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Research Article

ROLE OF CINACALCET PLUS CALCITRIOL FOR SECONDARY HYPERPARATHYROIDISM IN PATIENTS RECEIVING HEMODIALYSIS

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ABSTRACT
Treatment of secondary hyperparathyroidism with vitamin D and calcium in patients receiving dialysis is often complicated by hypercalcaemia and hyperphosphatemia, which may contribute to cardiovascular disease and adverse clinical outcomes. Calcimimetics target the calcium-sensing receptor and lower parathyroid hormone levels without increasing calcium and phosphorus levels. We report the results of randomized trial of calcimimetic agent cinacalcet hydrochloride plus calcitriol among patients receiving haemodialysis. Patients who were receiving haemodialysis and who had inadequately controlled secondary hyperparathyroidism despite standard treatment were randomly assigned to receive cinacalcet plus calcitriol (25 patients) or calcitriol alone (25 patients) for 6 months. Once-daily dose of cinacalcet was given i.e. 30 mg to achieve intact parathyroid hormone levels of 150-300 pg per milliliter. The primary end point was the percentage of patients with values in this range during a 26-week efficacy-assessment phase. Only one out of 25 (4%) in control group patients achieved >50% reduction in serum iPTH level at the end of study whereas 14 out of 25 (56%) in study group patients achieved >50% reduction in serum iPTH levels at the end of study. 11 (74%) out of 15 patients in study group achieved target goal of iPTH (150-300 pg/ml) whereas only 3(18%) out of 17 subjects achieved the target value in control group receiving calcitriol alone. Our study concludes that cinacalcet plus calcitriol lowers parathyroid hormone levels and improves calcium–phosphorus homeostasis in patients receiving hemodialysis who have uncontrolled secondary hyperparathyroidism.

Keywords: *Metabolic Bone Diseases (MBD), Chronic Kidney Disease (CKD), Secondary hyperparathyroidism, Parathyroid Hormone (PTH), Cinacalcet, Calcitriol*

INTRODUCTION
Metabolic bone disease is a common complication of chronic kidney disease (CKD) and is a part of broad spectrum of disorders of mineral metabolism that occurs in its clinical setting. This disorder of metabolic bone disease in CKD is considered not only with regard to the bone itself but also with regard to the consequences of disturbed mineral metabolism at extra-skeletal sites including the vasculature. In recognition of broad spectrum of disorders of mineral metabolism in this clinical setting, the term chronic kidney disease — mineral and bone disorder (CKD-MBD) is used which develops as a systemic disorder of mineral and bone metabolism as a result of CKD that can be manifested by any one or combination of the following:

1. Abnormalities of calcium, phosphorous, parathyroid hormone (PTH) and vitamin D metabolism leading to secondary hyperparathyroidism.
2. Bone disease (renal osteodystrophy)
3. Vascular or soft tissue calcification (Martin & Gonazalez, 2007).

Out of the above CKD-MBD, the prevalence of secondary hyperparathyroidism is very high (Sherred *et al.*, 1993). Secondary hyperparathyroidism occurs as a direct result of decreased renal functions, vitamin D deficiency, and impaired mineral metabolism. These abnormalities begin early in course of CKD when kidney function is reduced to approximately 60 ml/min/1.72m^2 (Pitts *et al.*, 1988).

Research Article

Secondary hyperparathyroidism (SHPT) is an adaptive response to chronic kidney disease (CKD) that results in elevated serum parathyroid hormone (PTH) levels due to increased production and secretion of intact PTII (iPTIH) by hyperplastic parathyroid gland chief cells. SHPT is an indolent and progressive disorder, and can become resistant to therapy as a result of down-regulation of the vitamin D receptor (VDR) and calcium sensing receptor (CaSR). Consequently, control of PTH becomes increasingly difficult over time. Without effective intervention, adenomatous transformation of the parathyroid gland can develop, leading to autonomous PTH secretion and necessitating parathyroidectomy (National Kidney Foundation guidelines, 2003 & Jorna *et al.*, 2004).

Apart from using treatment modalities to impede progression of chronic kidney disease to end stage renal disease (angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs)), other therapies to prevent the complications include calcium supplementation, dietary phosphate restriction, oral phosphate binding agents and vitamin D hormone replacement.

Calcimimetics agents are potential candidates for reducing secondary hyperparathyroidism. Calcimimetics agents act by increasing sensitivity of calcium sensing receptor in Parathyroid gland. Calcimimetics bind to transmembrane region of Ca^{++} sensing receptor which leads to change in structural configuration that is more sensitive to serum Ca^{++} on Parathyroid gland. Calcimimetics also reduces Ca^{++} and Po_4^{3-} levels in addition to PTH level which is helpful in reducing the vascular calcifications (British National Formulary, 2011 & Ajoy *et al.*, 2004)

Calcimimetics are ligands that either mimic or potentiate the effects of extracellular calcium at the calcium receptor (CaR) of parathyroid cells. The calcimimetic agent cinacalcet increases the sensitivity of parathyroid cells to extracellular calcium, shifting the calciumP1H response curve to the left and inhibiting PTH release (Nemeth el al, 1998). Cinacalcet simultaneously reduced plasma iPTH and serum P and Ca levels in dialysis patients with SHPT, and allowed more patients to achieve the recommended. Kidney Disease Outcomes Quality Initiative (KDOQITM) targets for bone and mineral metabolism (Geoffery *et al.*, 2004 & Lindberg *et al.*, 2005)

There is no study available in literature regarding the comparison of calcitriol and cinacalcet with calcitriol alone for treatment of secondary hyperparathyroidism. Further, cinacalcet is a relatively new calcimimetic agent devoid of problems of the earlier vitamin D analogues and not much studies are available regarding the role of cinacalcet in secondary hyperparathyroidism associated with chronic kidney disease patients and hence the present study has been planned to compare the efficacy of cinacalcet and calcitriol with calcitriol alone in patients of chronic kidney disease with secondary hyperparathyroidism.

Aims and objectives

To compare the combined effect of cinacalcet and calcitriol and calcitriol alone in chronic kidney disease patients who are on dialysis.

MATERIALS AND METHODS

The study was carried out on 50 adult patients of chronic kidney disease stage V on haemodialysis (as per National Kidney Foundation-Disease Outcome Quality Initiative (NKF-DOQI) classification of CKD), already on regular follow up of kidney and dialysis clinic at Pt. B.D. Sharma PGIMS, Rohtak fulfilling the underlying criteria.

Inclusion criteria

1. Adult patients of chronic kidney disease stage V on haemodialysis
2. Patient having iPTH level of >150pg/ml

Exclusion criteria

Exclusion criteria included evidence of cancer, active infection, diseases known to cause hypercalcaemia, or a serum calcium level below 8.4 mg per deciliter. Because cinacalcet can inhibit cytochromeP-450 2D6, patients were excluded if they were receiving drugs such as flecainide, thioridazine, and most tricyclic antidepressants, which have a narrow therapeutic index and are metabolized by this enzyme.

A total of fifty patients with chronic kidney disease stage V fulfilling the above criteria and consenting for the study was enrolled. Each patient was subjected to detailed physical examination and investigation at the beginning of the study. Patients were randomized into one of two groups in alternating fashion.
Group I — (n=25) received calcitriol in dosage of 0.5pg/day.
Group II — (n=25) received cinacalcet in dosage of 30mg/day and calcitriol 0.5 µg/day
The patients continued to receive other medications required for treatment of chronic kidney disease including phosphate binders. A dialysate calcium concentration of 2.5 meq/l was used in all subjects.
The study was carried out for duration of 6 months. The patients were subjected to baseline investigations which included Complete haemogram, Blood urea (mg%),Serum creatinine (mg%),Serum phosphorous (mg°/a),Calcium phosphorous product (mg2/dl2),Serum protein with A:G ratio (gm%), GFR (ml/min), iPTH levels (pg/ml),Serum electrolytes-Na/K, Blood sugar — Fasting/Postprandial, Urine complete examination,24 hours urine (Volume, Creatinine, Protein), Radiological investigations, Chest x-ray PA view USG abdomen for bilateral kidneys (size and echo-texture)
The patients were examined and investigated on monthly basis. Plasma parathyroid hormone levels and serum calcium and phosphorus levels were measured at each study visit before hemodialysis, approximately24 hours after the preceding dose but before the next daily dose of study medication. On each visit patient was investigated for side effect profile such as nausea, vomiting, headache, malaise, palpitation, constipation, dyspepsia, allergic reaction, excessive thirst, frequency of micturition and abdominal pain.

Statistical analysis

Data are reported as mean± SD or median [interquartile range (IQR)] as appropriate. Students `t' test was employed for comparison of various values between the two groups. $P<0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics 20 (IBMSPSS, Tokyo, Japan).

RESULTS

Table 1: Baseline biochemical characteristics of patients

Variables	Group I	Group II
Mean Age	48.88±15.48	46.92±13.45
Hemoglobin (gm%)	8.46±1.20	7.79±1.32
Serum potassium (meq/L)	4.37±0.65	4.15±0.87
Serum sodium (meq/L)	141.00±6.228	139.48±5.285
Blood urea (mg%)	146.36±52.66	151.32±43.14
Blood sugar fasting (mg%)	108.08±73.88	89.28±2.33
Blood sugar post prandial (mg%)	117.36±26.0	111.08±28.35
Serum creatinine (mg%)	4.92±1.93	5.52±1.41
Serum calcium (mg%)	9.084±0.542	9.196±0.478
Serum phosphorous (mg%)	6.136±0.793	5.768±0.3194
Serum calcium phosphate product (mg^2/dl^2)	55.69±7.86	53.00±5.121
GFR (in ml/min)	17.88±4.21	18.00±3.99

Table 2: Biochemical determinations in study and control groups at different periods

Variables	Group	Basal values	At end of 3rd month	At the end of study
Hb	**I**	8.44±1.22	8.308±0.922	8.284±1.006
	II	7.872±1.3202	8.176±1.16	8.224±1.11
Urea	**I**	136.36±52.66	129.40±43.67	127.08±37.52
	II	151.32±43.14	153.92±49.43	151.08±48.25
Creatinine	**I**	4.92±1.93	4.82±1.95	4.96±2.02
	II	5.52±1.41	5.78±1.45	6.00±1.69
Calcium	**I**	9.084±0.5421	8.948±0.5221	8.800±0.7931
	II	9.196±0.4783	8.848±0.255	8.596±0.2669
Phosphorous	**I**	6.136±0.793	5.96±0.772*	5.776±0.794*

	II	5.768±0.3194	5.380±0.5156	5.348±0.476
Cal Pho Product	**I**	55.69±7.86	53.08±7.294*	50.75±7.015*
	II	53.00±5.121	47.816±4.30	46.05±4.43
Intact PTH (iPTH)	**I**	490.52+271.763	443.80+271.07	420.80+288.61*
	II	432.80+229.86	329.52+204.76	246.40+219.99

Independent t-test applied, (*)-significant

Only one out of 25 (4%) in group I patients achieved >50% reduction in serum iPTH level at the end of study whereas 14 out of 25 (56%) in group II patients achieved >50% reduction in serum iPTH levels at the end of study.
None of the patients in any group developed significant side effects so as to warrant reduction in dosage or withdrawal of the drug.

DISCUSSION

Our results indicate that cinacalcet plus calcitriol effectively reduces parathyroid hormone levels in patients with secondary hyperparathyroidism who are receiving hemodialysis and ameliorates disturbances in serum calcium and phosphorus associated with adverse clinical outcomes. Out of 15 subjects treated with cinacalcet plus calcitriol having serum iPTH values >300 pg/ml, 11 (74%) achieved target goal of iPTH (150-300 pg/ml) whereas only 3(18%) out of 17 subjects achieved the target value in control group receiving calcitriol alone. The reductions in parathyroid hormone in those given cinacalcet were accompanied by decreases in serum calcium, phosphorus, and the calcium–phosphorus product.
In OPTIMA study, which was a randomized, open label study recruited 522 haemodialysis patients. In this study, more patients achieved primary end points (iPTH<300 pg/ml) with cinacalcet as compared to conventional therapy group (71% vs 22%, p<0.001). Greater reduction (iPTH) was seen in patients with severe secondary hyperparathyroidism with mean iPTH decreased by 46% in group receiving cinacalcet (Piergiorgio *et al.*, 2008).
Another study done by Geoffrey *et al.*, in their multicentric study recruited 444 subjects with moderate to severe secondary hyperparathyroidism to see the effect of cinacalcet and low doses of vitamin D sterols against placebo. 43% of the subjects in cinacalcet group reached the primary end point (<250 pg/ml), as compared with 5 percent of the placebo group (p<0.001). Overall, mean parathyroid hormone values decreased 43 percent in those receiving cinacalcet but increased 9 percent in the place bogroup (p<0.001). This study concluded that combined therapy with cinacalcet and low dose vitamin D sterols improved achievement of target for CKD-MBD (Geoffrey *et al.*, 2004).
Studies done else-where have reported similar results (Steven *et al.*, 2008 & Chartyn, 2005 and Chonchol *et al.*, 2009). The results of our study are consistent with the results of the studies mentioned above. It should be noted, however, that over suppressed PTH levels may not be beneficial and indeed could be associated with increased risk of low bone turnover disease or other adverse outcomes. Therefore, long term follow up studies are required. Treatment with cinacalcet was generally well tolerated. Episodes of nausea (24%) and vomiting (12%) occurred more often in cinacalcet-treated patients but were generally mild to moderate in severity and transient.

Conclusion

The observations of this study reveal that cinacalcet plus calcitriol reduces parathyroid hormone level significantly with a relatively low incidence of hypercalcemia compared with calcitriol without any significant side effects. Long term follow up studies needs to be undertaken to assess the efficacy of cinacalcet in the treatment of secondary hyperparathyroidism.

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