Port J Nephrol Hypert 2007; 21(3): 225-229

Treatment of secondary hyperparathyroidism with Cinacalcet is associated with an increase in haemoglobin levels

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Received for publication: 19/05/2007
Accepted in revised form: 12/07/2007

ABSTRACT

Introduction: There are several potential mechanisms through which hyperparathyroidism secondary to chronic renal failure can worsen anaemia. These include a direct toxic effect of parathyroid hormone on endogenous erythropoietin synthesis, red blood cell production and survival or an indirect mechanism via the induction of bone marrow fibrosis. Several studies have demonstrated a significant increase in the mean haematocrit value after parathyroidectomy or calcitriol administration.

With this study we attempt to answer the question: what effect do calcimimetics have on haemoglobin levels in chronic haemodialysis patients?

Methods: We selected all patients starting treatment with cinacalcet in our haemodialysis unit and who completed 12 months of follow-up (n=28). We retrospectively evaluated levels of haemoglobin, serum ferritin, transferrin saturation, mean weekly dose of darbepoetin alfa, serum calcium, serum phosphorus and serum intact parathyroid hormone.

We compared the difference between mean values in the 3 months before calcimimetic use (-3M) and at 3, 6, 9 and 12 months of treatment using paired samples t-test.

Results: A statistically significant (p=0.01) increase in haemoglobin levels (g/dl) was observed at 9 months (11.88±0.75 *vs.* 12.48±1.02) after calcimimetic introduction. This increase (p=0.04) was also seen at 12 months (12.29±0.98).

The mean weekly dose of darbepoetin alfa (µg/kg/ /week) showed no significant difference (p=0.40) before and after calcimimetic: 0.39±0.28 at -3 M *vs.* 0.44±0.33 at 12 M.

There were no significant differences (p>0.05) in serum ferritin or transferrin saturation before treatment, at 6 M or at 12 M.

Conclusions: The treatment of secondary hyperparathyroidism with cinacalcet seems to have a beneficial effect on haemoglobin levels in haemodialysis patients.

Key-Words:
Anaemia; calcimimetics; cinacalcet; haemodialysis; secondary hyperparathyroidism.

INTRODUCTION

The negative influence of secondary hyperparathyroidism (SHPT) on the anaemia of uraemic patients was first described approximately 3 decades ago[1].

There are several potential mechanisms by which SHPT can worsen anaemia. These include a direct toxic effect of parathyroid hormone (PTH) on endogenous erythropoietin (EPO) synthesis. The rise of serum EPO concentration after parathyroidectomy (PTX) in dialysis patients has been reported in several studies in the literature[2,3]. A negative direct effect of PTH on red blood cell production and survival has been proposed[4,5] but the studies have conflicting data. Meytes *et al*. demonstrated that bovine PTH inhibits human and mouse erythroid burst forming directly. On the contrary, Komatsuda *et al* [6] reported that human PTH does not directly inhibit human erythropoiesis. An indirect mechanism is described via the induction of bone marrow fibrosis and a concomitant reduction of space for erythrogenesis.

Zingraff *et al* [1] demonstrated a significant increase on the mean haematocrit value after subtotal PTX. Serial bone biopsies suggested a relationship between the amount of marrow fibrosis and the improvement of anaemia after surgery. They cannot explain the mechanism behind this fact. Rao *et al* [7] reported that response to EPO therapy depends largely on the extent and severity of bone marrow fibrosis due to SHPT.

Several studies have demonstrated that treatment with intravenous calcitriol in patients on haemodialysis controls SHPT, improves anaemia and decreases the need for EPO[8-10].

Calcimimetics suppress the secretion of PTH by increasing the sensitivity of the calcium receptors (CaR) of parathyroid cells to extracellular ionised calcium. The US Food and Drug Administration and the European Medicines Agency have recently approved Cinacalcet HCl for the treatment of SHPT of dialysis patients.

If PTX and the use of vitamin D have a positive effect on the haematocrit of uraemic patients, may we expect a similar favourable effect from calcimimetics?

With this study we attempt to answer the question: what is the effect of calcimimetics on haemoglobin levels in chronic haemodialysis patients?

PATIENTS AND METHODS

We selected all patients starting treatment with cinacalcet in our haemodialysis unit and who completed 12 months of follow-up (n=28; 16 female and 12 male; 55.0±17.4 years old).

The criteria for beginning cinacalcet were severe SHPT without response to standard vitamin D therapy, vitamin D dose limited by hypercalcaemia, hyperphosphataemia, and/or increased calcium-phosphorus (Ca x P) product.

We excluded patients with prior PTX and documented bleeding.

Oral cinacalcet (marketed as Mimpara® in the EU and as Sensipar® in the USA by Amgen Inc) was titrated from 30 mg/day and the therapeutic schedule was initially maintained without changes when cinacalcet was introduced.

The vitamin D metabolite dosing remained unaltered (Alphacalcidol: Etalpha® by Leo Pharma; Calcitriol: Calcijex® by Abbott; Paricalcitol: Zemplar® by Abbott), given in intravenous pulses immediately after haemodialysis sessions.

A combination of calcium-based phosphate binding agents (calcium carbonate), aluminium-containing phosphate-binding agents (aluminium hydroxide) and non-calcium, non-aluminium, non-magnesium-containing phosphate-binding agents (Sevelamer: Renagel® by Genzyme) were used to achieve the serum phosphorus target.

Doses were adjusted according to patient response. Criteria for vitamin D metabolites and/or cinacalcet dosage adjustment were based on the K/DOQI guidelines recommended levels of calcium, phosphorus and/or PTH.

The doses of darbepoetin alfa – Aranesp® by Amgen – and iron sucrose – Venofer® by Vifor International – underwent changes throughout the study period to maintain haemoglobin level between 11-14 g/dl and serum ferritin levels between 200-500 µg/l.

We retrospectively evaluated haemoglobin (Hb), serum ferritin (Ferritin), transferrin saturation (TSAT), mean weekly dose of darbepoetin alfa (W/Dα), serum calcium (Ca), serum phosphorus (Pi), serum intact PTH (iPTH) and C–reactive Protein (CRP).

These parameters were measured before (last 3 months mean – avg-3M) and at 3rd (3M), 6th (6M), 9th (9M) and 12th months (12M) management with cinacalcet. Ferritin and transferrin saturation were evaluated before and at the 6th and 12th months.

The differences where evaluated by paired samples t-test using MedCalc Statiscal Software®.

RESULTS

We confirmed the effectiveness of cinacalcet in the management of secondary hyperparathyroidism (Table I).

The mean initial values of iPTH, calcium and phosphorus were 716.9±471.6 pg/ml; 10.16±0.43 mg/dl and 5.72±1.20 mg/dl respectively. We observed a statistically significant (p≤0.0001) decrease of iPTH, calcium and phosphorus levels from the 3rd month of treatment.

At the 12th month the NKF-K/DOQI objectives for iPTH (150-300 pg/ml) were achieved in 64.28% patients; for calcium (8.4-9.5 mg/dl) in 71.43% and for phosphorus (3.5-5.5 mg/ml) in 51.14% patients.

The mean daily dose of cinacalcet prescribed at 12th months was 57.85±29.35 mg (30-120 mg/day).

A statistically significant (p=0.01) increase in haemoglobin levels was observed at the 9th month (11.88±0.75 g/dl *vs*. 12.48±1.02 g/dl) after calcimimetic introduction. This increment was sustained at the 12th month (12.29±0.98 g/dl) (p=0.04). (Table I)

The improvement of anaemia was further emphasised by no concomitant significant difference (p=0.40) in the mean weekly dose of darbepoetin alfa: 0.39±0.28 µg/Kg/week at -3M *vs*. 0.44±0.33 µg/Kg/week at the 12th month.

There are no significant differences (p>0.05) in serum ferritin or transferrin saturation levels before treatment, at the 6th month or the 12th month.

Cinacalcet was well tolerated, with no cases of symptomatic hypocalcaemia.

The most common side effects, nausea and vomiting in four patients, were usually mild to moderate in severity, were transient and did not lead to suspension of the treatment.

DISCUSSION

We describe the association of cinacalcet treatment and an increase in the haemoglobin levels in 28 chronic haemodialysis patients. We found a statistically

Table I

Effects of Cinacalcet on secondary hyperparathyroidism and anaemia

n=28	-3M	3M	6M	9M	12M
iPTH	716.9±471.6	441.9±297.4	269.5±201.6	283.5±185.2	307±220.3
pg/ml		P=0.0001	P<0.0001	P=0.0001	P=0.0001
Ca	10.16±0.43	8.67±0.78	8.87±0.69	8.76±0.93	9.06±0.69
mg/dl		P<0.0001	P<0.0001	P<0.0001	P<0.0001
Pi	5.72±1.20	4.45±1.27	4.72±1.95	4.80±1.55	4.63±1.62
mg/dl		P<0.0001	P=0.0014	P=0.0042	P=0.0016
Hb	11.88±0.75	12.07±1.07	11.98±0.93	12.48±1.02	12.29±0.98
g/dl		P=0.28	P=0.72	P=0.01	P=0.04
W/D	0.39±0.28	0.41±0.30	0.44±0.30	0.47±0.32	0.44±0.33
g/Kg/week		P=0.42	P=0.31	P=0.16	P=0.40
Ferritin	389.00±220.48		356.32±233.98		332.57±126.60
g/l			P=0.58		P=0.18
TSAT	30.60±10.20		31.28±14.21		30.95±9.39
%			P=0.84		P=0.86
CRP	0.49±0.54	0.53±0.60	0.68±1.12	0.5±0.52	0.54±0.85
mg/dL		P=0.62	P=0.41	P=0.98	P=0.79

significant increase in haemoglobin levels after 9 months of cinacalcet induced secondary hyperparathyroidism control.

No direct or indirect beneficial effect of calcimimetics on anaemia in chronic kidney disease patients has been reported so far. Drüeke[11] comments that it would be interesting to examine this possibility in future studies.

This is a retrospective single centre study with a small number of patients who are their own controls before and after initiation of treatment. A small number of patients were enrolled because only cinacalcet-naïve patients with severe secondary hyperparathyroidism in steady treatment were included.

This study does not provide an understanding of the mechanisms behind the effect of cinacalcet. We observed that the iPTH decreased rapidly during the first 6 months of treatment and then remained stable. The haemoglobin level only increased significantly after 9 months on cinacalcet and then remained constant. This delayed response suggests an indirect mechanism rather than a direct toxic effect of iPTH in erythropoiesis.

It is possible that the erythropoiesis improvement is due to the bone marrow fibrosis reduction. A decrease in bone marrow fibrosis has been demonstrated in dialysis patients treated for a year with cinacalcet in a randomised, double-blind, placebo-controlled study with bone biopsies at baseline and after one year of treatment[12].

However, a direct effect of calcimimetic in haematopoiesis through its action in the calcium-sensing receptor (CaR) is a possible hypothesis. Several observations strongly suggest that osteogenesis and haematopoiesis are functionally linked. During mammalian ontogeny, haematopoietic stem cell moves from the foetal liver to the bone marrow, where haematopoiesis occurs throughout adulthood. Unique features of bone that contribute to a microenvironmental niche for stem cells might include the known high concentration of calcium ions. Cells respond to extracellular ionic calcium concentrations through the calcium-sensing receptor (CaR), which Adams *et al.*[13] identified as being expressed on haematopoietic stem cells. They showed that through the CaR, the Ca content of the niche may dictate the preferential location of adult mammalian haematopoiesis in bone. Stier *et al.*[14] suggested that extracellular matrix components might play a dynamic role not just in establishing the stem cell pool size, but also in governing its responsiveness to expansion signals.

CONCLUSION

The treatment of hyperparathyroidism with cinacalcet seems to have a positive effect on haemoglobin levels in haemodialysis patients. The mechanism is still unknown. Further larger and prospective studies are needed to confirm and understand these results.

Conflict of interest statement. None declared.

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