

## Intermittent Dosing of Cinacalcet is also Effective in Treating Secondary Hyperparathyroidism in Hemodialysis Patients

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### Abstract

**Background:** The calcimimetic, cinacalcet hydrochloride acting on the calcium-sensing receptors is being used quite often in the management of secondary hyperparathyroidism (SHPT). It is given in daily dose of 30-180 mg but there have not been enough comparative trials with intermittent dosing schedule.

**Aim:** To evaluate effectiveness of daily cinacalcet hydrochloride dose and its 3 weekly doses in reducing serum intact PTH levels and relative concentrations of calcium and phosphorous in patients with end stage renal diseases (ESRD) with SHPT on maintenance hemodialysis (HD).

**Material and methods:** Chronic kidney disease (CKD) patients (n=29) who were receiving daily dose (OD) of cinacalcet for SHPT for 1 year were shifted to an intermittent dosing regimen of cinacalcet at the end of each hemodialysis session (HD), 3 times per week (study patients). After taking baseline measurements of PTH, its monthly assessment along with serum calcium, phosphorous and alkaline phosphatase level estimations at 1, 3, 6, 9 and 12 months were then compared with the baseline levels.

**Results:** Overall the mean intact PTH value was 174.2 ± 16.8 pg/ml at the end of one year treatment prior to the study, while receiving a mean dose of 83.7 ± 11 mg cinacalcet OD. This controlled value of PTH did not show any statistically significant difference over the next 12 months when the study patients were given intermittent dosing (3/week) at the end of each hemodialysis session. Similarly the calcium values did not change to a significant level in the study subjects, although the serum phosphorus showed a significant rise at the end of the study period (p=0.003).

**Conclusion:** Cinacalcet effectively controls parathyroid hormone levels and uncontrolled secondary hyperparathyroidism both when given daily and intermittently (3/week). Frequent monitoring and adequate replacement with calcium and vitamin D sterols prevent hypocalcemia with cinacalcet therapy. Thus intermittent dosing of cinacalcet is an excellent cost-effective therapeutic option in HD patients with SHPT. In addition, it improves drug compliance.

**Keywords:** SHPT; PTH; Calcium; Phosphorous; ESRD; Hemodialysis; Cinacalcet

### Introduction

Bone mineral disorder in chronic kidney disease (CKD-MBD) is one of the most common metabolic complications with diverse clinical manifestations and serious impact on the morbidity and mortality of the entire spectrum of CKD population [1,2]. Contrary to the popular belief, mineral abnormalities are fairly common even in early stages of CKD itself. Serum phosphorous starts rising even with GFR < 60 ml/min and low calcitriol values are seen in 13% of those with eGFR >80 ml/min, and in 60% of those with eGFR <30 ml/min. A PTH value of > 65 pg/dl occurred in 12% of patients with eGFR >80 ml/min with progressive increase as eGFR declines [3].

The conventional therapeutic options include dietary phosphate restriction, use of calcium and non-calcium based phosphate binders, supplementation with calcitriol, all of which targets normalization of Ca/P/Vitamin D axis and as a consequence PTH levels [4]. The other approach includes the use of a novel calcimimetic drug, which actually bypasses the physiological control system and directly stimulates the calcium sensing receptor (Ca-SR) allosterically and decreases its threshold of suppression of PTH by serum calcium [5,6]. This Ca-Sensing receptor stimulator (cinacalcet) was approved for the treatment of secondary hyperparathyroidism (SHPT) by US Food and Drug Administration (USFDA) in 2004 [7].

The use of cinacalcet for the treatment of SHPT is easy and convenient. A daily dosing of cinacalcet effectively controls PTH

values in dialysis dependent patients with SHPT not managed with traditional therapy [8]. There is plenty of clinical evidence to support the effectiveness of cinacalcet in this situation. In the OPTIMA trial, about 70% of the patients receiving cinacalcet achieved the KDOQI targets for dialysis patients as compared to 22% of those receiving only conventional therapy (p<.001) [9,10]. The development of the calcimimetic cinacalcet has already changed the treatment of SHPT in renal patients. Its effectiveness on the control of PTH secretion, along with simultaneous reduction in calcium, phosphorus and calcium-phosphorus product, gives this agent an advantage over traditional therapies in all levels of severity of SHPT.

This breakthrough in the pharmacological management of SHPT has been corroborated in different population subgroup, including our previous study in the middle-east dialysis population, where once daily cinacalcet effectively decreased the PTH values in hemodialysis and peritoneal dialysis patients with SHPT [11].

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One of the most intriguing data from preclinical cinacalcet trial was the fact that one single dose of cinacalcet rapidly decreases PTH and serum calcium levels and the result is surprisingly sustained for a period of not less than 30 hours [1]. This indicates that cinacalcet can possibly be prescribed more infrequently without losing its effectiveness. Since cinacalcet in the immediate cost-benefit consideration is far more costly than the conventional phosphate binder and vitamin D based treatment of SHPT, less frequent dosing may actually improve the overall usage behavior in terms of cost and compliance. There is, however, very little clinical evidence supporting a different regimen for cinacalcet at present [12].

## Materials and Methods

This study is the extension of our previous study [11], and was conducted at King Fahd Hospital of the University, Al Khobar, Saudi Arabia after being approved by our Institutional Ethics Committee. The study was conducted according to the *Helsinki declaration* and carried out over a period of one year (June 2011 to May 2012). Twenty-nine prevalent hemodialysis dependent patients who were receiving cinacalcet on daily basis (OD) for more than one year agreed to participate in the study and signed an informed consent. Their last biochemical profile (that is at the beginning of the current study) was taken as a baseline. They were then shifted to a different cinacalcet regimen; i.e. three times/week under supervision. The dose was administered after each HD session. The dose of cinacalcet ranged from 30 mg 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. The drug was reduced or withdrawn if iPTH levels dropped below 150 pg/ml, if serum Ca decreased below 8.5 mg/dl, or if any adverse events appeared. Replenishment of calcium with calcium carbonate and Vitamin D sterols when there was a reducing trend in serum calcium even with normal range. The patients were followed-up with monthly iPTH, serum Ca, serum P and alkaline phosphatase (ALKP) levels and these values were then compared against the baseline levels. All the other previous medications including phosphate binders and Vitamin D3 were given at the same doses as before.

## Safety measures

Laboratory measures (iPTH, serum calcium, serum phosphorus and serum ALKP values) were determined from blood samples that were collected before dialysis and post-dialysis doses 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 determination of parathyroid hormone was made in Immulite 2000 using Chemiluminescent Immunoassay.

## Statistical analysis

It was done with IBM SPSS 20.0 software. Paired sample t-test was used to compare the daily cinacalcet (OD group) versus the three times a week cinacalcet (HD group). Results were expressed as mean  $\pm$  SD or median and interquartile range (IQR; 25<sup>th</sup> to 75<sup>th</sup> percentiles) 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 ALKP at baseline, at 6 and 12 months in the study population, and p value <0.05 was considered significant.

## Results

The baseline characteristics of patients are depicted in table 1. A

total of 29 patients with stable serum iPTH, calcium and phosphorous were enrolled in the study. The patients were shifted from daily to intermittent, post HD (3/week) cinacalcet dose. The mean age of the patients was  $51.6 \pm 4.7$  years, and 39.7% of them were females. As shown in table 1, the cause of ESRD was diabetic nephropathy in 44.8% of patients. The mean duration of dialysis was  $72.3 \pm 5.4$  months and the mean Kt/V was  $1.4 \pm 0.2$ . Throughout the study period 89.7%, 86.2% and 93% of patients were also treated with calcium carbonate, sevelamer carbonate and vitamin D sterols respectively. Post hemodialysis cinacalcet was introduced to the study subjects (HD) in a phased manner with a mean dose of  $83.7 \pm 11$  mg [median 60 (IQR 60-120) mg]. Patients with serum calcium less than 8.5 mg/dl were managed with increasing dose of calcium carbonate with or without vitamin D (1,25 (OH)<sub>2</sub>-vitamin D, calcitriol). All the patients were CKD stage V, and were prevalent patients undergoing hemodialysis. The comparative values of different parameters in the context of HD subjects throughout the study period are shown in table 2.

Compared to baseline values, the mean iPTH in subjects receiving post hemodialysis (3/week) cinacalcet was  $174.2 \pm 12.3$  pg/ml,  $170.4 \pm 21.6$  pg/ml and  $177.1 \pm 13.3$  pg/ml at baseline, 6 months and 12 months respectively. Using multiple paired t-test; iPTH values were not statistically different ( $p=0.316$ ) (Figure 1). At the end of the 12-months study period, serum calcium was comparable to baseline [mean  $8.95 \pm 0.61$  mg/dl vs.  $8.9 \pm 0.81$  mg/dl and median, 8.8 (IQR 8.7-9.2) mg/dl vs 8.85 mg/dl (IQR 8.76-9.1) respectively],  $p=0.285$  (Figure 2). Alkaline phosphatase, however, showed significant difference at the end of study compared to baseline values [mean  $158 \pm 18.1$  IU/L vs.

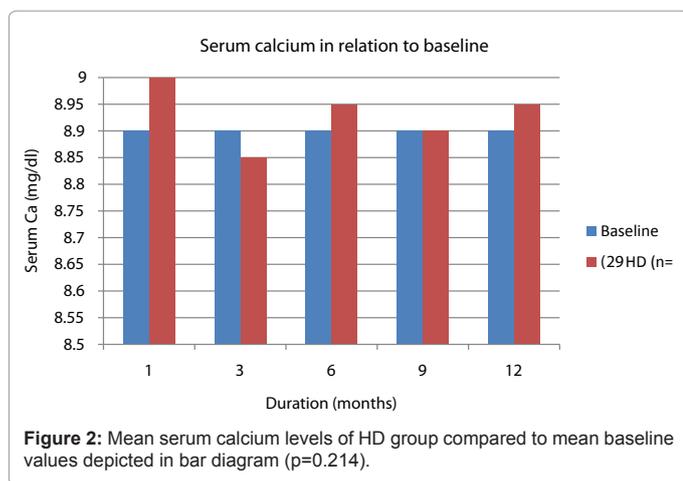
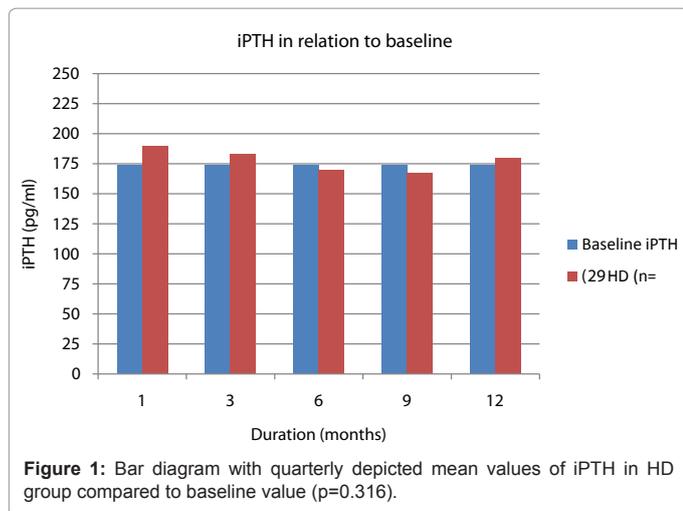
<b>Age, years</b>	
mean $\pm$ SD	45.8 $\pm$ 7.94
Median (IQR)	45 (39-52.5)
Female gender, n (%)	11 (37.9)
<b>Cause of ESRD, n (%)</b>	
Diabetes mellitus	13 (44.8)
Hypertensive renal disease	5 (17.2)
Chronic glomerulonephritis	5 (17.2)
Chronic interstitial nephritis	4 (13.8)
Others	2 (6.9)
Duration of dialysis (months)	72.34 $\pm$ 5.38
Kt/V (mean $\pm$ SD)	1.4 $\pm$ 0.2
<b>Medications, n (%)</b>	
Calcium carbonate	26 (89.7)
Sevelamer carbonate	25 (86.2)
Vitamin D sterols	27 (93.1)

Table 1: Patients' characteristics.

	Baseline	6 months	12 months	p
<b>PTH (pg/ml)</b>				
Mean $\pm$ SD	174.24 $\pm$ 12.3	170.45 $\pm$ 21.6	177.11 $\pm$ 13.3	0.316
Median (IQR)	169 (156-182)	169 (148-178)	167 (154-186)	
<b>Serum Calcium</b>				
Mean $\pm$ SD	8.9 $\pm$ 0.81	8.95 $\pm$ 0.66	8.95 $\pm$ 0.61	0.285
Median (IQR)	8.85 (8.76-9.1)	8.8 (8.78-9.2)	8.8 (8.7-9.2)	
<b>Serum phosphorous</b>				
Mean $\pm$ SD	5.2 $\pm$ 1.58	6.3 $\pm$ 2.2	6.1 $\pm$ 2.6	0.003
Median (IQR)	5.0 (4.8-5.6)	6.2 (5.1-6.8)	5.9 (5.3-6.8)	
<b>ALKP</b>				
Mean $\pm$ SD	227.4 $\pm$ 21.8	176.8 $\pm$ 15.3	158.5 $\pm$ 18.1	<0.001
Median (IQR)	184 (159-207)	161 (134-170)	138 (121-152)	

IQR= interquartile range; ALKP= alkaline phosphatase

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



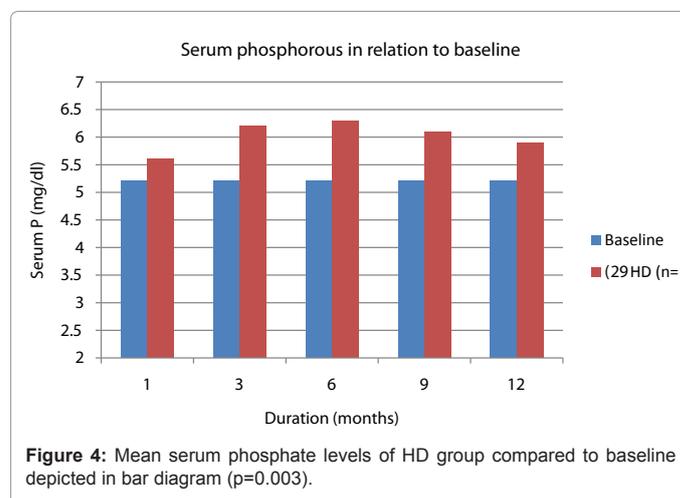
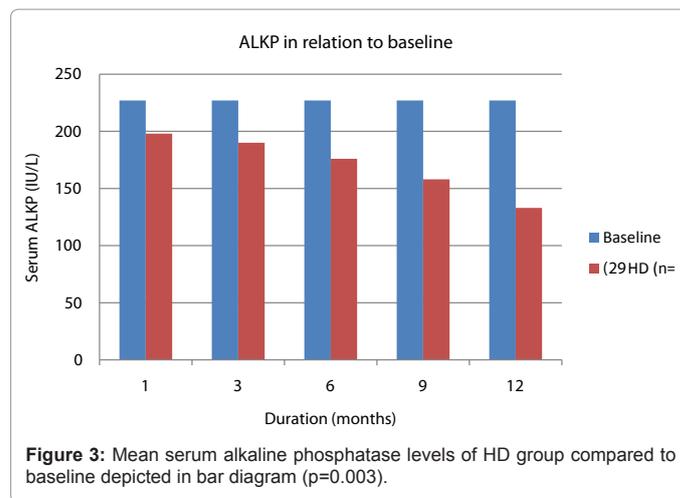
227.4+21.8 IU/L, median 138 IU/L (IQR 121-152) vs. 184 IU/L (IQR 159-207) respectively],  $p < 0.001$  (Figure 3). On the other hand serum phosphate levels during the study period in the HD patients differed significantly as depicted in figure 4 [mean 6.1+2.5 mg/dl vs 5.2+1.6 mg/dl, median 5.9 mg/dl (IQR 5.3-6.8) vs 5.0 mg/dl (IQR 4.8-5.6) at 12 months and baseline respectively]  $p=0.003$  (Figure 4). No major adverse events were recorded during the study period and symptomatic hypocalcemia was not observed.

## Discussion

In this study, we have shown that the 3/wk post HD regimen of cinacalcet is as effective as daily regimen in controlling the PTH values in dialysis dependent SHPT patients. The scientific basis underlying our pre-test hypothesis resulted from the study of the pharmacokinetics of cinacalcet [13]. After oral absorption, cinacalcet takes 2-6 hours to achieve maximum serum concentration. The elimination of cinacalcet from the body follows biphasic kinetics and the terminal half-life is approximately 30-40 hours. The PTH value after a single cinacalcet dose remains suppressed for almost 30 hours [14]. This time frame not only is related to the elimination kinetics of cinacalcet but it is somehow analogous to the post antibiotic effect of some commonly used antibiotics including aminoglycosides. Cinacalcet, however, is different from gentamicin as it is metabolized by CYP3A4, CYP2D6, and CYP1A2; 80% of these inactive metabolites are excreted renally

and hemodialysis does not affect the pharmacokinetics of the drug [15]. Gentamicin, on the other hand, is not metabolized. It is excreted by glomerular filtration in an active, unchanged form. Gentamicin, then, accumulates in the renal cortical tissue and a critical concentration is reached when the concentration ability of the kidney becomes impaired [16]. Considering this favorable pharmacokinetic and pharmacodynamic profile, cinacalcet could possibly be as effective even if used in a more widely spaced dosing regimen [12].

Cinacalcet is rapidly emerging as the preferred agent in treating SHPT in dialysis dependent patients [17]. Not only it effectively and quickly reduces PTH values, but it also has several other potential advantages as compared to the conventional therapy. Since it decreases the serum calcium levels as well as the requirement of active vitamin D, so the incidences of vascular calcification would be less with cinacalcet [18,19]. This effect may be mediated through altered mechanism of osteoprotegerin and fetuin-A following cinacalcet administration as shown by Messa et al. [20]. These factors have been closely related to the occurrence of SHPT and vascular calcification in CKD. Whether it has some direct effect on the vascular wall is still a matter of debate [14]. From animal experiments, there is also some evidence that cinacalcet regresses the parathyroid hyperplasia in SHPT patients which is not known with conventional therapies of SHPT [1]. Although the recently published EVOLVE study failed to demonstrate any cardiovascular mortality benefit of cinacalcet [21], this effect needs further exploration.



Despite the above mentioned advantages of cinacalcet in controlling of PTH and reducing risk of vascular calcification in CKD, the main concern with its long term use is the incremental cost to patients who are already overburdened with the cost of maintenance hemodialysis particularly in the developing countries. Cinacalcet is often used as an add-on therapy in treatment of difficult-to-control SHPT. In the OPTIMA trial more than 65% of the study subjects needed a dose of 30 mg of cinacalcet per day [9]. In a developing country that amounts to almost 12-15% of the total patient-care-cost in dialysis dependents per month.

In our previous study, we have shown the effectiveness of cinacalcet therapy compared to conventional treatment in controlling SHPT in dialysis patients [11]. In the present study we had taken up the issue of a different dosing regimen of cinacalcet applicable to the same patient population. We have shown that intermittently administered cinacalcet dosing 3 times per week is as effective as daily administered dose in controlling the mineral abnormalities in CKD patients on maintenance hemodialysis. The PTH values continued to be controlled ( $177.1 \pm 13.3$  ng/ml), which is well within the KDOQI prescribed range [10] during the 12- month period of the study. Indirectly there was no rebound increase in PTH values which usually happens once cinacalcet dose is reduced inappropriately or discontinued completely. Effectively, this study proves that once the PTH level is already lowered, 3/wk cinacalcet can maintain its adequate level of control resulting in a lower cost and a better compliance.

The only study that has evaluated the intermittent dosing of cinacalcet was published by Al-Hilali et al. [12] who compared a regimen of 30 mg cinacalcet daily with 90 mg and 120 mg at the beginning of the week and at the mid week respectively. Like in our study both regimens were equivalent in controlling the PTH values, although the trial period was only 12 weeks. Instead our study has given the answer to the stability of PTH control even with the modified (HD regimen) dosing schedule during the 12 months study period. It is however significant to note that the study of Al-Hilali et al. [12] has shown that even the de novo administration of intermittent dosing can effectively control PTH whereas our study patients were already well controlled on daily regimen before changing to the intermittent dosing.

There was no serious complication in any of the intermittent therapy regimens just discussed. This may be attributed to the intermittent regimen with smaller doses, in addition to the replenishment of calcium once we found a reducing trend in serum calcium even with normal range. Serum calcium values were similar to the standard regimen and in none of the patients cinacalcet had to be discontinued due to symptomatic hypocalcemia.

Overall this study creates path for larger randomized control trials which may finally give the verdict whether a costly but increasingly essential medicine like cinacalcet can be customized to a much simpler and cheaper regimen. Another interesting aspect that would merit further research is to test this intermittent cinacalcet regimen with respect to other potential actions of cinacalcet like bone histomorphology, risk of fracture, preventing parathyroid hyperplasia, progression of CKD and potential cardiovascular protection.

## Conclusion

Cinacalcet effectively controls parathyroid hormone levels and uncontrolled secondary hyperparathyroidism both when given daily and intermittently (3/week). Our study demonstrated the stability of

PTH control even with the modified (HD regimen) dosing schedule. Frequent monitoring and adequate replacement with calcium and vitamin D sterols prevent hypocalcemia with cinacalcet therapy. Serum calcium values were similar to the standard regimen and in none of the patients cinacalcet had to be discontinued due to symptomatic hypocalcemia. Intermittent dosing of cinacalcet seems to be an excellent cost-effective therapeutic option in ESRD patients with SHPT. In addition, it improves drug compliance.

## Conflict of Interest

The authors have no relationship with pharmaceutical companies or other entities, such as, employment contracts, consultancy, advisory boards, speaker bureaus, membership of Board Directors, or stock ownership that could be perceived to represent a financial or any other forms of conflict of interest.

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