Journal of Applied Pharmaceutical Science Vol. 5 (05), pp. 049-051, May, 2015
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2015.50509
ISSN 2231-3354

Cinacalcet Hydrochloride: a new dose schedule in the Management of Secondary Hyperparathyroidism in Indian Chronic Kidney Disease Patients

Kumaresan Ramanathan[1], Giri Padmanabhan[2*]

[1]Department of Biotechnology, Periyar Maniammai University, Vallam, Thanjavur-613 403, India.
[2]Kidney Care, C-50,10th B Cross, Thillai Nagar, Tiruchirappalli-620 018, India.

ARTICLE INFO

Article history:
Received on: 24/02/2015
Revised on: 16/03/2015
Accepted on: 07/04/2015
Available online: 27/05/2015

Key words:
Secondary hyperpathyroidism, cinacalcet hydrochloride, Chronic kidney disease, parathyroid hormone.

ABSTRACT

Secondary hyperparathyroidism is common in patients with chronic kidney disease (CKD). Currently, cinacalcet has evidently improved the management of secondary hyperparathyroidism in patients on hemodialysis. Though, to the best of our knowledge, there are no studies addressing the dose regimen of cinacalcet in CKD stage II to IV. Hence we decided to study and evaluate the efficacy of cinacalcet in the treatment of secondary hyperparathyroidism in two different dose schedules. A total of 174 patients (M: 138, F: 36), ages ranging from 23 to 87 years with CKD stage II –IV not on dialysis and intact PTH (iPTH) >150 pg/dl were enrolled in this study. The study population was divided into two groups. Group I: daily 30 mg cinacalcet hydrochloride and Group II: weekly twice 30 mg cinacalcet hydrochloride. Both groups received cinacalcet hydrochloride 30 mg with the main meal. In group I, 42 patients (48 %) stopped the drug within one month due to various side effects. During the follow up, the levels of iPTH decreased significantly in both the groups within a period of four weeks & persisted till the end of the study. No significant side effects requiring stoppage of the drug were noted in the group II study population. In conclusion, cinacalcet hydrochloride 30 mg twice weekly is a safe regimen in suppressing high PTH levels in CKD patients.

INTRODUCTION

The incidence of chronic kidney disease (CKD) is increasing progressively around the world. Secondary hyperparathyroidism (SHPT) is one of the major complications of CKD (Joy *et al*., 2007). SHPT develops as a result of impaired calcium homeostasis when the failing kidneys disturb the complicated interactions between parathyroid hormone (PTH), calcium, phosphorus, and vitamin D. Changes in the mineral metabolism develop early in the course of CKD and worsen with the progressive loss of kidney functions. The level of these changes may also be influenced by various therapeutic interventions (K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, 2003, Martin , Gonzalez , 2007, Nabieh Al-Hilali *et al*., 2011) Existing treatments of secondary hyperparathyroidism could reduce the serum phosphorus (P) or increase serum calcium (Ca), which might result in the increase of calcium × phosphorus product (Brown EM, 2000). Currently, it has become clear that the calcium sensing receptor (CaSR) plays a key role in regulating the secretion of parathyroid hormone and subsequent minerals (cinacalcet HCL package insert, Amgen, 2004).

Cinacalcet hydrochloride, a first-in-class calcimimetic agent, offers a new therapeutic approach to the treatment of SHPT. Cinacalcet puts forth its action by binding to the parathyroid Ca sensing receptor (CaSR).

This leads to a decrease in the circulation of parathyroid hormone (PTH) levels in CKD (Valle *et al*., 2008). Serum intact PTH levels above 70 pg/dl, but not serum Ca and P levels, have been reported to be associated with cardiovascular disease (CVD) in CKD stage III and IV patients (Bhuriya *et al*., 2009, Kumaresan., Giri, 2012). Patients are considered to have a severe SHPT when serum calcium, phosphorus, Ca×P product, intact PTH cannot be adequately controlled by conventional medical management (De Francisco, 2004).

* *Corresponding Author*
Dr. P. Giri MD., DNB (Nephrology), Senior Consultant Nephrologist Kidney Care C-50,10th B Cross, Thillai Nagar, Tiruchirappalli-620 018 India. Email:kpgiri@yahoo.com

Whether cinacalcet hydrochloride should be used for the management of secondary hyperparathyroidism in patients with CKD stage III and IV patients is controversial (Cannata-Andia, Fernandez-Martin, 2009, Coyne, 2008). Literature survey revealed that a small study has reported the efficacy of cinacalcet to lower PTH level in predialysis patients and its safety with regard to serum Ca and P levels (Charytan *et al*., 2005). To address this controversy in usage of cinacalcet in CKD stage II-IV, we aimed to study and evaluate the efficacy of cinacalcet in the treatment of secondary hyperparathyroidism in two different dose schedules in CKD patients.

MATERIALS AND METHODS

Patients

A total of 174 patients (M: 138, F: 36), ages ranging from 23 to 87 years with CKD stage II –IV not on dialysis and intact PTH (iPTH) >150 pg/dl were enrolled in this study. Written informed consent was obtained from all the study participants prior to the study and this protocol has been approved by local human ethics committee. All patients underwent routine evaluations including serum Calcium (Corrected with albumin), Serum phosphorus, Serum alkaline phosphatase and iPTH (done 12 hrs after cinacalcet dose) once in a month and all side effects were noted for a period of 6 months.

Grouping of patients and drug dosage

The study population was divided randomly in two groups, Group I: daily 30 mg cinacalcet hydrochloride (No: 87, M:71 F:16), Group II: Weekly twice 30 mg cinacalcet hydrochloride (No: 87, M:67 F:20). Both groups were administered cinacalcet hydrochloride 30 mg with the main meal.

Laboratory Assessment

Plasma iPTH and serum calcium (corrected with albumin) and phosphorus were assessed at end of 2 week intervals during the titration phase and at end of 4 week intervals throughout the efficacy assessment phase. Plasma iPTH was measured using the chemiluminisence method (Immulite, USA) and serum calcium, phosphorus, alkaline phosphatase, serum creatinine, urea, and all parameters were analysed using a fully automated analyser (Biosystems,USA).

RESULTS

In group I, forty two patients (48%) stopped the drug within one month due to various side effects including nausea and vomiting (Table 1). During the follow up, the levels of iPTH decreased significantly in both the groups within a period of four weeks & persisted till the end of the study (Table 2). Serum calcium (corrected with albumin), phosphorus and Ca × Po_4 product also decreased significantly in both the groups. Side effects such as muscle tightness, numbness or tingly feeling around mouth, rapid weight gain were observed with 42 patients (48%) in group I, warranting the stoppage of cinacalcet within a month. No significant side effects requiring stoppage of the drug were noted in the group II study population.

Similarly the serum calcium (corrected with albumin), phosphorus and Ca × Po_4 product also decreased significantly to normal levels. There were no significant differences between the reductions in serum creatinine, alkaline phosphatase and sugar levels.

DISCUSSION

Secondary hyperparathyroidism is a frequently encountered problem in the management of patients with chronic kidney disease (CKD). Early diagnosis of secondary hyperparathyroidism is crucial in the management of patients with CKD. The treatment remains a challenge for patients and their clinicians. It should include a combination of dietary phosphorus restriction, phosphate binders, vitamin D analogues, and calcimimetics (Wissam Saliba, Boutros El-Haddad, 2009). Current classification of CKD is based on the presence of parenchymal damage for stages I and II and a decrease in glomerular filtration rate (GFR) regardless of parenchymal damage for stages III and higher (Poggio and Rule, 2009).

The development of new therapeutic agents that can suppress PTH without exacerbating hyperphosphatemia or causing hypercalcemia is the intention of research into this issue (Nabieh Al-Hilali *et al*., 2009). Controlling calcium homeostasis by regulating the PTH secretion was the key role of CaSR on the parathyroid cells (Nemeth, 2004). Calcimimetics are agents that allosterically increase the sensitivity of the CaSR in the parathyroid gland to calcium (Sterret *et al*., 2007). Cinacalcet is the only available calcimimetic in the global market. The administration of calcimimetics produces a dose dependent reduction in PTH and decrease in the levels of calcium and phosphorus (Sprague *et al*., 2009, Arenas *et al*., 2007, Fishbane *et al*., 2008). Our results also supported this observation. The literature survey revealed that there is no specific study addressing the dose regimen of cinacalcet hydrochloride in CKD patients. However, the effectiveness of cinacalcet in hemodialysis patients has been proved (Al-Hwiesh, Abdul-Rahman, 2013). In the present study, cinacalcet treatment resulted in a 69% decrease in plasma iPTH levels group I and 51 % in group II. Irrespective of CKD stage, most cinacalcet participants achieved a 60% decrease in iPTH level. This data confirms previous findings of cinacalcet efficacy in this population (Charytan *et al*., 2005).

CONCLUSION

The study strengthens the theory that these findings may be applicable to the general stage 3 and 4 CKD populations. Cinacalcet hydrochloride 30 mg twice weekly is a safe regimen in suppressing high PTH levels in CKD patients. The role of calcimimetics in patients with CKD stages 3 and 4 currently is unclear. It is recommended that is required to explore the potential for a favourable benefit-risk profile in this patient population.

Table 1: Laboratory values of group I.

Daily dose of 30 mg	Before Treatment	After Treatment (in 45 Patients)	*P* Value
PTH pg/dl	340.21±196.37	68.94 ±47.61	<0.0001
Creatinine mg/dl	6.13±3.35	6±2.97	0.7868 (NS)
Calcium mg/dl (corrected with albumin)	11.62±1.73	9.14±1.36	<0.0001
Phosphorus mg/dl	5.83±1.81	4.2±1.26	<0.0001
Ca×Po4 Product	63.52±5.15	41.92±2.61	<0.0001
Sugar mg/dl	150.28±32.91	148.53±30.28	0.7156 (NS)
Serum Alkaline Phosphatase IU/l	476.10±80.74	408.35±30.28	NS
Male: Female (No:87)		71:16	

Table 2: Laboratory values of group II.

Weekly twice dose of 30 mg	Before Treatment	After Treatment	P Value
PTH pg/dl	331.53±203.18	91.86 ±45.96	<0.0001
Creatinine mg/dl	6.52±3.35	6.31±3.05	0.6567 (NS)
Calcium mg/dl (corrected with albumin)	11.80±1.46	10.16±1.22	<0.0001
Phosphorus mg/dl	5.94±1.60	4.87±1.32	<0.0001
Ca×Po4 Product	66.65±6.37	52.50±3.39	<0.0001
Sugar mg/dl	146.34±78.21	143.11±54.43	0.7523 (NS)
Serum Alkaline Phosphatase IU/l	513.61±78.35	478.26±37.26	NS
Male: Female (No:87)		67:20	

REFERENCES

Joy MS, Karagiannis PC, Peyerl FW. Outcomes of secondary hyperparathyroidism in chronic kidney disease and the direct costs of treatment. *J Manag Care Pharm* 2007;13:397-411.

K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *Am J Kidney Dis* 2003;42: S1.

Martin KJ, Gonzalez EA. Metabolic bone disease in chronic kidney disease. *J Am Soc Nephrol* 2007;18: 875.

Nabieh Al-Hilali, Nasser Hussain, Yasser A.Kawy, Mohammed Al-Azmi. A novel dose regimen of cinacalcet in the treatment of severe hyperparathyroidism in hemodialysis patients. *Saudi J Kidney Dis Transpl* 2011;22(3):448-455.

Brown EM. Calcium receptors and regulation of parathyroid hormone secretion. *Rev EndocrMetab Dis* 2000;1:307-315.

Sensipar™ (cinacalcet HCL) package insert. Thousand Oaks,CA, Amgen;2004 March.

Valle C, Rodriguez M, Santamaria R, et al. Cinacalcet reduces the set point on the PTH-calcium curve. *J Am SocNephrol* 2008;19:2430–2436.

Bhuriya R, Li S, Chen SC, McCullough PA, Bakris GL. Plasma parathyroid hormone level and prevalent cardiovascular disease in CKD stages 3 and 4: an analysis from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2009;53(Suppl 4):S3–10.

Kumaresan.R, P.Giri. Correlation between parathyroid hormone and left ventricular Function in chronic kidney disease patients. Int J Pharm Bio sci 2012;3(3):229-233.

De Francisco AL. Secondary hyperparathyroidism: review of the disease and its treatment. *Clin Ther* 2004;26:1976-1993.

Cannata-Andia JB, Fernandez-Martin JL. Mineral metabolism: Should cinacalcet be used in patients who are not on dialysis? *Nat Rev Nephrol* 2009;5:307–8. 45.

Coyne DW. Cinacalcet should not be used to treat secondary hyperparathyroidism in stage 3-4 chronic kidney disease. *Nat Clin Pract Nephrol* 2008;4:364–5.

Charytan C, Coburn JW, Chonchol M, et al. Cinacalcet hydrochloride as an effective treatment for secondary hyperparathyroidism in patients with CKD not receiving dialysis. *Am J Kidney Dis* 2005;46:58–67.

WissamSaliba, Boutros El-Haddad. Secondary Hyperparathyroidism: Pathophysiology and Treatment. *J Am Board Fam Med* 2009;22(5):574-581

Poggio ED, Rule AD. A critical evaluation of chronic kidney disease-should isolated reduced estimated glomerular filtration rate be considered a disease? *Nephrol Dial Transplant* 2009; 24: 698–700.

Nemeth EF. Calcimimetic and calcilytic drugs: just for parathyroid cells? *Cell Calcium* 2004;35:283-289.

Sterret JR, Strom J, Stummvoll HK. Cinacalcet HCL (Sensipar/ Mimpara) is an effective chronic therapy for hemodialysis patients with secondary hyperparathyroidism. *ClinNephrol*2007;68:10.

Sprague SM, Evenepoel P, Curzi MP. Simultaneous control of PTH and Ca×P is sustained over three years of treatment with cinacalcet HCL. *Clin J Am SocNephrol* 2009;4:1465.

Arenas MD, Alvarez-Ude F, Gil MT. Implementation of K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease after the introduction of cinacalcet in a population of patients on chronic hemodialysis. *Nephol Dial Transplant* 2007;22:1639.

Fishbane S, Shapiro WB, Corry DB. Cinacalcet HCL and concurrent low dose vitamin D improves treatment of secondary hyperpathyroidism in dialysis patients compared with vitamin D alone:the ACHIEVE study results. *Clin J Am SocNephrol 2008;3:1718.*

Al-Hwiesh AK,Abdul-Rahman IS. Intermittent Dosing of Cinacalcet is also effectivein Treating Secondary Hyperparathyroidism in Hemodialysis Patients. *Pharmaceut Anal Acta* 2013; 4: 229.

How to cite this article:

Kumaresan Ramanathan, Giri Padmanabhan. Cinacalcet Hydrochloride: a new dose schedule in the Management of Secondary Hyperparathyroidism in Indian Chronic Kidney Disease Patients. J App Pharm Sci, 2015; 5 (05): 049-051.