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Cinacalcet as symptomatic treatment of hypercalcaemia in primary hyperparathyroidism prior to surgery

Przydatność cynakalcetu w przygotowaniu do leczenia operacyjnego pierwotnej nadczynności przytarczyc

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Abstract

Intriduction: The aim of presented study was to assess the efficacy of cinacalcet in reducing serum calcium concentrations in primary hyperparathyroid (PHPT) patients with hypercalcaemia exceeding 12.5 mg/dL, awaiting parathyroidectomy.

Material and methods: The study included 23 patients with PHPT with hypercalcaemia > 12.5 mg/dL, qualified for surgery. We recorded clinical and biochemical data at baseline, and after every week of treatment. We also monitored adverse events. Cinacalcet was administered in increasing doses until the corrected serum calcium concentration was 11.3 mg/dL or less, the patient reached the highest possible dosage of 90 mg four times daily, or the patient experienced an adverse event that precluded further dosage increases.

Results: The primary end point of reduction in corrected serum calcium concentration to 11.3 mg/dL was achieved in 19 patients (83%), and normocalcaemia (S-Ca < 10.3 mg/dL) was achieved in 55% of patients. The medication was usually well tolerated (83.4%). Most common adverse events were nausea and vomiting, especially at the beginning of therapy; however, only one patient withdrew from the study because of adverse events.

Conclusion: Cinacalcet rapidly reduced serum calcium in PHPT patients with severe hypercalcaemia and can be useful as a short-term pretreatment prior to surgery, allowing the completion of diagnostics and safe awaiting for operation. **(Endokrynol Pol 2017; 68 (3): 306–310)**

Key words: *primary hyperparathyroidism; hypercalcaemia; cinacalcet*

Streszczenie

Wstęp: Celem prezentowanej pracy była ocena skuteczności cynakalcetu w kontroli stężenia wapnia w surowicy u chorych na pierwotną nadczynność przytarczyc (PHPT) z hiperkalcemią przekraczającą 12,5 mg/dl — w oczekiwaniu na leczenie operacyjne.

Materiał i metody: Badaniem objęto 23 pacjentów z PHPT z hiperkalcemią > 12,5 mg/dl, zakwalifikowanych do leczenia operacyjnego. Dane kliniczne i wyniki badań biochemicznych oceniano na początku i po każdym tygodniu leczenia. Monitorowano występowanie działań niepożądanych. Cynakalcet podawano w dawkach rosnących, zaczynając od 30 mg dwa razy dziennie, do uzyskania redukcji stężenia wapnia w surowicy skorygowanego poniżej 11,3 mg/dl, maksymalnej dopuszczalnej dawki 90 mg cztery razy na dobę, lub u pacjenta wystąpiły działania niepożądane, które uniemożliwiły dalsze zwiększanie dawkowania leku.

Wyniki: Obniżenie skorygowanego stężenia wapnia w surowicy poniżej 11,3 mg/dl (pierwotny punkt końcowy) osiągnięto u 19 pacjentów (83%), a normalizację stężenia wapnia w surowicy (S-Ca < 10,3 mg/dl) uzyskano u 55% pacjentów. Lek był zwykle dobrze tolerowany (83,4%). Najczęstszymi działaniami niepożądanymi były nudności i wymioty, zwłaszcza na początku terapii, jednak tylko jeden pacjent wycofał się z badania z powodu działań niepożądanych.

Wnioski: Leczenie cynakalcetem umożliwia szybką redukcję stężenie wapnia w surowicy u pacjentów z ciężką hiperkalcemią w przebiegu pierwotnej nadczynności przytarczyc. Może szczególnie być użyteczne jako objawowe przygotowanie przed planowanym leczeniem operacyjnym, umożliwiając bezpieczne ukończenie diagnostyki i oczekiwanie na zabieg. **(Endokrynol Pol 2017; 68 (3): 306–310)**

Słowa kluczowe: *pierwotna nadczynność przytarczyc; hiperkalcemia; cynakalcet*

Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcaemia in the outpatient setting and is usually discovered by routine laboratory testing. PHPT is frequently asymptomatic, but its clinical presentation ranges in severity from nonspecific complaints to life-threatening hypercalcaemia [1, 2]. Increased serum calcium and PTH concentrations mediate the complications associated with PHPT, including skeletal and renal disease, gastrointestinal problems, and neuropsychiatric manifestations [3]. The goal of therapy in patients with PHPT is to normalise serum calcium and PTH levels, and to improve the associated clinical manifestations. Parathyroidectomy, the only curative treatment, has a high success rate when performed by experienced surgeons [2, 4].

Although in the majority of patients serum calcium levels do not exceed the upper limit of normal by more

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than 1 mg/dL, individual patients present more severe hypercalcaemia. These patients often have nonspecific symptoms such as fatigue, weakness, anorexia, mild depression, and mild cognitive or neuromuscular dysfunction, and are at substantial risk of hypercalcaemic crisis, thus requiring symptomatic treatment in anticipation of surgery [3]. Until recently, the standard treatment for hypercalcaemia was bisphosphonates [5]. Approval of cinacalcet for the symptomatic treatment of hypercalcaemia in primary hyperparathyroidism creates a new opportunity for emergency stabilisation of serum calcium and improvement of the overall well-being of patients waiting for surgery [5, 6].

The aim of presented study was to assess the efficacy of cinacalcet to reduce serum calcium concentrations in primary hyperparathyroid patients with hypercalcaemia exceeding 12.3 md/dL, awaiting parathyroidectomy.

Study design

This was an open-label, single-arm, dose-titration study. Ethical considerations precluded a control group of hypercalcaemic patients with PHPT not receiving cinacalcet. Study visits occurred weekly. Patients initially received 30 mg cinacalcet twice daily. The dosage was increased to the next sequential dosage every week, depending on the patient's serum calcium concentration during the previous week and an adverse event assessment. Dosage escalation continued until the corrected serum calcium concentration was below 11.3 mg/dL, the patient reached the highest possible dosage of 90 mg four times daily, or the patient experienced an adverse event that precluded further dosage increases. The secondary endpoint of the study was the achievement of a normal corrected total serum calcium concentration of ≤10.3 mg/dL.

Material and methods

Twenty-three patients (16 females, 7 males, aged 28––74 years; mean + SD: 56.9 ± 11.9 years) with PHPT and hypercalcaemia > 12.5 mg/dL were enrolled, of whom 21 (82%) completed the study. One patient discontinued prematurely because of an adverse event (because of nausea and vomiting), and one patient was lost to follow-up. Baseline characteristics of patients are shown in Table I. Six patients had nephrolithiasis, 18 had low bone mineral density, three had previous vertebral fractures, and one had a hip fracture. Arterial hypertension was present in 16% of patients, and one had history of peptic ulcer disease. The median duration of cinacalcet treatment was 64 days (range 21–98 days). The median effective cinacalcet dose was 60 mg twice daily (range 30 mg twice daily to 90 mg twice daily) (n = 21).

Table I. *Basal characteristic of patients (mean ± SD)*

Tabela I. *Podstawowa charaterystyka pacjentów (średnia ± SD)*

Corrected serum calcium (n = 8.4–10.3 mg/dL)	13.33 ± 0.45 mg/dL
Serum phosphorus (n = 2.8–5.0 mg/dL)	2.7 ± 0.4 mg/dL
Serum PTH (n = 15.00–65.00 pg/mL)	187.84 ± 87.1 pg/mL
Serum creatinine (n = 0.50–0.90 mg/dL)	0,89 ± 0,08 mg/dL

Samples of venous blood were taken in the morning after fasting overnight. Baseline and study blood samples were obtained for measurement of serum calcium, phosphorus, albumin, creatinine, and intact PTH weekly, after an overnight fast and before the morning dose of cinacalcet. Corrected total serum calcium was calculated according to the following formulas if albumin < 4 g/dL:

Corrected calcium (mg/dL) = measured total calcium (mg/dL) + 0.8 (4.0 – serum albumin (g/dL)

Serum PTH was measured using an electrochemiluminescence (ECLIA) immunoassay (intra-assay coefficient of variation 4.2–6.4%; Cobas 8000, Roche Diagnostics, USA), the normal range being 15.00–65.00 pg/mL. Serum calcium, serum phosphorus, serum albumin, and serum creatinine were determined using standard methods.

Adverse events were recorded throughout the study.

Statistical analysis

Results are expressed as mean ± standard deviation. The Shapiro-Wilk test was used to assess the normality of variables distribution and the Student t -test for dependent variables to assess the statistical significance. The number and percentage of subjects achieving a reduction in corrected serum calcium to below 11.3 mg/dL, and to below the upper limit of the normal range (< 10.3 mg/dL), were determined. All adverse events were tabulated by body system affected, preferred term within body system (according to a modified World Health Organisation Adverse Reaction Terminology directory), seriousness, and relationship to study drug. Data for categorical variables are presented as numbers or percentages.

Results

Changes in serum calcium

The baseline mean ± SD corrected calcium concentration was 13.33 ± 0.45 mg/d (range 12.7–14.2 mg/dL). The primary end point of reduction in corrected serum

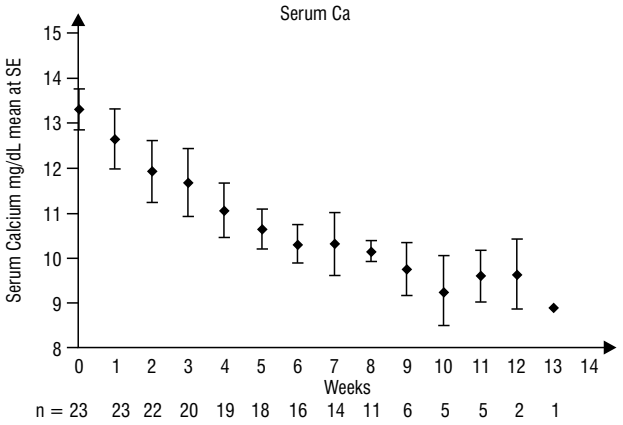

Figure 1. *Mean corrected serum calcium levels during the study period*
Rycina 1. *Średnie stężenie skorygowane wapnia w trakcie stosowanego leczenia*

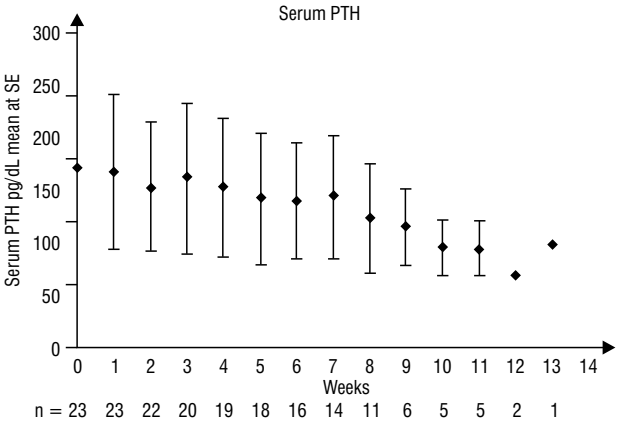

Figure 2. *Mean serum PTH levels during the study period*
Rycina 2. *Średnie stężenie PTH w trakcie stosowanego leczenia*

calcium concentration to 11.3 mg/dL was achieved in 19 patients (83%), and 17 patients (74%) achieved normal corrected serum Ca < 10.3 mg/dL. The mean serum calcium concentration was reduced significantly to 10.2 ± 0.3 mg/dL, $p < 0.001$ (Fig. 1)

Changes in plasma intact PTH

At baseline, the mean ± SD pre-dose serum PTH concentration was 187.84 ± 87.1 pg/mL (range 87.55––416.75 pg/mL). At the end of the study, the minimal obtained plasma PTH concentrations were highly variable, with a mean ± SD serum PTH concentration of 134.68 ± 49.78 pg/mL; ranging from 66.1 to 254 pg/mL (n = 21) (Fig. 2). The change in the PTH from baseline to the end of study was statistically significant ($p < 0.01$); however, no patient reached normal serum PTH concentration

Changes in other biochemical values

Mean ± SD serum phosphorus levels were in the low-normal range at baseline at 2.7 ± 0.4 mg/dL, and increased not statistically significantly to 2.9 ± 0.3 mg/dL, $p > 0.01$, at the end of the study.

Adverse events

All patients experienced at least one adverse event. Nausea, vomiting, and paraesthesias were the most common adverse events, occurring in ten (31.25%), six (18.75%), and five (15,6%) patients, respectively, and considered to be treatment related. Treatment-related hypocalcaemia was not seen during the study; however, paraesthesias occurred in some patients when serum calcium concentrations were within the normal range, but significantly lower than at baseline. No patient died during the study. One patient withdrew from the study because of adverse events.

Discussion

This study demonstrates the ability of cinacalcet to substantially lower serum calcium concentrations in hypercalcaemic PHPT patients qualified for surgery.

Medical options for treating the skeletal complications of PHPT include antiresorptive treatments, such as bisphosphonates, hormonal replacement therapy (HRT), and raloxifene [5]. Bisphosphonates and HRT effectively decrease bone turnover and increase BMD in PHPT patients; however, none of these antiresorptive therapies significantly alters serum calcium or PTH during long-term therapy [7–9]. Parenteral administration of a more potent bisphosphonate, pamidronate, often lowers the serum calcium concentration substantially within 48 to 72 hours, with the effect prolonged to approximately 14 days. Zolendronate, the most potent bisphosphonate that is FDA approved for the treatment of hypercalcaemia of malignancy, could also be considered in this situation [10].

The calcimimetic cinacalcet is an allosteric modulator of the calcium-sensing receptor (CaSR), which is strongly expressed on the surface of parathyroid cells as well as in other tissues. Cinacalcet enhances the sensitivity of the CaSR to the prevailing extracellular calcium, resulting in an increase in the intracellular calcium concentration and a concomitant reduction in PTH released by the parathyroid gland [11]. The calcimimetic cinacalcet, initially intended for the treatment of secondary and tertiary hyperparathyroidism in patients with renal failure [12], effectively lowers serum calcium and PTH levels during long-term therapy in PHPT [13–16]. At present, use of this agent in PHPT is limited to control of serum calcium in patients with symptomatic hypercalcaemia, who are unable to undergo corrective surgery [5, 17].

In this study, the all participants were qualified for surgery according to the Guidelines for Asymptomatic PHPT Management (serum calcium > 1.0 mg/dL [0.25 mmol/L] above the upper limit of normal) [2]. The treatment with cinacalcet resulted in lower serum calcium concentrations in almost all patients with significant hypercalcaemia and in normalisation of calcaemia in nearly 75%, as a short-term pre-treatment prior to surgery. The reduction of serum PTH was also significant, but it varied among single patients and no patient reached normal serum PTH.

Several studies have demonstrated that cinacalcet effectively controls hypercalcaemia while only modestly reducing PTH levels in a heterogeneous sample of patients with PHPT, including patients with and without an indication for parathyroidectomy and patients with a history of failed parathyroidectomy [17–21]. In pooled analysis of the data from three multicentre clinical trials of cinacalcet in patients with PHPT, Peacock et al. [20] examined the efficacy and the safety profile of cinacalcet therapy in patients with PHPT across a wide spectrum of disease severity, from mild to severe, as judged by biochemistry and BMD. Cinacalcet treatment rapidly normalised serum Ca and thereafter maintained normocalcaemia for the length of follow-up. However, relationships between baseline serum Ca and effective cinacalcet dose could not be accurately established. Although mean plasma PTH decreased in all three studies, PTH concentrations decreased more slowly than serum Ca concentrations and never normalised. The difference in serum Ca and PTH responses may reflect cinacalcet actions on CaSRs in tissues other than parathyroid glands, particularly kidneys, in which it directly reduces tubular reabsorption of Ca, and perhaps also in bone.

More recently, similar results were also obtained from the first multicentre, international, phase 3 randomised, double-blind, placebo-controlled (RCT) trial of cinacalcet in subjects with PHPT who met the criteria for parathyroid surgery but were unable to undergo parathyroidectomy [21].

Our results are consistent with previous studies and demonstrate the stabilisation of serum calcium in the medium term. This is the first study, however, devoted entirely to the patients selected for surgery. Similar results presented Inés Luque-Fernández et al., but in their study, patients with progressive hypercalcaemia awaiting surgery were only a fraction of the total number of 34 subjects [22].

Cinacalcet was generally well tolerated when titrated to as high as 90 mg two times daily, and the overall safety profile of cinacalcet observed in this study was generally similar to that observed in previous trials, across a wide range of PHPT. Nausea and vomiting were the most common adverse events, but only one patient withdrew from the study due to gastrointestinal events.

An important but unavoidable limitation of this study is the single-arm design. Ethical considerations, however, precluded enrolment of a control group because the patients we studied represent a group with high risk of hypercalcaemic complications up to hypercalcaemic crisis.

In conclusion, the demonstrated efficacy of cinacalcet in reducing (and even normalising) serum calcium concentrations in PHPT patients with severe hypercalcaemia indicate that this intervention can be used as a short-term pretreatment prior to surgery, allowing the completion of diagnostics and safe awaiting for operation.

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