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Efficacy of Cinacalcet for the Treatment of Secondary Hyperparathyroidism in CKD Patients on Peritoneal or Hemo Dialysis: *The Middle-East Experience*

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Abstract

Background: Management of secondary hyperparathyroidism is challenging with traditional therapy. The calcimimetic cinacalcet hydrochloride acts on the calcium-sensing receptors to increase its sensitivity to calcium, thereby reducing parathyroid hormone (PTH) secretion. Calcimimetics lower parathyroid hormone levels without increasing calcium and phosphorus levels.

Aim: To evaluate effectiveness of cinacalcet hydrochloride in reducing serum intact PTH levels in patients with end stage renal diseases and secondary hyperparathyroidism.

Material methods: The study included patients who were receiving regular dialysis and had inadequately controlled secondary hyperparathyroidism despite standard treatment (calcium based phosphorus binders and/or sevlamer carbonate at ceiling doses with or without vitamin D sterols - 1,25(OH)2-vitamin D). They were assigned to receive cinacalcet (Group I, n= 69; 45 on hemodialysis and 24 on peritoneal dialysis) or their usual drugs without cinacalcet (Group II, n= 40; 20 on hemodialysis and 20 on peritoneal dialysis) for 12 months. Once-daily doses of cinacalcet hydrochloride was increased from 30 mg to 180 mg to achieve intact parathyroid hormone levels of < 300 pg/ml. Serum calcium, phosphorous and iPTH were monitored before starting cinacalcet, at 3 months, 6 months and 12 months.

Results: Overall the mean intact PTH before start of therapy was 1086 ± 84.52 pg/ml (cinacalcet-group I) and 644.9 ± 86.58 pg/ml (no-cinacalcet group II) [p= 0.60]. At the end of the study these levels changed to 465.1± 46.51 pg/ml and 914± 173.6 pg/ ml respectively [p=0.01]. Serum calcium at 12 months was higher in the cinacalcet group compared to controls. Serum phosphorus was higher in the cinacalcet group at the start of therapy and persisted to remain so till end of study at 12 months

Conclusion: Cinacalcet effectively lowers parathyroid hormone levels in patients receiving dialysis and having uncontrolled secondary hyperparathyroidism. Frequent monitoring and adequate replacement with calcium and vitamin D sterols prevent hypocalcemia with cinacalcet therapy. Thus, cinacalcet is a goad therapeutic option for controlling secondary hyperparathyroidism in end-stage renal disease patients on both hemo and peritoneal dialysis.

Introduction

Secondary hyperparathyroidism (SHPT) develops very early in chronic kidney disease (CKD) and is most severe in dialysis patients [1,2] with varied manifestations of bone mineral metabolism, anemia, extra-osseous calcification and cardiovascular mortality [3-5]. There are multiple mechanisms involved in this process, including parathyroid hyperplasia with increased synthesis and secretion of parathyroid hormone mainly due to disturbances of calcium, phosphorus and Vitamin D metabolism [5-7]. In addition recent data suggests that fibroblast growth factor-23 (FGF-23), a bone derived phosphaturic hormone plays a central role in the pathogenesis of SHPT [8,9].

Conventional management of SHPT [10] includes the provision of active vitamin D derivatives and phosphorus binders (Ca and non–Ca-based). However, these measures fail to acheive the targets recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines [11,12] and Kidney Disease Improving Global Outcomes (K-DIGO) guidelines [13].,12).

Parathyroid secretion is controlled by the calcium-sensing receptor (CaSR) which is a G-protein coupled, transmembrane receptor that responds to changes in Ca2+ levels - increased secretion of intact parathyroid hormone (iPTH) when serum calcium is low (CaSR not stimulated) or decreased iPTH secretion when serum calcium is elevated (CaSR activated) [14,15]. Calcimimetic compounds activate the CaSR and decrease iPTH secretion by either potentiating (cinacalcet) or mimicking (spermine) inhibitory effects of extracellular calcium on parathyroid cells [16,17]. Currently, Cinacalcet is approved by US-FDA and European medicines agency for treatment of secondary HPT in CKD-5D and parathyroid carcinoma [18].

Safety and efficacy of the calcimimetic cinacalcet has been evaluated in many randomized, and controlled trials which showed that the cinacalcet significantly reduces iPTH in patients with CKD on dialysis (CKD-5D) versus control [19,20].Among these studies only few have studied the efficacy of cinacalcet in PD patients with secondary HPT

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including those by Lindberg et al. [20] and Urena et al. [21] who showed that Cinacalcet had comparable efficacy in HD and PD patients; 50% of PD patients achieved a mean iPTH ≤300 those studies.

Although numerous studies pertaining to the efficacy of cinacalcet in HD patients have been reported from USA, Europe, Japan and Korea, only a few studies pertaining to its efficacy has been reported in the dialysis population of the Middle-East and that too only in HD patients [22]. The present study was conceived to assess the effectiveness of cinacalcet hydrochloride in the management of secondary hyperparathyroidism in ESRD patients on hemo- and peritoneal dialysis in this region.

Material Methods

The study was carried out in the King Fahd Teaching Hospital of University of Dammam over a period of 1 year (Jan. to Dec., 2010). It included adults aged ≥ 18 years, on either thrice week hemodialysis or automated peritoneal dialysis with an iPTH>300 pg/ml (at least 3 readings over 3 weeks) and serum calcium level ≥ 8.0 mg/dl at 1 week prior to the cinacalcet administration. Exclusion criteria were parathyroidectomy within 24 weeks prior to the treatment, percutaneous ethanol injection therapy (PEIT) into the parathyroid gland, severe impairment of hepatic function; severe hypertension; uncontrolled diabetes mellitus; cancer; severe infection and advanced cardiac failure as well as use of any cytochrome P 450 inhibitors or inducers.

The study was initially planned as an open label study (n=109) to evaluate effectiveness of cinacalcet hydrochloride in the treatment of secondary hyperthyroidism. However, forty patients (36.69%) refused to consent and 69 (63.31%) including 45 on hemodialysis and 24 on peritoneal dialysis patients consented for cinacalcet hydrochloride administration. Forty patients (20 on hemo and 20 on peritoneal dialysis) acted as control. The study was conducted in accordance with the principles originating in the Declaration of Helsinki. Written and informed consent for cinacalcet administration was obtained in 69 patients and all 109 patients consented for regular follow up and investigation as per protocol.

Intervention

Oral cinacalcet hydrochloride was initiated at 30 mg/day. The treatment phase was for 48 weeks. The dose of cinacalcet was increased every 2 weeks sequentially as 60, 90, 120 mg to maximum of 180 mg/day if iPTH was > 300-pg/ml and serum calcium was ≥ 8.0 mg%. Patients with serum calcium <8.0 mg% were managed with increasing dose of calcium carbonate with or without Vitamin D (1,25(OH)2-vitamin D, Calcitiol). Primary endpoint was proportion of randomised patients with a serum iPTH of ≤ 300 pg/ml. secondary end points were percentage change in serum iPTH, calcium and phosphorus.

Safety Measures

Laboratory measures (iPTH, serum calcium, serum phosphorus and serum alkaline phosphatase (ALKP values) were determined from blood samples that were collected before dialysis and daily dose of cinacalcet hydrochloride at study visits starting from 1st week till the end of study at 12 months every 2 weeks.

Biochemical measurements were carried out at the University Hospital biochemistry department. Quantitative determinations of Parathyroid hormone was made in Immulite 2000 using chemiluminescent Immunoassay.

Statistical Analysis

The baseline biochemical parameters and patients details were noted during the initial screening period. Mean serum calcium, phosphorus, iPTH and serum alkaline phosphatase were calculated and recorded 5 times (initial, 3 months, 6 months, 9 months and at 12 months). Results were expressed as mean± SD or mean± SE as indicated. Unpaired "T" test was used to compare mean between the two groups and paired T test was used to compare mean serum calcium, phosphorus, iPTH and alkaline phosphatase (ALKP) at baseline and 12 months in both cinacalcet and control group, and p value <0.05 was considered significant. Statistical calculation was made using "Graph pad prism 5" software.

Results

The baseline characteristics of patients are depicted in table 1. Total of 109 patients with end stage renal disease on either peritoneal or hemodialysis were enrolled into the study with 69 (63.31%) identified (after consent) for cinacalcet administration and 40 (36.69%) to serve as as control. Fifty eight (84.05%) patients were on calcium carbonate and 50 (72.46%) were on sevlamer carbonate in the cinacalcet group. Eight patients (11.5%) in the cinacalcet group did not receive vitamin D sterols due to hypercalcemia, hyperphosphatemia or both. All patients in the control group received calcium carbonate, sevlamer carbonate and vitamin D sterols (Table 1). There were no significant differences in age, sex, and duration on dialysis between the two groups.

The biochemical parameters at baseline and at 12 months are shown in table 2. Baseline serum calcium and iPTH were comparable between cinacalcet and control group. However, baseline serum phosphorus was higher in cinacalcet group. Serum iPTH was significantly lower in patients on cinacalcet vs. control group (Figure 1) at the end of 12 months (p<0.05) whereas in the control group there was an increase in serum iPTH (p=0.056) (Table 2). The serum calcium and phosphorus was significantly higher (Figure 2, 3) in the cinacalcet vs. the control group. Serum ALKP at baseline was significantly higher in the cinacalcet group vs. controls and persisted to remain so at the end of 12 months (Figure 4). Serum calcium increased significantly from baseline in patients receiving cinacalcet (p=0.001) compared to control group (p=0.07).

Primary end points were achieved in 29(42.02%) patients in cinacalcet group and 11 (27.5%) in control group. Serum iPTH reduced

	Cinacalcet group (n=69)		Control group (n=40)	
	HD (n=45)	PD (n=24)	HD (n=20)	PD (n=20)
Age (years)	44.67±2.32	42.04±3.99	56.50±3.87	51.85±4.69
Duration of dialysis (months)	70.16±6.63	36.63±5.58	73.8±6.7	39.38±4.93
Therapy details				
Calcium carbonate	43 (95.5%)	15 (62.5%)	40(100%)	
Sevlamer carbonate	39 (86.6%)	11 (45.8%)	40(100%)	
Vitamin D sterols				
Baseline	18 (40%)	11 (45%)	36 (90%)	
At end of therapy	45 (100%)	16 (66.6%)	40(100%)	

Table 1: Baseline characteristics of patients in cinacalcet and control group.

by 57.16% at 12 months of therapy in cinacalcet group vs. 41.75% rise in the control group. The sequential decrease in iPTH with cinacalcet therapy is depicted in figure 1. Serum calcium increased by 6.59% in cinacalcet group and by 3.95% in the control group. Serum phosphorus decreased by 6.01% in the cinacalcet group and 4.21% in the control group. Serum alkaline phosphatase increased by 4.73% in the cinacalcet group and 9.10% in control group (p=0.016).

No major adverse events were recorded during the study period. However, six patients (8.7%) developed asymptomatic hypocalcemia (<8.5 mg%) at one year of therapy with cinacalcet hydrochloride.

	Cinacalcet group (n=69)	Control (n=40)	"p" value
PTH (pg/ml)			
Baseline			
Mean±SD	1086 ± 84.52[a]	644.9 ± 86.58[c]	0.60
Median(Range)	950 (104-3805)	530 (52-2764)	
12 months			
Mean±SD	465.1 ± 46.51[b]	914.2±173.6[d]	0.01
Median(Range)	504 (88-2000)	435 (44-440)	
Sr Calcium(mg/dl)			
Baseline	8.35 ± 0.95[e]	8.16 ± 0.84[g]	0.28
12 months	8.89 ± 0.81[f]	8.48 ± 0.89[h]	0.01
Sr Phosphorus(mg/dl)			
Baseline	5.51 ± 1.58[i]	4.75 ± 1.7[k]	0.02
12 months	5.18 ± 1.58[j]	4.57±1.4[l]	0.04
ALKP (IU/ml)			
Baseline			
Mean±SD	305.3 ± 30.46[m]	165.2±29.32[o]	0.002
Median(Range)	218 (16-1326)	112 (65-941)	
12 months			
Mean±SD	319.8±40.30[n]	180.2±27.45[p]	0.016
Median(Range)	221(68-2351)	122 (56-942)	

a*b (<0.0001) c*d (0.056) e*f (0.001) (g*h, i*j, k*l,m*n,o*p>0.05)

Table 2: Biochemical parameters at baseline and at 12 months in both the groups.

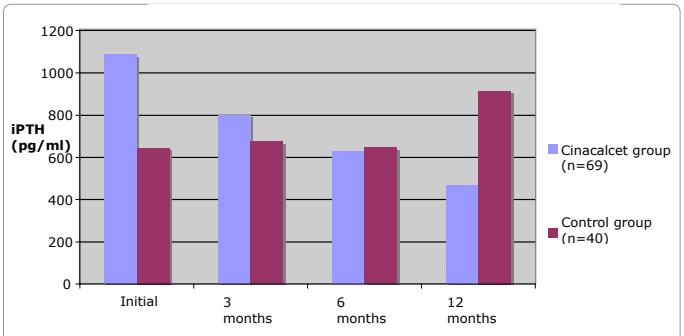

Figure 1: Comparison of iPTH between cinacalcet and control grouop.

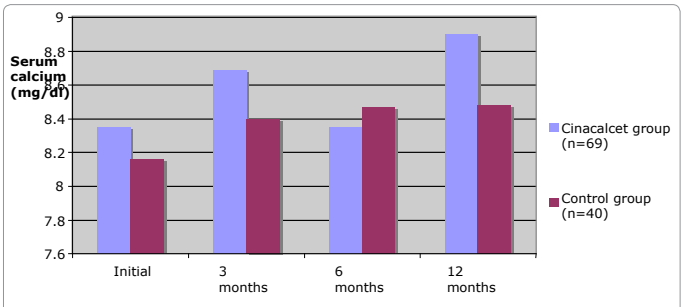

Figure 2: Comparison of serum calcium between cinacalcet and control group.

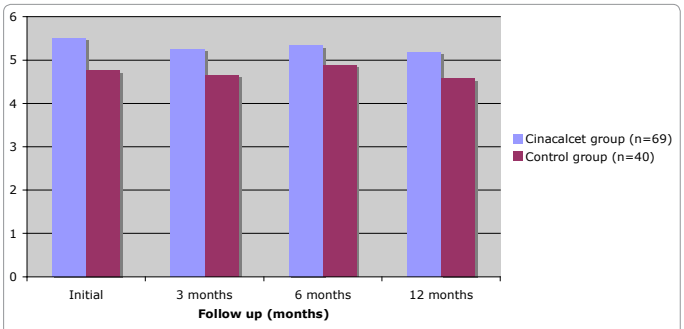

Figure 3: Comparison of serum phosphorous between cinacalcet and control group.

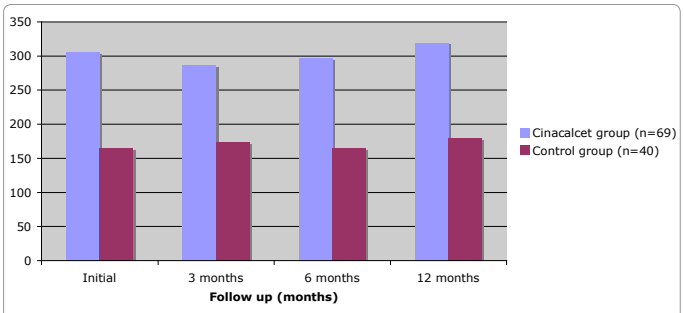

Figure 4: Comparison of serum Alkaline phosphatase between cinacalcet and control group.

Discussion

Our results show that cinacalcet hydrochloride significantly reduces the intact PTH levels at the end of 12 months in patients receiving hemo and peritoneal dialysis. All the patients in the non-cinacalcet group were not able to control their intact PTH levels inspite being on phosphorus binders and calcitriol at maximum doses. There was a significant increase in serum calcium levels in the cinacalcet group.

There have been numerous studies which have shown reduction of serum intact PTH with cinacalcet in patients on hemodialysis [19-23]. In the first large randomised controlled study (RCT) with 741 patients on maintenance dialysis and secondary HPT, Geofry et al in 2004 concluded that cinacalcet significantly reduces iPTH in patients with CKD-5D versus control [19]. More than 90% of the included patients were treated with a phosphorus binder and two-thirds with an active vitamin D sterol. In comparison to placebo, treatment with cinacalcet was more effective in lowering serum PTH (cinacalcet, –43% vs. placebo, +9% P < 0·001), serum calcium (–6·8% vs. +0·4%, P < 0·001) and serum phosphorus (cinacalcet , –8·4% vs. placebo, +0·2%, P < 0·001). Cardiovascular hospitalization was significantly decreased in cinacalcet group vs. placebo. However, there was no mortality benefit of difference in all cause hospitalization [19]. Another randomised trial to evaluate the effect of cinacalcet hydrochloride to control secondary hyperparathyroidism in Japanese patients, concluded that target iPTH (<250 pg/ml) was achieved in 51.4% in cinacalcet group vs. 2.8% in the control group [23]. The results of our study were similar to above mentioned studies.

Vitamin D sterols (calcitriol/ alphacalcidol) effectively reduced intact PTH levels but caused hypercalcemia and hyperphosphatemia as a result of increased calcium and phosphorous absorption from

gastrointestinal tract [24]. Thus, hypercalcemia and hyperphosphatemia would be a contraindication for use of vitamin D sterols and thus, in our study vitamin D sterols were withheld in 11.5% of cases in cinacalcet group. However, cinacalcet reduces intact PTH levels without causing hypercalcemia and hyperphosphatemia [19,20,23]. Cinacalcet reduces serum calcium and phosphorous levels along with decrease in intact PTH. To evaluate the efficacy of cinacalcet to reduce intact PTH on patients on dialysis, Geoffrey et al. [19] observed reduction in calcium and phosphorus by 6.8% and 8.4% respectively. While assessing the effect of cinacalcet to reduce iPTH in Japanese dialysis dependent patients, Fukagawa et al observed significant reduction in serum calcium and phosphorus in the cinacalcet group [23]. In the present study, serum calcium and phosphorus levels significantly increased after cinacalcet introduction. This effect could be due to replenishment of calcium with calcium carbonate and vitamin D sterols when there was a reducing trend in serum calcium even within normal range in the cinacalcet group, whereas such approach was not used in the control group. Serum ALKP was high even at end of study in cinacalcet group compared to baseline (p=0.58) inspite of reduction serum iPTH levels. The exact cause for above is not clear. Osteomalacia might contribute to raise serum ALKP persisting at end of 12 months as forty patients (58%) patients in the cinacalcet group did not receive calcitriol/ vitamin D receptor agonist at baseline compared to only 10% in the control group (Table 1). However, wide range in the serum ALKP levels at baseline and at 12 months could have affected analysis and will require larger patient population and bone biopsy to exactly find out the cause of elevated ALKP inspite of reduction in PTH levels.

Use of cinacalcet is thus equally efficacious in patients on hemo and peritoneal dialysis with severe SHPT. This has also been amply demonstrated in the phase 3; multicenter, randomized, placebo-controlled, double-blind study which evaluated the efficacy and safety of cinacalcet in hemodialysis (HD) and peritoneal dialysis (PD) patients with PTH ≥300 pg/ml despite traditional therapy [20]. This study further demonstrated that cinacalcet is effective regardless of the modality of dialysis. A similar response was observed in patients who were treated with PD and HD; 65% of patients in both groups experienced ≥30% reductions in iPTH levels with cinacalcet therapy. Similar efficacy in PD patients was demonstrated by Urena et al. [21].

Traditional therapies for SHPT are limited by their side effects including higher risk for vascular calcification because of the Vitamin D (calcitriol) induced hypercalcemia (up to 44%) and hyperphosphatemia (up to 65%) because of increased intestinal reabsorption of these minerals (facilitation by Vitamin D) and consequent elevated Ca X P product (> 55 mg/dl). Poor control of mineral metabolism is also associated with a higher risk for calcification of the coronary arteries and aorta, increased arterial stiffness, cardiac valve calcification and death [5,8,24,25]. Raggi et al documented that hemodialysis patients with moderate to severe SHPT cinacalcet plus low-dose vitamin D sterols displayed attenuated vascular and cardiac valve calcification compared with those on flexible vitamin D therapy [26].

In the pathogenesis of ESRD and SHPT, serum fibroblast growth factor-23 (FGF23) levels are elevated and have been independently associated with adverse outcomes [8]. In addition, use of calcitriol analogs is associated with increased serum FGF23 levels in humans with ESRD [9], consistent with observations that calcitriol increases FGF23 gene transcription. Cinacalcet plus low-dose calcitriol on the other hand have recently been shown to lower FGF23 levels compared with a treatment regimen using calcitriol analogs alone in ESRD patients [27,28].

Our study had certain limitations. The study was not a double blind randomised control study and the study sample was small in number. The study finally concludes that in our population also cinacalcet hydrochloride is effective in reducing raised iPTH in patients on dialysis (both hemo- and peritoneal) and secondary hyperparathyroidism, which are refractory to phosphorus binders and vitamin D sterols. Hypocalcemia is not a side effect of cinacalcet hydrochloride therapy if frequently monitored and adequately substituted.

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