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Doxercalciferol Versus Calcitriol for Treatment of Secondary Hyperparathyroidism in Patients of Chronic Kidney Disease-Efficacy and Safety

H.K. Aggarwal, Deepak Jain and Ashwani Kumar

Secondary hyperparathyroidism is most common complication arising in chronic kidney disease as a part of mineral bone disorder. Doxercalciferol effectively suppresses parathyroid hormone level without having side effects like hypercalcemia and hyperphosphatemia, which are much common with earlier vitamin D analogues. It was an open, prospective study of three months duration conducted on fifty adult patients of chronic kidney disease stage III or IV already on regular follow up of kidney and dialysis clinic at Pt. B.D. Sharma PGIMS, Rohtak. Patients were randomly assigned to one of the two groups, Group I (n = 25) patients received calcitriol in dosage of 0.5 μg day^{-1} and Group II (n = 25) received doxercalciferol in dosage of 1 μg day^{-1}. Patients were followed and renal investigations were carried out on monthly basis, iPTH levels were measured in the beginning and at the end of the study. The mean iPTH level decreased by 13.44% in group I and 43.1% in group II after 12 weeks of treatment ($p<0.05$). There were less episodes of hypercalcemia with doxercalciferol (3 patients) as compared to calcitriol (8 patients). No statistically significant difference was observed in serum phosphorous, serum calcium phosphate product and GFR in both the groups. Doxercalciferol is more effective than calcitriol in controlling secondary hyperparathyroidism in patients of CKD without any adverse effects like hypercalcemia.

Key words: Chronic kidney disease, mineral bone disease, doxercalciferol, calcitriol secondary hyperparathyroidism

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For further information about this article or if you need reprints, please contact:

H.K. Aggarwal
2/8 FM, Medical Campus
PGIMS, Rohtak-124001
(Haryana), India

Tel: +91-9896111831

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Division of Nephrology, Department of Medicine, Pt. B.D. Sharma University of Health Sciences, ROHTAK-124001 (Haryana), India

INTRODUCTION

Disorders of calcium, phosphate metabolism and mineral bone disease are common complications of Chronic Kidney Disease (CKD) (Martin and Gonazalez, 2007). In recognition of broad spectrum of disorders of mineral metabolism in this clinical setting, the term chronic kidney disease-mineral bone disorder (CKD-MBD) is used which develops as a systemic disorder of mineral and bone metabolism as a result of CKD. It can be manifested by any one or combination of the following-Abnormalities of calcium, phosphorous, parathyroid hormone and vitamin D metabolism leading to Secondary Hyperparathyroidism (SHPT); renal osteodystrophy and vascular and soft tissue calcification. Out of different CKD-MBD manifestations, the prevalence of secondary hyperparathyroidism is very high (Sherrard *et al*., 1993). The development of progressive secondary hyperparathyroidism and renal osteodystrophy in patients with chronic kidney disease involves complex interaction between phosphorous retention, reduction in serum calcium level and alteration in Vitamin D metabolism. Deficiency of Vitamin D and increased phosphate leads directly or indirectly to increased parathyroid stimulation with resulting increase in the synthesis of parathyroid hormone. Evidence indicate that these abnormalities begin early in the course of CKD, when kidney function is reduced to approximately 60 mL/min/1.73 m^2 (Lucas *et al*., 1983; Pitts *et al*., 1988; Reichel *et al*., 1991; Martinez *et al*., 1996).

As SHPT leads to various complications it is necessary to treat this abnormality at the earliest. Vitamin D and vitamin D analogues have been the mainstay of treatment for predialysis patients of End Stage Renal Disease (ESRD) with elevated PTH levels that exceed the K/DOQI targeted range for the CKD stage (Locatelli *et al*., 2002; National Kidney Foundation, 2003).

Calcitriol is a Vitamin D analogue commonly used for treatment of secondary hyperparathyroidism. It increase serum calcium levels and decreases PTH levels indirectly. It also acts directly on parathyroid gland and decreases PTH formation and proliferation of parathyroid gland but therapeutic index for suppressing PTH secretion is quite low and side effects like hypercalcemia limits its use (Brannaccio *et al*., 2007). Doxercalciferol (1-alpha hydroxyl vitamin D2) is a second generation prohormone analogue. It suppresses serum intact parathyroid hormone (iPTH) effectively without having the side effects like hypercalcemia and hyperphosphatemia as caused by earlier vitamin D analogues (Cobum *et al*., 2004).

MATERIALS AND METHODS

This was an open, prospective, case controlled study of 3 months duration conducted on fifty adult patients of chronic kidney disease stage III or IV (as per NKF-K/DOQI guidelines of CKD) (National Kidney Foundation, 2003) already on regular follow up of kidney and dialysis clinic at Pt. B.D. Sharma PGIMS, Rohtak (India) fulfilling the underlying criteria. Preinformed written consent was obtained before registration of patients for the study. The study was approved by ethical committee of University of Health Sciences, Rohtak, India.

Inclusion criteria:

- Patients with age of 18-75 years
- Presence of stage III or IV CKD (CREATININE CLEARANCE 15-59 mL min^{-1}) not on dialysis
- Patients having iPTH level of >70 pg mL^{-1}

Exclusion criteria:

- Patients with primary hyperparathyroidism and other causes of secondary hyperparathyroidism and hypercalcemia such as Vitamin D intoxication, sarcoidosis and malignancy were excluded
- Any underlying medical condition such as malabsorption syndrome or severe liver disease
- Any condition that preclude a patient from remaining in the study such as alcohol/drug abuse, malignancy, psychiatric illness, pregnancy
- Parathyroid surgery in previous 12 months
- Patients on medication interacting with calcitriol or doxercalciferol like digoxin, cholestyramine, Vitamin D supplements etc

Patients were divided into two groups. Group I (n = 25) received calcitriol in dosage of 0.5 μgm day^{-1} and group II (n = 25) received doxercalciferol in dosage of 1 μgm day^{-1} alongwith their antihypertensive and anti diabetic medications, if required. Non calcium based phosphate binders like lanthanum carbonate were given in patients of both the groups depending upon their phosphate levels. All patients were examined in details clinically and all relevant laboratory investigations were done with special emphasis on renal parameters. Patients were followed on monthly basis and relevant investigations were carried out on each visit. Intact PTH (iPTH) was measured in the beginning and at the end of the study by suing Chemilumenence Immunoassay (CLIA) method.

Creatinine clearance was calculated by using 24 h urine estimation method using following:

$$\text{Creatinine clearance} = \frac{\text{Urine creatinine (Ucr)} \times \text{Urine volume (Uv)}}{\text{Serum creatinine} \times 1440}$$

If serum albumin is <4.0 gm dL^{-1} serum calcium was corrected by the formula:

$$\text{Corrected serum calcium} = \text{Measured serum calcium} \times [0.8 \times (4 - \text{measured serum albumin})]$$

All the patients were carefully observed for the side effects of doxercalciferol like headache, palpitation, malaise, dyspepsia, constipation, allergic reactions, abdominal pain, insomnia.

Statistical analysis: The results were analysed by using unpaired t-test. The various values were expressed as Mean±1SD.

RESULTS

The mean age of patients in doxercalciferol group was 48.88±15.86 years with a range of 20-75 years. The mean age was 46.92±13.45 years for calcitriol group with a range of 20-65 years. Majority of patients were above 40 years of age. There were 13 male and 12 female in group I and 15 male and 10 female patients in group II (Table 1). Etiological factors for chronic kidney disease were equally distributed in both the groups. Chronic glomerulonephritis was the most common etiology for chronic kidney disease (11 patients in group I and 13 in group II) followed by diabetic nephropathy (7 in group I and 3 in group II), hypertensive nephropathy (3 in group I, 5 in group II), adult polycystic kidney disease (2 patients in each group), obstructive uropathy (2 in group I and 1 in group II), renal amyloidosis (1 in group II).

The mean baseline values of blood urea, serum creatinine, haemoglobin, serum phosphorous, serum calcium phosphate product and creatinine clearance did not differ significantly between the two groups (Table 2).

There was no significant difference in values of hemoglobin, Blood urea, serum creatinine, serum phosphorous, creatinine clearance during the follow up period at one, two and three months in both the groups.

The mean basal values of corrected serum calcium level were 8.94±0.96 mg% and 8.55±0.84 mg% in group I and group II, respectively. The mean values of serum calcium at the end of second months were 9.38±0.84 for group I and 8.81±0.94 for group II which were statistically significant ($p<0.05$). Similarly at the end of study the mean value of serum calcium were 9.72±0.85 and 9.12±1.10 in group I and II, respectively. This shows that there was significantly more increase in serum calcium level in group I ($p<0.05$). There were 8 episodes of hypercalcemia (serum calcium >10.5 mg dL^{-1}) in group I while 3 episode occurred in group II. This is equivalent to 1 episode per 100 weeks of treatment with doxercalciferol and 2.67 episodes per 100 weeks of treatment with calcitriol (Table 3).

The mean basal serum phosphorous values were 5.52±0.70 and 5.76±0.71 in group I and II, respectively. The mean serum phosphate level did not change much during the 3 months study and the differences in two groups were not statistically significant.

The mean basal serum calcium phosphate product was 48.92±5.65 mg^2 dL^{-2} and 48.88±4.56 mg^2 dL^{-2}, respectively in group I and II. There was slow increase in calcium phosphate product during the study but this was not statistically significant ($p>0.05$). The mean values at the end of the study were 51.85±5.36 mg^2 dL^{-2} and 50.70±2.90 mg^2 dL^{-2} in group I and II, respectively.

The mean iPTH levels decreased in both the groups. In group I (calcitriol group) iPTH level decreased from

Table 1: Age and sex of the patients

	No. of patients	
Parameter	Group I	Group II
Age (in years)		
20-29	3	3
30-39	4	5
40-49	6	3
50-59	5	7
60+	7	7
Total	25	25
Sex		
Male	13	15
Female	12	10
Total	25	25

Table 2: Basal values of renal function test

Investigations	Group I	Group II	p-value
Hemoglobin (g m%)	8.46±1.20	7.79±1.32	>0.05
Serum potassium (meq L^{-1})	4.37±0.65	4.15±0.87	>0.05
Blood urea (mg%)	136.36±52.66	151.32±43.14	>0.05
Serum creatinine (mg%)	4.92±1.93	5.52±1.41	>0.05
Serum calcium (mg%)	8.94±0.96	8.55±0.84	>0.05
Serum phosphorus (mg%)	5.52±0.70	5.76±0.71	>0.05
Serum calcium phosphate product (mg^2 dL^{-2})	48.92±5.65	48.88±4.56	>0.05
GFR (mL min^{-1})	17.88±4.21	18.00±3.99	>0.05

Table 3: Corrected serum calcium levels (mg%)

Group	Basal	At end of Ist month	At end of 2nd month	At end of the study
I	8.94±0.96	9.10±0.90	9.38±0.84	9.72±0.85
II	8.55±0.84	8.62±0.94	8.81±0.94	9.12±1.10
p-value comparison				
I vs. II	>0.05 N.S.*	>0.05 N.S.*	<0.05 S**	<0.05 S**

*NS: Non significant, **S: Significant

Table 4: Serum intact PTH levels (in pg mL^{-1})

Group	Basal	At end of study
I	490.52±271.76	424.56±284.88
II	432.80±224.86	246.20±220.00
p-value comparison		
I vs. II	>0.05 NS*	<0.05 S***

NS: Non significant statistically, **S: Significant statistically

490.52±271.76 pg mL^{-1} to 424.56±284.88 pg mL^{-1} with 13.44% reduction. In group II (doxercalciferol group) it decreased from 432.80±224.86 to 246.20±220.0 pg mL^{-1} with 43.1% reduction. In group I, one out of 25 patients (4%) achieved >50% reduction in serum iPTH level at the end of study, whereas 14 out of 25 patients (56%) achieved 50% reduction in serum iPTH level at the end of the study. The iPTH in group I ranged from 168-992 and 86-998 pg mL^{-1} at baseline and at the end of study, respectively in group II. These results show that there was significantly more decrease in iPTH levels of group II patients ($p<0.05$) (Table 4).

During the study, patient were assessed for side effects due to doxercalciferol which included headache, palpitation, malaise, constipation, dyspepsia, abdominal pain, fever etc. None of the patients in any of the groups developed any significant side effect so as to warrant reduction in dosage or withdrawal of drug.

DISCUSSION

The present study is one of the first studies to compare the efficacy of doxercalciferol and calcitriol in lowering the serum levels of intact PTH in stage III and IV CKD patients with moderate to severe secondary hyperparathyroidism. This study differs from previous studies that evaluated calcitriol, alfacalcidol or doxercalciferol independently without comparing their efficacy.

In the present study, the comparison was made by using reduction in iPTH levels after three months of calcitriol and doxercalciferol treatment. Incidence of hypercalcemia in both the groups was calculated. The reduction in serum iPTH levels was significantly more in doxercalciferol group (43.1%) than calcitriol group (13.44%). Only one of twenty five patients (4%) of calcitriol group achieved >50% reduction in serum iPTH level, while fourteen out of 25 patients (56%) in doxercalciferol group achieved >50% reduction in serum iPTH levels at the end of study.

There were lesser episodes of hypercalcemia (serum calcium >10.5 mg dL^{-1}) in the doxercalciferol group (3 in number) as compared to calcitriol group (8 in number). There was 1 episode of hypercalcemia for 100 weeks of treatment with doxercalciferol while 2.67 episodes per 100 weeks of treatment were noted with calcitriol. The mean serum phosphorous and calcium phosphate product levels did not change significantly during the study.

Doxercalciferol (1 alpha, hydroxyl vitamin D2) is a second generation prohormone analogue, which undergoes activation within liver and get converted into active metabolite such as 1.25 dihydroxy vitamin D2 (major) and 1.24 dihydroxy vitamin D2 (minor). 1.25 dihydroxy vitamin D2 is equivalent to calcitriol stimulating intestinal calcium absorption and mobilizing bone calcium but higher doses of this compound are required to produce hypercalcemia and vitamin D toxicity. A portion of inactive 1 alpha hydroxyl vitamin D2 also enters directly into target cells (parathyroid gland) and undergoes 24 hydroxylation to produce active metabolite, 1.24 dihydroxy vitamin D2. This compound has been shown to be an extremely potent antiproliferative agent with minimal calcemia potential. This has been proposed as an explanation for better efficacy and lower toxicity of doxercalciferol with chronic treatment. Present results were similar with study conducted by Cobum *et al.* (2004) which was a randomized, double blinded, placebo controlled, multicenter trial including fifty five adults with mean age of 18-55 years with stage III and IV CKD and having iPTH level of >85 pg mL^{-1}. Patients were randomly assigned to one of the two groups. Group A received doxercalciferol in dosages of 1 μg day^{-1} for a period of 24 weeks while group B were given placebo. In the doxercalciferol group, mean iPTH level decreased from a baseline of 219±22 pg mL^{-1} to 118±17 pg mL^{-1} at 24 weeks. Conversely mean iPTH level in the placebo group did not change significantly from a baseline of 171±14 to 167±15 pg mL^{-1} at 24 weeks. Twenty of twenty seven (74%) subjects treated with doxercalciferol achieved 30% or greater reduction in mean iPTH level from the baseline during weeks 20 and 24 while only 7% of placebo group patients achieved >30% of reduction in iPTH. This study showed that doxercalciferol was highly effective in reducing elevated iPTH levels in patients with secondary hyperparathyroidism associated with mild to moderate renal insufficiency. It was also noted that there was no significant increase in calcium and phosphorus product at the dosage which achieved significant decrease in iPTH levels. Hence the study showed that doxercalciferol was safer for treatment of secondary hyperparathyroidism in CKD III and IV patients (Cobum *et al.*, 2004).

Tan Jr *et al.* (1977) in another multicenteric study evaluated the safety and efficacy of doxercalciferol in 24 hemodialysis patients with SHPT (serum iPTH >400 pg mL^{-1}). Calcium based phosphate binder alone were used to maintain serum phosphorus <6.9 mg dL^{-1}. Oral doxercalciferol was used in dosage of 4 μgm thrice

weekly with dose adjustment done over 12 weeks to maintain iPTH between 130-250 pg mL^{-1}. In this study, by the end of first week of treatment the serum iPTH levels had decreased significantly and there was a steady decline throughout the remainder of treatment period. Pretreatment serum iPTH fell from 672±70 to 289±36 pg mL^{-1} after treatment ($p<0.05$). Serum calcium increased moderately from 8.8±0.2 to 9.5±0.2 mg dL^{-1} after treatment ($p<0.001$). Neither the average serum phosphorus level, nor the dose of phosphate binders were changed from washout period. Thus, this study showed that oral doxercalciferol is highly effective, in suppressing SHPT in haemodialysis patients and is safe despite exclusive use of calcium based phosphate binders (Tan Jr *et al*., 1977).

There is paucity of studies in literature comparing the efficacy of doxercalciferol and calcitriol to reduce SHPT. Although our study is of short duration with small sample size, this is one of the earliest studies and has revealed that doxercalciferol is highly effective in reducing elevated iPTH level in patients with secondary hyperparathyroidism associated with CKD. The side effects like hypercalcemia were less with the use of doxercalciferol which is likely to cause lesser vascular calcification and decrease other risk associated with hypercalcemia. However, long term follow up studies have to be undertaken to assess the efficacy of doxercalciferol in treatment of secondary hyperparathyroidism.

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