Original Article

Cinacalcet: A Viable Therapeutic Option for Primary Hyperparathyroidism in the Elderly

Hussam Abusahmin, Ashutosh Surya, Andrew Aldridge, Onyebuchi Okosieme, Gautam Das

Department of Diabetes and Endocrinology, Prince Charles Hospital, Cwm Taf University Health Board, Merthyr Tydfil CF47 9DT, United Kingdom

Abstract

Objective: Parathyroidectomy is usually curative in primary hyperparathyroidism (PHPT), but its utility would be limited if patients are elderly who may either refuse surgery or may have advanced frailty and multimorbidity. We evaluated the effectiveness of cinacalcet, an allosteric modulator of calcium-sensing receptor in PHPT in an elderly cohort of patients. **Methods:** A prospective analysis of 29 patients who had PHPT and despite fulfilling criteria for surgery were unable to undergo parathyroidectomy either due to self-refusal ($n = 12$) or due to advanced multimorbidity ($n = 17$). All patients completed treatment with cinacalcet for at least for 6 months. Analysis were performed as per age (<75 and ≥75 years) and Charlson comorbidity index (CCI) score (≤5 and >5). **Results:** Our patients were the elderly (77 ± 12.7 years). In the whole group, complete normocalcemia was observed in 72.4% of patients (mean reduction: −0.55 mmol/l [confidence interval (CI) 0.4–−0.7; $P < 0.0001$]) and parathormone (PTH) normalized (≤6.9 pmol/l) in 33.4% of patients [mean reduction: −5.5 pmol/l (CI −11.6–0.6; $P = 0.0015$)]. In subgroup analysis, the severity of hypercalcemia was found to be higher patients with age <75 years and also in patients with CCI score >5. Cinacalcet lowered adjusted calcium in both age groups ($P < 0.0001$) with a greater reduction (20.5% vs. 16.2%; $P < 0.0001$ for both) in patients with CCI score >5. PTH fell in both age groups but significantly (−6.7 pmol/l [CI −14.9–1.5]; $P = 0.008$) in ≥ 75 years category and likewise, the drop was greater in patients with higher CCI scores (−7.1 pmol/l [CI −15.8–1.6); $P = 0.009$] vs. [−4.5 pmol/l [CI −3.9–−5.10]; $P = 0.001$). Patients with age <75 years and with CCI score ≤5 needed higher doses of cinacalcet to achieve biochemical targets. **Conclusion:** Cinacalcet is a viable and valuable treatment strategy for elderly patients with multiple comorbidities who suffer from PHPT but either cannot or refuse to undergo parathyroidectomy.

Keywords: Cinacalcet, elderly, multimorbidity, parathyroidectomy

Introduction

Primary hyperparathyroidism (PHPT) is characterized by hypercalcemia and elevated or inappropriately normal parathyroid hormone (PTH) levels.[1] It occurs most commonly in the older population and in females, and screening studies report a prevalence of 2.1% in European postmenopausal women.[2] The widespread availability of modern multichannel analyzers has led to the increased diagnosis in "asymptomatic" patients and although, such patients do not manifest classical symptoms of hypercalcemia, a proportion progress to more advanced disease.[3] In addition, patients with moderate-to-severe disease suffer significant morbidity from the effects of hypercalcemia and may develop progressive loss of bone mineral density leading to osteoporosis and fractures.[1] Parathyroid surgery is usually curative but is not always feasible or desirable, especially in elderly patients with multiple medical morbidities.[1]

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Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_684_17

A potential nonsurgical therapeutic option for patients with PHPT is cinacalcet, an allosteric modulator of the calcium-sensing receptor which acts by increasing receptor sensitivity to extracellular calcium, effectively suppressing PTH secretion and reducing serum calcium.[4] Although the efficacy and safety of cinacalcet are well documented, the bulk of published data on its use has emerged from participants in highly specialized controlled trial settings[5,6] or from cohorts with secondary hyperparathyroidism and chronic kidney disease.[7] Whether such data are applicable to patients with PHPT in routine practice settings who may exhibit a more

Address for correspondence: Dr. Gautam Das, Department of Diabetes and Endocrinology, Prince Charles Hospital, Cwm Taf University Health Board, Merthyr Tydfil CF47 9DT, United Kingdom.
E-mail: gautam.das@wales.nhs.uk

How to cite this article: Abusahmin H, Surya A, Aldridge A, Okosieme O, Das G. Cinacalcet: A viable therapeutic option for primary hyperparathyroidism in the elderly. Indian J Endocr Metab 2018;22:485-8.

diverse range of disease severity and multimorbidity remains uncertain.

Methods

We enrolled 29 patients from the general endocrine clinic who had PHPT and met at least one criteria for surgery as mentioned in the guidelines suggested at the Fourth International workshop in 2014 for asymptomatic PHPT.[8] Biochemical parameters such as bone profile, kidney function test, PTH, thyroid function, and Vitamin D (25[OH]D3) were measured at baseline and at 6 months. All biochemical parameters were assayed using Roche Cobas 6000 and 8000 instruments (Roche, Basel, Switzerland). 25(OH)D3 was assayed using tandem mass spectrometry (shorthand term, LC-MS/MS) using Chromsystems Vitamin D kits (Chromsystems, Munich, Germany). The adjusted calcium was calculated by an in-house equation: Total calcium + (0.0159 × (50.41-albumin). All patients had a urinary calcium-creatinine ratio (Urinary Ca/Cr) and Dexa bone scan was also requested as part of investigation work up. A Charlson comorbidity index (CCI) score was calculated for each patient based on age and the presence or absence of 16 medical conditions[9] and they were categorized into two groups: with mild-to-moderate CCI score (≤5) or severe CCI score (>5).

Cinacalcet was started in these patients if they were deemed unsuitable for surgery either due to multimorbidity (n = 17; CCI score >5) or due to patient preference for nonsurgical management (n = 12; CCI score ≤5). Cinacalcet was initiated at a dose of 30 mg once daily and was gradually titrated upward at 4–6 weekly intervals in discussion with their general practitioners aiming for a normal serum adjusted calcium level which were being checked frequently in the community. All patients completed at least 6 months treatment with cinacalcet. Patients with Vitamin D insufficiency (25[OH]D3 levels = 30–50 nmol/L; n = 6/24) or deficiency (25[OH]D3 levels <30 nmol/l; n = 18/24) identified during initial evaluation were treated with Vitamin D supplementation (cholecalciferol or calcitriol) for at least 6 months (5 patients did not have their Vitamin D levels checked during initial visit). Amongst the patients who refused surgery initially, four patients had parathyroidectomy at a later date after having completed treatment with cinacalcet for at least 6 months. Statistical analysis was performed on the whole group and in subcategories of patients (as per age and CCI scores). The value of $P < 0.05$ was considered statistically significant. The study was registered with the clinical audit Department of Cwm Taf University health board (PCH-351).

Results

Our patients were predominantly females (79.3% [23/29]) and elderly [mean age −77 ± 12.7 years]. In the whole group, serum adjusted calcium was reduced in all patients with complete normalization (<2.60 mmol/l) in 21/29 (72.4%) patients with a mean reduction of −0.55 mmol/l (95% confidence interval (CI) −0.4–−0.7; $P < 0.00001$). In subgroups, hypercalcemic severity was higher in patients <75 years than those ≥75 years at onset, but both groups achieved statistically significant reduction in mean adjusted calcium levels (−0.6 mmol/l [95% CI − 0.5–−0.7]; $P < 0.0001$) and (−0.4 mmol/l [95% CI − 0.1–−0.7]; $P < 0.0001$), respectively [Table 1]. In patients with CCI scores of > 5, base line mean serum adjusted calcium levels were higher in comparison to those with CCI scores of ≤5 [Table 2] and the former group achieved a greater mean percentage reduction in serum adjusted calcium levels of 20.5% (−0.63 mmol/l [95% CI − 0.38–−0.88]; $P < 0.0001$) than the latter group who achieved a reduction of 16.2% (−0.47 mmol/l [95% CI − 0.5–−0.54]; $P < 0.0001$).

In the whole group, mean PTH levels fell by 33.4% (−5.5 pmol/l [95% CI − 11.6–0.6]; $P = 0.0015$) with complete normalization (≤6.9 pmol/l) in 11/29 patients (37.9%). In the ≥75 years age category reduction in mean PTH levels was statistically significant (−6.7 pmol/l [95% CI −14.9–1.5]; $P = 0.008$) but not in the <75 years group (−3.7 pmol/l [95% CI −2.9–−4.5; $P = 0.07$) [Table 1]. Similarly, in patients with CCI scores of >5, PTH fell by a greater extent (−7.1 pmol/l [95% CI −15.8–1.6]; $P = 0.009$) when compared to patients who had lower CCI scores of ≤5 (−4.5 pmol/l [95% CI −3.9–−5.10]; $P = 0.001$) [Table 2]. Improvements in phosphate levels were noted in both age categories though statistically insignificant and effective lowering of alkaline phosphatase (ALP) was noted in the <75 years age group ($P = 0.03$) only. The eGFR worsened in both age category but was statistically significant in the ≥75 years ($P = 0.01$) age group. Cinacalcet was well tolerated by most patients. Minor reactions such as nausea and abdominal discomfort were seen in 5/29 (17.2%) of patients, but none discontinued the medication as a result. Hypocalcemia was not observed in any patient. Most patients (24/29 [82.8%]) needed cinacalcet in a dose between 30 and 90 mg to lower calcium levels, but higher doses (>90 mg) were only required in five patients with severe hypercalcemia predominantly in the <75 years age group.

Discussion

The study findings show that cinacalcet is a viable therapeutic option in elderly patients with PHPT regardless of age, disease severity, or comorbidity burden. Cinacalcet administered in doses of 30–90 mg normalized serum calcium in most patients with additional modest benefits seen in serum PTH, phosphate, and ALP concentrations. These results are consistent with data from previous controlled trials[10] and observational studies,[6] but our patient characteristics differ from these cohorts in several respects. With a mean age of 77 ± 12.7 years, our patients were relatively older than trial participants (mean age <65 years).[10] In addition, most of our patients were precluded from surgery on the grounds of multi-morbidity in contrast to previous observational study participants most of whom were deemed fit for surgery and only received cinacalcet following unsuccessful operations or parathyroid gland localization.[6] Thus, our cohort had a greater degree of frailty that may be more reflective of the range of the elderly patients encountered in everyday practice. In addition, our patients

Table 1: Demographic and biochemical parameters at baseline and after 6 months of treatment with cinacalcet according to age

Variables	Age <75 years (*n*=11)			Age ≥75 years (*n*=18)		
	Baseline	6 months	*P*	Baseline	6 months	*P*
Age (years)	63.0±8.2			85.0±5.8		
Sex (male/female)	4/7	-	-	2/16	-	-
Calcium (adjusted) (mmol/L)	3.0±0.2	2.4±0.3	<0.0001	2.8±0.4	2.4±0.1	<0.0001
Phosphate (mmol/L)	0.8±0.3	1.0±0.2	0.09	0.9±0.2	1.1±0.3	0.27
Parathormone (pmol/L)	14.8±6.7	11.1±5.9	0.07	17.5±14.6	10.8±6.4	0.008
Vitamin D (nmol/L)	34.7±15.5	-	-	38.9±31.1	-	-
Alkaline phosphatase (U/L)	101.2±26.9	86.2±17.9	0.03	87.2±37.1	91.0±29.9	0.73
Creatinine (µmol/L)	76.3±21.5	79.5±29.1	0.47	84.1±25.1	87.5±23.2	0.41
eGFR (ml/min/1.73 m^2)	78.2±13.7	74.5±19.4	0.08	65.9±16.4	64.8±18.4	0.01
Urinary calcium creatinine ratio (mmol/mmol)	1.0±0.2	-	-	0.8±0.1	-	-
TSH (mU/L)	1.4±1.3	-	-	1.8±1.1	-	-
FT4 (pmol/L)	18.0±4.7	-	-	16.5±2.2	-	-
Dose of cinacalcet (mg)	81.8±40.5	-	-	68.3±26.8	-	-
CCI	4.6±3.2	-	-	6.7±1.6	-	-
Biochemical parameters			Reference range			
Calcium (adjusted)			2.2-2.6			
Phosphate			0.8-1.5			
Parathormone			1.6-6.9			
Vitamin D			>50			
Alkaline phosphatase			30-130			
Creatinine			58-110			
eGFR			>90			
TSH			0.27-4.2			
FT4			11-25			

eGFR: Estimated glomerular filtration rate, TSH: Thyroid stimulating hormone, FT4: Free thyroxine, CCI: Charlson comorbidity index

Table 2: Demographic and biochemical parameters at baseline and after 6 months of treatment with cinacalcet according to Charlson comorbidity index

Variables	CCI ≤5 (*n*=12)			CCI >5 (*n*=17)		
	Baseline	6 months	*P*	Baseline	6 months	*P*
Age (years)	69.1±13.5			82.0±8.9		
Sex (male/female)	2/10	-	-	4/13	-	-
Calcium (adjusted) (mmol/L)	2.9±0.1	2.3±0.2	<0.0001	3.1±0.4	2.4±0.2	<0.0001
Phosphate (mmol/L)	1.0±0.2	1.0±0.2	0.05	0.9±0.2	1.0±0.3	0.16
Parathormone (pmol/L)	14.5±6.3	10.0±5.7	0.0008	18.2±15.0	11.1±6.4	0.004
Vitamin D (nmol/L)	43.0±33.8	-	-	33.9±20.5	-	-
Alkaline phosphatase (U/L)	98.7±32.6	89.0±24.7	0.14	86.9±29.5	88.7±27.8	0.43
Creatinine (µmol/L)	69.7±21.5	70.5±22.4	0.19	88.1±23.4	93.0±24.5	0.15
eGFR (ml/min/1.73 m^2)	78.6±11.8	77.1±14.8	0.23	65.0±17.4	62.5±20.1	0.27
Urinary calcium creatinine ratio (mmol/mmol)	1.1±0.3	-	-	1.6±0.4	-	-
TSH (mU/L)	1.9±1.7	-	-	1.4±0.5	-	-
FT4 (pmol/L)	17.7±4.1	-	-	16.9±2.8	-	-
Dose of cinacalcet (mg)	79.1±38.6	-	-	67.1±27.1	-	-

CCI: Charlson comorbidity index, eGFR: Estimated glomerular filtration rate, TSH: Thyroid stimulating hormone, FT4: Free thyroxine

were also classified as per comorbidity score and we found that patients with higher scores had greater hypercalcemic severity at onset which may be a reflection of a more severe form of PHPT (serum calcium relating to higher PTH levels) or particular comorbidities may have been a contributory factor. Interestingly, this cohort of the patient's achieved a greater reduction in adjusted calcium and PTH levels in comparison to patients with lower comorbidity scores, suggesting that cinacalcet is very effective when advanced multimorbidity coexist with PHPT and limits surgical options.

The study is limited by its observational design and small patient numbers precluding more robust subgroup analysis. Furthermore, our patients were followed up for only 6 months; although, it is doubtful whether longer follow-up would have yielded additional benefits. Long-term studies show that maximum biochemical improvements are attained by 6 months and maintained for up to 4 years.[10] Finally, we only determined biochemical response which may not necessarily equate to more clinically relevant end-points such as bone mineral density and fracture rates. However, we were unable to obtain the results of Dexa bone scans for all patients as some were still waiting for the test when this paper was written.

Conclusion

The study findings show that the benefits of cinacalcet observed in controlled trials extend to an elderly population with PHPT managed in routine practice settings. Long-term prospective studies are needed to demonstrate sustained effects of cinacalcet on clinical as well as biochemical parameters in elderly individuals with PHPT.

Acknowledgments

We sincerely acknowledge the support of Mr. Brian P Tennant, senior clinical scientist in the Department of Clinical Biochemistry, Prince Charles Hospital for this project.

Financial support and sponsorship

This article did not receive any specific grant from funding agencies in the public, commercial or not for profit sectors.

Conflict of Interest

There are no conflicts of interest.

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