.27 ± 0.1	−0.08 (−23%)	< 0.05
Alkaline phosphatase (U/L)	72 ± 24	88 ± 35	+16 (+22%)	< 0.01

Plasma calcium: mean ± SD; iPTH: median (25th-75th percentile); plasma phosphorus: mean ± SD; urinary calcium: mean ± SD; calcium/creatinine: mean ± SD; alkaline phosphatase: mean ± SD.

initially, and the remaining patient after a dose reduction. The mean maximum response of calcemia compared to pre-treatment baseline values was 9.6 ± 0.5 mg/dL, with a maximum serum calcium reduction of 1.5 mg/dL. As regards the extent of serum calcium reduction (n = 14), this was > 1.5 mg/dL in six patients, ranging from 1.1.-1.5 mg/dL and from 0.5-1.0 mg/dL in three patients, and was ≤ 0.5 mg/dL in two patients (Table 4).

Of all the patients recruited into the study (n = 17), 13 of them (76.4%) met the objective of normalization of serum calcium levels (≤ 10.5 mg/dL) with cinacalcet. If the two patients who discontinued treatment due to intolerance and non-compliance (n =15) are excluded, the proportion is 86.6%: four patients (80%) treated with cinacalcet 60 mg/day and 11 patients (78.5%) treated with 30 mg/day (Table 4).

iPTH

iPTH levels were measured at study start and in each three-monthly laboratory test (Fig. 2E). A gradual decrease was seen in iPTH levels, reported as a median reduction (25^{th}-75^{th} percentile) from 144 pg/mL (99-182) in the test prior to drug administration to 119 pg/mL (86-167) after three months of drug use (n = 16, p < 0.01), 103 pg/mL (80-152) at six months (n = 8; p = NS), and 112 pg/mL (93-180) at nine months (n = 7; p = NS). Overall, iPTH levels remained lower than baseline levels, but did not reach the normal laboratory ranges (15-65 pg/mL).

Serum phosphorus levels

While serum phosphorus levels remained within the normal reference range in our laboratory (2.7-5.2 mg/dL) throughout the study, serum phosphorus levels increased from 2.6 ± 0.4 mg/dL before treatment to 2.92 ± 0.6 mg/dL three months after the start of cinacalcet treatment (p = 0.02). These values remained subsequently stable during follow-up (Fig. 2B).

Urinary calcium levels

Urinary calcium levels were reduced with cinacalcet from baseline values to 270 ± 111 mg/24 h to 204 ± 106 mg/24 h (p = 0.02). Values were also reported as the calcium/creatinine ratio, which decreased from 0,35 ± 0,15 mg/mg before treatment to 0.27 ± 0.16 mg/mg after cinacalcet use (p = 0.02) (normal range 0.06-0.2) (Fig. 2D).

Alkaline phosphatase

Mean serum alkaline phosphatase levels remained within the normal range (35-104 U/L) throughout the study, increasing after cinacalcet administration from 72.8 ± 24 U/L to maximum values of 88 ± 35 U/L (n = 14; p = 0.01). These values subsequently remained stable at the high normal limit (Fig. 2C).

Adverse effects

Cinacalcet tolerability was good in a majority of patients. Twelve patients (70.5%) experienced no side effects attributable to the drug. Three patients (two treated with 60 mg/day and one treated with 30 mg/day) reported adverse effects consisting of dizziness, weakness, and paresthesia, which were transient except in one patient and led to cinacalcet discontinuation because of symptom persistence after drug downtitration. No patient in our series experienced nausea or vomiting.

Table 4 Decrease in serum calcium levels depending on cinacalcet dose

Serum calcium decrease (mg/dL)	D SCa	≤ 0.5	0.6-1.0	1.1-1.5	> 1.5	SCa goal ≤ 10.5
A. Total group	−1.6	1 (5.8%)	3 (17.6%)	4 (23.5%)	9 (52%)	13 (76.4%)
B. 60 mg/day	−1.7	–	–	2 (40%)	3 (60%)	4 (80%)
C. 30 mg/day	−1.5	2 (14.2%)	3 (21.4%)	3 (21.4%)	6 (42.8%)	11 (78.5%)

A. Maximum decrease (mg/dL) and range of reduction [n (%)] in serum calcium levels (SCa) after cinacalcet administration as compared to pre-treatment levels in the total group of patients starting the study (n = 17).
B and C. Maximum decrease (mg/dL) and range of reduction [n (%)] in SCa as compared to pre-treatment levels in the group of patients given 60 mg/day (n = 5) or 30 mg/day (n = 17) initially or after adjustment of cinacalcet dose.

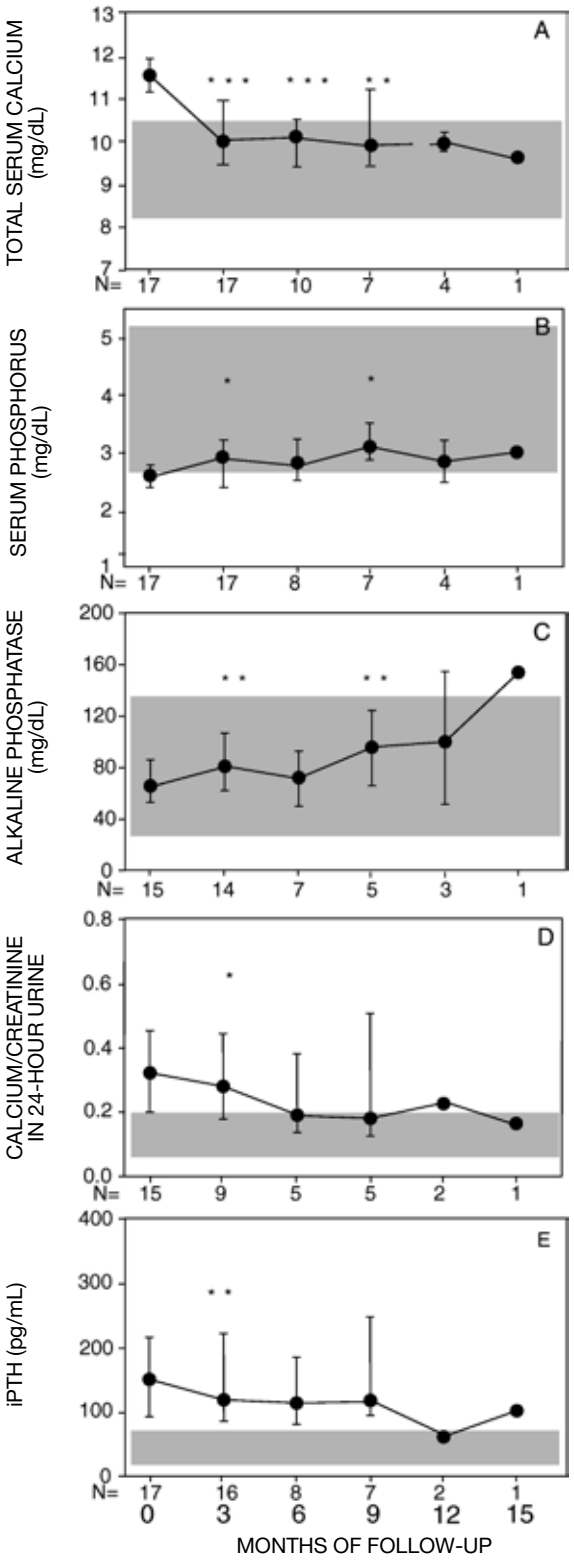

Figure 2 Biochemical response to cinacalcet over time. Mean levels of serum calcium (A), serum phosphorus (B), alkaline phosphatase (C), urinary calcium/creatinine ratio (D), and intact iPTH (E) before and after cinacalcet administration. *p < 0.05; **p < 0.01; ***p < 0.001. A comparative analysis of variables recorded at 12 and 15 months was not performed due to the paucity of the data available.

Discussion

This study reports our experience with cinacalcet in patients with PHPT not eligible for surgery. Our aim was to increase the number of cases reported of patients with PHPT treated with cinacalcet. In the specific case of Spain, there have been only two prior publications reporting four patients and one patient respectively[6,7]. Overall, our results agree with those previously reported, but the effective response of serum calcium to low cinacalcet doses in a majority of patients should be stressed.

Cinacalcet is a molecule with a phenylalkylamine structure that allosterically modulates the CaSR located in the chief cells of the parathyroid gland, i.e. it modifies the adjustment point of PTH versus extracellular calcium levels increasing CaSR sentitivity[8,9], which slows PTH secretion in parathyroid cells and therefore decreases serum calcium levels[3]. In the kidney, CaSR activation blocks the tubular reabsorption of calcium.

Cinacalcet has been clinically used since 2005 in patients with hyperparathyroidism secondary to chronic renal failure on dialysis. Its formal indication in PHPT has been reserved to the rare cases due to a parathyroid carcinoma.

Since 2008 it has also been prescribed to patients with PHPT in whom parathyroidectomy would be indicated based on calcium levels (according to the main treatment guidelines) but is not clinically adequate or is contraindicated[5].

This study recruited patients with PHPT having associated comorbidities causing an inacceptable increase in surgical/anesthetic risk, patients with persistent disease after one or more unsuccessful surgical procedures, or patients who refused surgery. Patients with these characteristics are often elderly and in some cases also have a certain degree of chronic renal failure.

In agreement with other studies[10], vitamin D insufficiency (< 30 ng/mL) was seen in a high proportion of our patients. Such deficiency was corrected in all cases before initial assessment of the parameters of calcium-phosphorus metabolism and during the study. Changes in these parameters cannot therefore be partially attributed to vitamin D deficiency.

The overall response of serum calcium levels after cinacalcet administration was highly consistent. Calcium serum levels decreased by more than 1.1 mg/dL in two thirds of the patients, and by more than 1.6 mg/dL in more than half of the cases. As a result, normal serum calcium levels (< 10.5 mg/dL at our laboratory) were achieved in approximately 80% of our patients, in agreement with the results of other studies[11]. It should also be noted that, after initial adjustment of cinacalcet dosage and once target calcium levels were achieved, these remained stable during the follow-up phase with no need for subsequent dose adjustments.

This study shows that the daily dose of cinacalcet required to normalize serum calcium levels in patients with PHPT is often lower than that reported in previous studies. The fact that the drug was initially intended to be used in patients with hyperparathyroidism secondary to chronic renal failure may have influenced the general recommendation of more aggressive dosage schemes, as treatment in such patients was aimed at preventing

development of renal osteodystrophy by reducing compensatory PTH hypersecretion and parathyroid gland hyperplasia[12,13]. In patients with PHPT due to parathyroid carcinoma, higher doses should be administered because of the severity of their hypercalcemia[14]. However, patients with PHPT eligible for treatment with cinacalcet do not usually have the serum calcium or PTH levels seen in the above patients.

It should be noted that a majority of our patients were started on a dose of 30 mg/day of cinacalcet, which was sufficient to achieve normalization of serum calcium levels in a significant proportion of them. Although, as a group, a greater response was seen when 60 mg/day were given in two divided doses, similar reductions were achieved with 30 mg/day in individual patients, which possibly reflects the variability in intrinsic sensitivity of CaSR to the drug in each patient.

PTH levels decreased as compared to baseline values after cinacalcet administration, but did not normalize. This is explained by the pharmacokinetic profile of the drug, which reaches peak plasma levels from between two to six hours after dosing. The maximum pharmacodynamic impact of the drug on plasma PTH levels was seen during this time interval, with a reduction by up to 60% as compared to pre-dose levels[15]. In our study, biochemical parameters were tested in the early morning, 10-12 hours after the previous cinacalcet dose. Plasma PTH levels did not therefore reflect the PTH nadir, which did not prevent serum calcium levels from remaining stable despite these cyclic variations in PTH.

Variable decreases were seen in urinary calcium levels after cinacalcet administration in this study, but a marked reduction occurred in some patients in agreement with other reports[16]. It should be taken into account that there are several factors conditioning urinary calcium excretion in these patients. On the one hand, serum calcium reduction decreases the load filtered through the renal glomerulus; by contrast, tubular reabsorption of calcium is decreased due to partial reduction of PTH and activation of renal CaSR promoted by cinacalcet.

In agreement with prior studies, phosphorus levels increased in this study in response to cinacalcet administration and remained stable during follow-up.

The response of bone formation, and especially bone resorption, markers after cinacalcet use has not been adequately studied, and results are inconclusive. Previous studies have reported an increase in alkaline phosphatase levels after drug administration suggesting a certain stimulus of bone resorption that may induce bone loss in the long term[17], but other studies have postulated that daily PTH fluctuations resulting from the pharmacodynamic profile of cinacalcet may have an anabolic effect similar to the daily administration of PTH[18]. Our study tested total alkaline phosphatase levels, which slightly increased during follow-up. Bone mineral density (BMD) data are not reported here because of the short mean treatment time of our patients, but data from patients followed up for longer than one year remained stable as compared to prior values (data not shown).

According to data available from the different studies published, BMD experienced no changes after cinacalcet administration[2]. This is the main negative aspect of the drug, as it contrasts with the cumulative improvement in densitometric indices seen after parathroidectomy[19]. In this regard, data are lacking on the effects that could be provided by the use of combined treatment with CaSR modulators and antiresorptive agents, based on the assumption that the benefits to be obtained from them separately could complement each other.

Based on the foregoing, cinacalcet should not be considered as a curative treatment on the same level as surgery, but as an alternative to it in cases where a high risk exists because of patient comorbidities or where the surgical option has failed.

In patients with PHPT and significant hypercalcemia, without underestimating the bone impact of disease, morbidity inherent to hypercalcemia itself occurs in the cardiovascular, renal, and neuromuscular areas. No data are currently available on the potential effect of cinacalcet on these conditions, except for some non-controlled results based on quality of life scales in a few patients[20], but cinacalcet may undoubtedly represent an essential support for drug treatment aimed at normalization of calcemia, particularly when osteoporosis is not the main therapeutic target.

An aspect considered to be important is that many candidates for cinacalcet treatment are elderly patients with PHPT who have a deficient glomerular function and in whom the parathyroid response inherent to renal failure may be added to autonomous PTH hypersecretion, thus aggravating PTH hypersecretion and the development of osteodystrophy. In addition, these patients often experience exacerbation of renal failure due to intercurrent events, which usually worsen a previously mild to moderate hypercalcemia, converting it into a life-threatening metabolic disorder. In these patients, serum calcium normalization with cinacalcet minimizes the development of this severe complication.

Tolerability of low cinacalcet doses is clearly good. In our series, drug discontinuation for intolerance (fatigue and myalgia) was required in a single patient. Apart from this, only two other patients experienced mild transient adverse effects consisting of dizziness, weakness, and paresthesia.,The fact that, unlike in previous reports, no patients experienced nausea or vomiting can be attributed to the use of drug doses lower than, those used in dose-finding studies of patients with PHPT.

In conclusion, low-dose cinacalcet may normalize serum calcium levels in patients with PHPT and shows a good tolerability profile. It is therefore a therapeutic option in selected patients in whom surgery is contraindicated or involves a high risk, and in patients with persistent PHPT following unsuccessful surgery.

Conflict of interest

The authors state that they have no conflict of interest.

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