Efficacy of Cinacalcet in the Treatment of Secondary Hyperparathyroidism in the End Stage Renal Disease Patients on Hemodialysis Therapy

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ABSTRACT

Background: Chronic renal disease is associated with intrinsic abnormalities in parathyroid gland function, in addition to those caused by hypocalcaemia, low level of calcitriol and skeletal resistance to the actions of parathyroid hormone. In dialysis patients, cinacalcet results in significant fall in parathyroid hormone levels and can facilitate the control of hyperparathyroidism.

Objectives: To evaluate the efficacy of cinacalcet in patients with secondary hyperparathyroidism and end stage renal disease on hemodialysis.

Methods: This prospective study was performed in Imamain Al-Kadhimian teaching hospital in dialysis unit during the period from June 2018 to February 2019. Fifty patients complaining of secondary hyperparathyroidism and end stage renal disease on hemodialysis were involved in this study and all patients taken cinacalcet tablets for a period of six months (24 weeks).

Results: Cinacalcet made a significant reduction in serum parathyroid hormone, phosphorus and alkaline phosphatase while the serum calcium levels remained unchanged. The mean serum levels of intact parathyroid hormone, phosphorus, calcium, and alkaline phosphatase after six months of cinacalcet treatment were 278 ± 98 mg/ml, 4.5 ± 0.91 mg/dl, 8.8 ± 0.29 mg/dl, and 117 ± 58 IU/l, respectively.

Conclusions: Cinacalcet results in significant fall in parathyroid hormone levels and can facilitate the control of hyperparathyroidism.

Keywords: Chronic kidney disease, End-stage renal disease, Parathyroid hormone.

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Chronic renal disease (CKD) is associated with intrinsic abnormalities in parathyroid gland function, in addition to those caused by hypocalcaemia, low level of calcitriol and skeletal resistance to the actions of parathyroid hormone (PTH). Parathyroid hyperplasia is an early finding within few days after the induction of CKD and can be prevented by dietary phosphate restriction or by the use calcimmietic agents. Cinacalcet HCl is a calcimimetic agent that binds the calcium-sensing receptor (CaR) of the parathyroid gland, leading to suppressing secretion of PTH[(1)]

Cinacalcet acts by allosterically modifying the CaR, increasing the sensitivity of the CaR to extracellular calcium and, thus, doing a suppressive effect on PTH secretion[(2)].

In contrast with vitamin D, when using cinacalcet the decreasing in PTH secretion has been associated by simultaneous suppressing of the calcium x phosphorus product (Ca × P), serum calcium, and phosphorus[(3)].

Decreased persistence, adherence and/or compliance with oral medications are a prevalent problem, especially in CKD patients, the non-adherence rates reported of 3-80%. Non-adherence was accompanied with increased mortality in the dialysis population[(4)]. Standard therapy for secondary hyperparathyroidism includes dietary phosphorus limitation, phosphate-binding agents, calcium supplementation and treatment with calcitriol and other active vitamin D sterols. These therapies have major effects directly or indirectly on serum levels of calcium and phosphorus, and their use must be observed closely[(5)]. In spite of

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the introduction of new drugs over the past decade, like calcium-free phosphate binders and newer vitamin D sterols, a significant portion of patient's routinely receiving dialysis have unacceptably high plasma PTH levels, hyperphosphatemia, marked hypercalcemia and elevated Ca x P product levels[6].

The recommended starting oral dose of cinacalcet is 30 mg once daily. Serum calcium and serum phosphorus should be monitored within one week and intact parathyroid hormone (iPTH) should be monitored one to four weeks after initiation or dose adjustment of cinacalcet. Cinacalcet should be titrated no more frequently than every two to four weeks through sequential doses of 30, 60, 90, 120, and 180 mg once daily to target iPTH levels of 150 to 300 pg/ml. Serum iPTH levels should be measured no earlier than 12 hours after dosing with cinacalcet[7]. Calcimimetics decrease the secretion of PTH by increasing the sensitivity of the calcium receptors (CaR) of parathyroid cells to extracellular ionized calcium to lower circulating PTH levels within 1 to 2 h of administration and consequently reducing serum calcium and phosphorus[5]. Cinacalcet can be used alone or in combination with vitamin D sterols and/or phosphate binders. During dose titration, serum calcium levels should be measured frequently and if levels reduce below the normal range, appropriate steps should be taken to elevate serum calcium levels, such by initiating or increasing the dose of calcium-based phosphate binder, providing supplemental calcium, initiating or increasing the dose of vitamin D sterols, or temporarily withholding treatment with cinacalcet [8]. Cinacalcet tablets are formulated as light-green, film-coated, oval-shaped tablets marked with "AMG" on one side and "30" or "60" or "90" on the opposite side of the 30 mg, 60 mg, or 90 mg strengths, respectively[1].

The aim of this study is the assessment of effectiveness of cinacalcet drug on secondary hyperparathyroidism and end-stage renal disease (ESRD) on hemodialysis.

Methods

This prospective observational study, (cohort study) was performed in Al-Imamain Al-Kadhimian teaching hospital, in dialysis unit during the period of (June 2018 to February 2019).

Inclusion criteria: Adult patients aged 18-65 years with ESRD with duration of dialysis of more than 6 months and on constant dialysis program.

Exclusion criteria: Active malignancy and patients allergic to any of the study medications.

Fifty patients (29 females and 21 males) involved in this study of different age groups ranging from (20 to 65) years complaining of end stage renal failure (ESRD) on regular hemodialysis. The normal range of iPTH in patient with CKD on hemodialysis was 150-300 Pg/ml and the target ≤ 500 Pg/ml[9]. The dose of cinacalcet ranged from 30 to 180 mg and was titrated against monthly PTH, Ca/P values. Cinacalcet was allowed to be increased by 30 mg steps every 15 days to a maximal dose of 180 mg per day[10]. The drug was reduced or withdrawn if iPTH levels dropped below 300 pg/ml, if serum Ca decreased below 8 mg/dl, or if any adverse events appeared like hypocalcemia, seizure and worsening heart failure.

All patients underwent history taking and physical examination, a pre-formed questionnaire was used to get information from studied population, which included demographic parameters (age and sex), clinical parameters (duration and virology on HD) and laboratory parameters (serum iPTH, calcium, phosphorus, bicarbonate and alkaline phosphatase) from the patients on hemodialysis.

Blood samples were collected, these samples were sent to the dialysis laboratory for analysis and measured in the same months. Each patient subjected to hemodialysis for period of 4 hours in two or three sessions per week using GAMBRO

AK95S hemodialysis apparatus with polyfluxTML dialyzer membrane with effective surface area range from 1.4 to 2.1 m^2, and flow rate ranging from 250 to 300 ml/min. the dialysate Ca 1.25 mmol/L. All patients taken phosphate binders in form calcium carbonate tabs, sevelmer tabs, active vitamin D (one Alfa tabs) and vitamin D supplements. Patients on hemodialysis were required to have dialysis adequacy (Kt/v) of 1.2 or more.

Measurement of serum intact parathyroid hormone PTH by Cobas e4 11 and measurement of calcium, phosphorus, alkaline phosphatase by spectrometer method. These assays were done by Cobas C1, 11 Roche.

The patients will be informed about the study purpose and its relevance and their verbal consent will be taken to conduct the study.

——————————Results

This study had included 50 patients who had been interviewed in in Al-Imamain Al-Kadhimian teaching hospital, in dialysis unit centers of nephrology

The demographic and clinical characteristics of the studied cases were shown the following findings: The mean age of them was 51.6 ±13.8 years, ranging between 20 and 65 years. Regarding the sex distribution of the sample, it seemed that the percentage of women was higher than men, 58% vs. 42% respectively. Of the patients studied, 46% were hepatitis negative with 54% hepatitis positive patients from them 40% hepatitis C and10% hepatitis B the rest were having hepatitis C with B, (Table 1).

All patients received vitamin D sterol and number of patients who received sevelamir carbonate tab (800-2400 mg) was 42 and patients who received calcium carbonate tab (500-2000 mg) was 43 and started cinacalcet after measurement of serum intact PTH and number of patients who received cinacalcet tab (30-90 mg) was 50.

The causes of chronic kidney diseases forty-two (48%) patients had diabetic nephropathy and most patients were on thrice a week hemodialysis, (Figure 1).

Compared to baseline values, the mean iPTH in subjects receiving post hemodialysis (3 weeks) cinacalcet was 755 ± 182 pg/ml, 494 ± 138 pg/ml and 278± 98 pg/ml at baseline, 3 months and 6 months, respectively. Using one sample t-test; iPTH values were statistically different ($p \leq 0.01$). At the end of the 6 months study period, serum calcium was comparable to baseline mean 8.8 ± 0.29 mg/dl vs. 8.9 ± 0.48 mg/dl, respectively were statistically not different ($p \leq 0.08$). Alkaline phosphatase, however, showed significant difference at the end of study compared to baseline values (mean117 ± 58IU/L vs. 308 ± 82 IU/L, respectively), $p \leq 0.01$. The level of circulating alkaline phosphatase offer an approximate index of osteoblast activity in patients with CKD. Higher levels are commonly present in hyperparathyroidism bone disease. On the other hand, serum phosphate levels during the study period in the HD patients differed significantly (mean 4.5 ± 0.91 mg/dl vs. 6.5 ± 1.19 mg/dl at 6 months and baseline, respectively) $p \leq 0.03$, (Table 2).

The percentage of reduction of iPTH, serum phosphate, and alkaline phosphatase after 3 months was 35, 14 and 10%, respectively. After 6 months, the reduction percentage was increased 44, 20 and 58%, respectively, (Table 3).

The analyzed data showed that there were 48% of the collected sample expressed drug related adverse effects and symptomatic hypocalcemia was not observed, (Table 4).

Table 1: Baseline demographics and characteristics of the patients.

Variable		Number of patients	%
Sex	Male	21	42
	Female	29	58
Virology screen	Hepatitis C positive	20	40
	Hepatitis B positive	5	10
	Hepatitis C&B positive	2	4
	Hepatitis negative	23	46
Duration of hemodialysis	6 months-1 year	4	8
	1-3 years	8	16
	3-6 years	24	48
	6-9 years	14	28

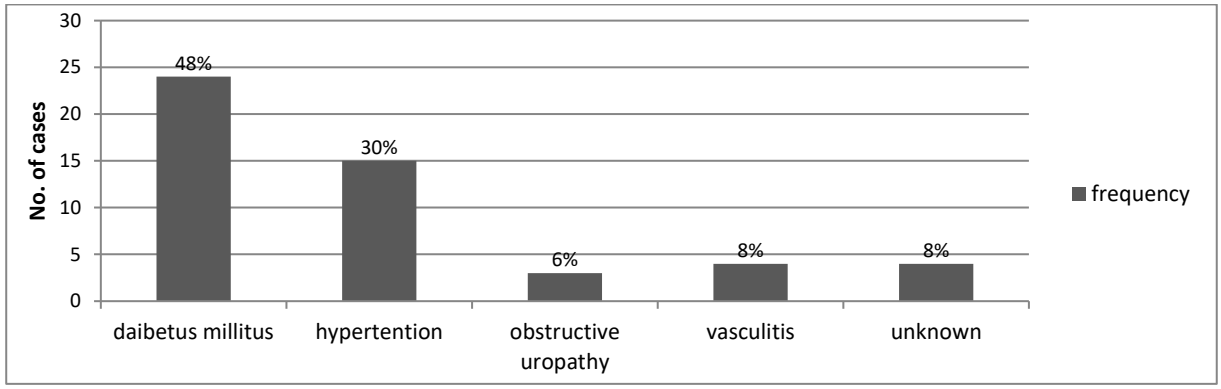

Figure 1: Causes of renal failure.

Table 2: Comparison of serum calcium, phosphorous and ALKP at baseline and throughout the study period.

	Baseline (Mean ± SD)	3 months (Mean ± SD)	6 months (Mean ± SD)	P value
PTH (pg/ml)	755 ± 182	494 ± 138	278± 98	0.01
Serum Calcium (mg/dl)	8.9 ± 0.48	8.5 ± 0.44	8.8 ± 0.29	0.08
Serum phosphate (mg/dl)	6.5 ± 1.19	5.6 ± 1.06	4.5 ± 0.91	0.03
Alkaline phosphatase (IU/L)	308 ± 82	276 ± 65	117 ± 58	0.01

Table 3: Percentage of reduction of iPTH, phosphorous and ALKP at baseline and throughout the study period.

	3 months	**6 months**
iPTH	35%	44%
Serum phosphate	14%	20%
ALKP	10%	58%

Table 4: Adverse reaction to cinacalcet.

Event	Number of patients (%)
Nausea and vomiting	8 (16)
Diarrhea	7 (14)
Myalgia	5 (10)
Stomach discomfort	2 (4)
Dizziness	2 (4)

Discussion

Management of secondary hyperparathyroidism is one of the challenging aspects of caring for a patient with chronic kidney disease. The safety and efficacy of cinacalcet for the control of secondary hyperparathyroidism in chronic kidney disease actually being revaluated in lieu of recent studies questioning its overall tolerance and efficacy[11].

The current study reported that females (58%) higher than males (42%). This result was similar to a study conducted by Al-hilali et al in Saudi Arabia (2011)[12] which showed 66.7% females versus 33.3% males.

In this study we found that the most common causes of renal failure were diabetes mellitus (48%) and hypertension (30%), this result was similar to studies conducted by Al-hilali et al. (2011) and Al-hwiesh et al. (2013) in Saudi Arabia which found that diabetes (44.4%), (44.8%) respectively[12,13].

Usually, cinacalcet is started at a dose of 30 mg/day, with stepwise increments to 60, 90 and 180 mg/day.

The patients included in the current study had persistently high serum iPTH levels despite conventional therapy with calcium, vitamin D sterols and phosphate binders.

Our results showed that the treatment of hemodialysis patients having severe secondary hyperparathyroidism with cinacalcet, was efficacious and well tolerated.

Significant reduction of serum iPTH, phosphate and alkaline phosphatase to the target levels was achieved and the percentage of reduction was increased (44, 20, 58%) respectively after six months duration. Serum calcium was not significantly changed with cinacalcet after the same period of the study.

Other studies by Al-hilali et al. (2011), Al-saran et al (2010) in Saudi Arabia[12,14] and Shigematsu et al in Japan (2009)[15]. They found that the mean serum iPTH and phosphate were lowered and reach the target after receiving cinacalcet.

Our study disagreed with Torun et al in Tukey(2016)[16] and Simo et al. in Spain (2015)[17] which found that cinacalcet treatment did not show any significant improvement in the serum levels of phosphate, and PTH levels and statistically significant changes only in serum calcium values in hemodialytic patients with secondary hyperparathyroidism.

Many medications have side effects that can participate to their irregular consumption. The GIT side effects of calcimimetics are widely known[18]. In our study, the most common side effects were nausea, vomiting (16%) and diarrhea (14%). These findings are in agreement with result conducted by Simo et al. in Spain (2015) who found the most common side effects are nausea (21-43%) and vomiting (13-30%)[17].

In conclusions; In dialysis patient, cinacalcet levels results in significant fall in PTH and can facilitate the control of hyperparathyroidism and help achieving guideline targets for calcium, phosphate, and iPTH. Our study in spite of inadequate sample size demonstrated the stability of frequent monitoring and adequate replacement with calcium and vitamin D sterols prevent hypocalcaemia with cinacalcet therapy, none of the patients cinacalcet had to be discontinued due to

symptomatic hypocalcaemia. Generally, the drug was well tolerated with fewer gastrointestinal effects and a higher level of satisfaction.

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