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Safety profile of Cinacalcet Compared to conventional therapy used in treatment of CKD-sHPT at teaching hospital, Saudi Arabia

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Abstract

Almost all patients who have kidney failure develop sHPT. Cinacalcet is a calcimimetic agent accepted for treatment of Secondary parathyroidism in End Stage Renal Disease patients. The frequently reported adverse events with cinacalcet were hypocalcaemia, diahorrea, vomiting and nausea. A retrospective cohort study to assess the safety profile of cinacalcet compared to the conventional therapy after 6 months of use in Al-Mana Hospitals Dammam, Saudi Arabia. In the study data were taken during the period from Dec-2017 to Jul-2019. Total 81 subjects were enrolled in this study. While 40 patients were taking cinacalcet and 41 patients were taking conventional therapy. The mean age for cinacalcet group was (63.75± 14.76) yrs. 25 (63%) males and 15 (37%) females).For the conventional therapy arm the mean age was (62.1±9.91) yrs. 85(91%) males and 6 (15%) females. After 6 months treatment, 75% (30 patients) has developed Hypocalcemia (Serum calcium<8.4 mg/dL) in patients using cinacalcet in comparison to 40% (16 patients) in the conventional therapy arm with significance (p = 0.001).

Nausea was experienced by 33 patients (83%) in the patients who was taking cinacalcet compared to 8 patients (21%) who were on conventional therapy with clear significance (P = 0.00). there is significant difference in incidence of vomiting (15 patients (38%) in the cincalcet Vs. 15% (6 patients) for the conventional therapy arm (p= 0 .02) Diarrhea was reported in 4 patients on cinacalcet (10%) and 2 patients in the conventional therapy arm (5%) with= 0.414).

Compared to conventional therapy, there was a significant difference in the hypocalcaemia, nausea and vomiting due to cinacalcet use, but there was no significant difference in the diahorrea incidence.

Key Word: Cinacalcet ,CKD, sHPT, Safety, Saudi Arabia

INTRODUCTION

Chronic kidney disease (CKD) proceed from early to late-stage disease. Estimated glomerular filtration rates (eGFR) range from 90 mL/min.in the early stages to 15 mL/min.in the late stages of disease. eGFR is less than 15 mL/min. is diagnosed as End-stage renal disease (ESRD). Complications known to be associated with CKD are anemia, fluid and electrolyte abnormalities, and cardiovascular disease, hyperparathyroidism [1].

The “trade-off” hypothesis best describes the events leading to changes in bone metabolism.As eGFR decreases, phosphorus excretion by the kidney decreases, resulting in hyperphosphatemia.

Hyperphosphatemia will lead to a decline in ionized calcium concentration, a primary stimulus for of parathyroid hormone (PTH) release. Higher concentrations of PTH decrease phosphorus renal reabsorption and promote its excretion. Serum phosphorus and calcium concentrations are corrected but the expense will be elevated PTH concentration (the “trade off”).

As kidney disease becomes more severe (eGFR <30 mL/minute/1.73 m2), this correction mechanism diminishes and sustained hyperphosphatemia and hypocalcemia develop. In response to hypocalcemia, calcium is mobilized from the bone, a mechanism largely controlled by PTH. These changes are common in Chronic Kidney Disease patients and add to the extravascular calcifications and the increased risk of cardiovascular mortality [2].

Virtually all kidney failure patients develop sHPT. The drop in PTH degradation by the kidney may also contribute to the hyperparathyroid state in kidney disease patients. The kidney is the principal organ responsible for vitamin D production and, as such, vitamin D metabolism is altered in the presence of uremia. Persistent hyperphosphatemia inhibits vitamin D activation [1,2].

Treatment of CKD patients is best achieved using a multidisciplinary approach. One of the drugs used is Cinacalcet [1].

Cinacalcet

Cinacalcet hydrochloride (Sensipar®, Mimpara®) is a calcimimetic agent was accepted for treatment of sHPT in CKD patients. Cinacalcet is the first agent in calcimimetics to receive FDA approval. It mimic the effect of extracellular ionized calcium and also increase the the calcium-sensing receptor sensitivity to calcium, which leads to reduction in PTH secretion. It’s maximum plasma concentration is attained in approximately 2 - 6 hours following oral administration. The half-life is approximately 30 - 40 hours [1].

In many RCTs, conducted in dialysis patients (predominantly hemodialysis) cinacalcet significantly decreased PTH within 6-month period, regardless of the severity of sHPT. The starting dose is 30 mg per day was increased every 3 or 4 weeks to avoid hypocalcemia incidence. If a patient has shown symptoms of hypocalcemia (or serum calcium drop <8.4 mg/dL),

calcium supplements could be increased. If ineffective, vitamin D dose increament is advised.

Adverse Effects.

The most frequently reported adverse events with cinacalcet were nausea, vomiting and diahorrea. Although vomiting and nausea occurred frequently with cinacalcet, these events were generally transient, mild - moderate in nature, and infrequently led to poor compliance. Cinacalcet may cause hypocalcemia; therefore this agent should not be started if the serum calcium is lower than the bottom limit of normal, approximately 8.4 mg/dL. Serum calcium is usually measured within one week after starting cinacalcet and then monthly. Clinical manifestations of hypocalcemia are paresthesia, myalgia, tetany, cramping and convulsions [2,3].

MATERIAL AND METHODS:

Study design

A retrospective cohort study to assess the safety profile of cinacalcet compared to the conventional therapy used in sHPT-CKD patients after 6 months of starting the drug in Al-Mana Hospitals during the period from Dec-17 to Jul-19.

Study Population

A total of 81 subjects were enrolled in this study.40 of them in the cinacalcet arm and 41 in the conventional therapy arm.

Inclusion Criteria

- Patients with sHPT-CKD over 18 years old who were on dialysis (HD or PD).
- Any gender
- Stage 4 & 5 Kidney disease patient were included in the study

Exclusion Criteria

- Patients under gone parathyroidectomy were excluded
- Patients less than 18 years old.
- Pregnant women

Study procedures and measurements

Data were based on medical records and on the laboratorial evaluation obtained between Dec-2017 and Jul 2019. For this purpose, the Hospital Information network was used. The following demographic variables were analyzed at baseline: age, sex. The following clinical variables were analyzed at baseline: CKD etiology. The following drug's related adverse reactions were evaluated after 6 months of treatment: Hypocalcaemia, Nausea, Vomiting and Diahorrea.

Statistical analysis

A descriptive analysis was initially carried out and the data were reported by the mean±standard deviation, median (interquartile range) or percentage, depending on the variable. The population was divided based on Cinacalcet use. Demographic & clinical records were compared between groups through chi-square. A p ? 0.05 was set to be used. Descriptive statistics used and differences in adverse reactions' incidence rates between two treatment arms were calculated and compared

Ethical Approval

Study has been approved form scientific research Mohammed Al-Mana College For Medical Sciences, Dammam Saudi Arabia. Study approval number SR/RP/13.

RESULTS

The demographic variables analyzed which includes age and sex were shown in table 1. The mean age for cincalcet group was found to be (63.75± 14.76) years and for the conventional therapy was (62.1±9.91) years. Gender analysis has shown that there were 25 (63%) males and 15 (37%) females in the cincalcet group.in the conventional therapy arm there were 35(85%) males and 6(15%) females.

In the cinacalcet group the cause of CKD was found to be in 27 patient (68%) was Diabetic nephropathy and in 13 patients (32%) was Diabetic nephropathy& Hypertension. In the conventional therapy arm 21 patients (51%) developed CKD due to Diabetic nephropathy and 13 patients (32%) due to Diabetic nephropathy& Hypertension. The cause of CKD in 7 patients (17%) in the conventional therapy arm is unknown.

Common study drug-related adverse events analysis in Table 2 has shown that 30 cases (75%) has developed Hypocalcemia (Serum calcium<8.4 mg/dL) in the cinacalcet arm in comparison to 16 cases (40%) in the conventional therapy arm with clear significance (p = 0.001). Nausea was experienced by 33 patients (83%) in the patients who was taking cinacalcet compared to 8 patients (21%) who were on conventional therapy (P = 0.00).

Table 1: Baseline demographics of study patients

	Cinacalcet group (N =40)	Conventional therapy group (N =41)
Age [year] Mean±SD	63.75± 14.76	62.1±9.91
Gender [N (%)] Male Female	25 (63%) 15 (37%)	35(85%) 6(15%)
Primary diagnosis [N (%)] Diabetic nephropathy	27(68%)	21(51%)
Diabetic nephropathy+ Hypertension	13(32%)	13(32%)
Unknown	0	7(17%)

Table 2: Common study drug-related adverse events

ADR	Total (N =81)		Cinacalcet group (N =40)		Conventional therapy group (N =41)		Group comparison Chi Square test *P Value
	cases	Subjects (%)	cases	Subjects (%)	cases	Subjects (%)	
Hypocalcemia	46	57%	30	75%	16	40%	0.001
Nausea	41	51%	33	83%	8	21%	< 0.05
Vomiting	21	26%	15	38%	6	15%	*0* .02
Diahorrea	6	7%	4	10%	2	5%	0.414

*P-value ≤ 0.05 considerd as significant

Significant difference was noticed in incidence of vomiting (15 patients (38%) in the cincalcet Vs. 6 patients (15%) in the conventional therapy group (p= 0 .02). Diarrhea was reported equally in 4 patients in the cinacalcet arm (10%) and 2 patients in the conventional therapy arm (5%, P = 0.414).

DISCUSSION:

In the safety profile, our study revealed that Hypocalcemia incidence was higher in the cincalcet group compared to the conventional therapy (73% vs 27%) with clear significance (P=0.001).

National Institute for Health and Clinical Excellence Final Appraisal in 2006 has reported a difference without significance in a comparison of cincalcet with placebo [4]. Also In 2016, Sekercioglu N and colleagues showed that Cinacalcet treatment results in increased the rate of hypocalcemia (RR 6.0) [5]. Torres PU concluded in there were hypocalcemia episodes in 5% of cinacalcet subjects versus 1% of placebo subjects [6].

Greeviroj P and colleagues in 2018 showed that Cinacalcet lead to significant increase in the risk of hypocalcemia. [7].

In a 238 subjects Double-blind, multicenter, placebo-controlled, randomized phase III study in china in 2016, Mei C and his colleagues showed that Mild - moderate episodes of hypocalcemia & low calcium levels were reported and interpreted as Cinacalcet- related[8].

Our study showed that Nausea incidence was higher in the cinacalcet arm in comparison to conventional therapy (91% vs 27%) (significance (P< 0.05)). Equivalent results were publicized by many previous analyses [4,5,9,10,11].

Results from our study has shown cincalcet was responsible for higher incidence of vomiting compared to conventional therapy (36% vs 18%) with clear significance (P= 0.02). these findings were consistent with many publications from the literature and many of them has shown significant difference[4,5,7,9,10].

On the hand our study didn't detect any difference in incidence of diarrhea, the incidence was in 4(10%) and 2(5%) for cinacalcet and conventional therapy respectively (P= 0.414), while results from previous studies demonstrated higher incidence of diahorrea in the cinacalcet arm when compared to other different secondary hyperparathyroidism regimens[4,6,7,9,10].

CONCLUSION

Compared to conventional therapy, there is a significant difference in the vomiting, nausea and hypocalcaemia incidence due to cinacalcet use but there was no significant difference in diahorrea incidence.

Conflict of interest: All author(s) declared that there is no Conflict of interest.

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