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Review

Possible renoprotection impact of cinacalcet; a review on current studies

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Abstract

Cinacalcet, as the first type II of calcimimetic restrains parathyroid hormone (PTH) secretion by enhancing the sensitivity of calcium-sensing receptors (CaSR) on the parathyroid glands and thereby reduces serum calcium concentrations. Calcimimetic agents would be supposed to affect urinary calcium excretion through PTH-dependent and PTH-independent responses since PTH-independent actions are mediated by renal CaSR. Renal CaSR is included in mineral ion metabolism, adjustment of urinary acidification, concentration, renin secretion and control of blood pressure. It is proved that renal CaSR is an element contributing in the reabsorption of calcium, independent of PTH. Cinacalcet can be administered for different kidney diseases associated to primary and secondary hyperparathyroidism concluding nephrolithiasis, dialysis, renal graft, chronic kidney disease (CKD) who is not receiving dialysis, acute kidney injury (AKI) and diabetic nephropathy (DN). Cinacalcet has renoprotective role especially in CKD patients.

Keywords: Parathyroid hormone, Calcimimetic, Calcium-sensing receptors, Chronic kidney disease, Acute kidney injury, Renal graft, Diabetic nephropathy

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Introduction

The kidneys present a critical character in the calcium equilibrium between the inside and outside environments of human body. If someone be had kidney disease, it is very important that calcium and phosphate balance is checked and managed correctly. When kidneys start to damage they cannot remove the excess phosphate from body and leads to an increase in production of parathyroid hormone (PTH). This also leads to accumulate too much phosphate in body. Phosphate and calcium imbalance has important implications in patients with chronic kidney disease (CKD). The excess phosphate binds to calcium, which, in turn, lowers body calcium levels (hypocalcemia) that may increase risk of osteoporosis and fracture. Extra-secretion of PTH by the parathyroid glands in feedback to hypocalcemia result to secondary hyperparathyroidism (SHPT). Treatment of calcium and phosphate imbalance is intended to avoid phosphate levels increasing in blood, preserve serum calcium amount, preserve serum activated vitamin D amount, reduce the secretion of PTH and avoid bone disease caused by the deficit of calcium. Presently, available treatment choices comprise regime phosphorus limit, vitamin D analogues, phosphate binders, calcimimetics, and in acute conditions, parathyroid surgery (1). Two types of calcimimetics bind to calcium-sensing receptors (CaSR) as agonists (type I interacts with special binding sites) and allosteric modulators (type II that interacts with non-special binding sites for calcium). Cinacalcet, first type II calcimimetic restrains PTH secretion by increasing the sensitivity of CaSR on the parathyroid glands and thereby reduces serum calcium concentrations (2). Most treatment methods, before the calcimimetics (such as vitamin D and calcium-based phosphate binders) used in the controlling of SHPT in patients with kidney disease resulted in increase in serum calcium concentrations. All medical trials assumed that cinacalcet is useful for the decrease of PTH, serum calcium, phosphorus, and calcium-phosphorus product levels. Although cinacalcet is available as an appropriate oral therapy for inpatient and outpatient use and has a very wide applicability (including primary hyperparathyroidism [PHPT], SHPT and parathyroid cancers), however its chief disadvantage is its high cost that restricts its consumption (3).

The CaSR is expressed in various other organs outside the parathyroid gland, such as the kidney, but the significance of extra-parathyroid CaSR in calcium metabolism remains unidentified. Calcimimetic drugs would be supposed to affect urinary calcium excretion via PTH-dependent and PTH-independent responses (4) that PTH-independent actions are mediated by renal CaSR. Renal CaSR is included in mineral ion metabolism,

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Implication for health policy/practice/research/medical education

Recent studies show cinacalcet has renoprotective efficiency especially in chronic kidney disease patients.

adjustment of urinary acidification, concentration, renin secretion and control of blood pressure. In the kidney, CaSR is signified in different sections of the nephron, including the proximal tubule, thick ascending limb of the loop of Henle, juxtaglomerular cells and inner medullar collecting duct (5). It is proved that renal CaSR is an element contributing in the reabsorption of calcium, independent of PTH, by change of the lumen-positive transepithelial electrical potential for paracellular calcium transport (6,7). Therefore, the effects of cinacalcet are not restricted to reduce the secretion of PTH, since it is extended to reduce hyperplasia and parathyroid cell proliferation and increase of the expression of the CaSR in kidney cells (8). Furthermore, cinacalcet seems to be able to inhibit the progression of vascular calcification both directly and indirectly through improved inorganic metabolism by increasing the matrix-Gla protein (MGP), decreasing of bone morphogenetic protein-2 (BMP-2), and decreasing secretion of type I collagen (9). It is reported that CaSR stimulation decreases powerfully cyclic adenosine monophosphate (cAMP) formation and renin secretion (10), which resulting to calcium-mediated renin inhibition and probably decreasing systolic blood pressure (12).

Serum PTH concentration of CKD patients should be checked repeatedly and kept up within standard ranges that are characterized in proportion the CKD stage in accordance with the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines. Indeed, when the plasma PTH concentration is higher than standard amount, drugs that lowering PTH secretion, for example cinacalcet, may be required (13).

There are at least two long-term chief trials EVOLVE and ADVANCE that try to assay the effects of cinacalcet on cardiovascular consequences. The EVOLVE (EValuation of Cinacalcet HCl Therapy to Lower CardioVascular Events) trial addresses to estimate the cinacalcet effects on all-cause mortality and cardiovascular events in almost 3900 CKD patients with SHPT on dialysis. The ADVANCE (a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis) trial designs to examine the cinacalcet effect accompanied by vitamin D on the progression of ischemic heart disease stages and intermediate endpoint of cardiovascular calcifications in 330 patients with CKD on dialysis (14).

Search strategy

For this review, we searched Web of Science, EBSCO, Scopus, PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase, and Google Scholar using the following keywords: Parathyroid hormone, calcimimetic, calcium-sensing receptors, chronic kidney disease, acute kidney injury, renal graft and diabetic nephropathy.

Cinacalcet application

Cinacalcet can be administered for different kidney diseases associated to primary and secondary hyperparathyroidism is explained in detail as follows:

1. Nephrolithiasis (kidney stone disease)

Cinacalcet is revealed a mathematical significant reduction in the total number and diameter of renal stones in patients with PHPT containing kidney stone. Also, it is shown a potential use of Cinacalcet as a long-term medicinal therapy for patients with PHPT and periodic renal stones who are inappropriate for parathyroidectomy (15,16).

2. Dialysis

The present guidance for cinacalcet is proposing that cinacalcet must not be consumed conventionally for the therapy of high serum PTH levels in CKD people and should be restricted to people with high PTH concentrations resistant to normal treatment who parathyroid surgery is complicated because the more disadvantages rather to the advantages. Similarly, US Food and Drug Administration agreement for cinacalcet is limited to patients at end-stage renal disease stage with SHPT for prevent from surgical parathyroidectomy and hypercalcemia. The effect of cinacalcet on the level of serum phosphorus and calcium-by-phosphorus product seems to be related with the CKD stage. Cinacalcet obviously reduced the level of serum phosphorus and calcium-by-phosphorous product in patients with stage 5 CKD treated with dialysis (17,18).

Renal graft

Hypercalcemia concomitant with parathyroid surgery is a public problem after renal graft. Naturally, serum calcium amounts reduce in the urgent post-graft stage and then gradually rise and fix at a period of six months in following of graft with slight differences afterward. In 5-25% of cases, serum calcium levels stay high despite long-term kidney transplant receiving.

Generally, the effects of cinacalcet on transplant function has inconsistent outcomes. While some studies reported a steady transplant function after treatment with cinacalcet as short-term use, others recognized a decline of renal transplant function. One long-term study shows that cinacalcet not only regulates hypercalcemic of renal transplant patients but also adjusts serum phosphate levels. Continuous increases in PTH secretion after renal graft can also tend decreasing phosphate tubular reabsorption. Thus, hypophosphatemia is detected until 90% of occurrence renal graft receivers in the initial post-transplant stage. Cinacalcet reduced serum calcium and

PTH and improved serum phosphorus levels in renal graft receivers with continuous hyperparathyroidism. Thus, it proposes a perfect therapy for hypercalcemic renal graft receivers with associated hypophosphatemia, which is hard to medicate because of the hazard of extra-skeletal calcification maybe accompanying with phosphate additive (19,20). Therefore, it is suggested that cinacalcet acts as an alternative to parathyroidectomy in the controlling of persistent post-kidney graft hyperparathyroidism (21,22).

3. CKD patients who are not receiving dialysis

While cinacalcet was only accepted for SHPT treatment in dialysis patients, its use in patients with CKD who are not receiving dialysis has also been examined. Presently, cinacalcet is showed in the medication of CKD patients with SHPT suffering care with dialysis. However, cinacalcet use in non-dialysis patients is really unclear. It is shown that cinacalcet was little efficient for patients with stage 3 or 4 CKD without dialysis treatment compared to the stage 5 CKD with dialysis treatment. Recently, it is suggested that cinacalcet treatment could be a logical choice for non-dialysis patients and it shows effectively after three months of treatment. Moreover, the efficiency of cinacalcet appears to be adapted by basic PTH values, nevertheless CKD stage (23). Patients with CKD have characterized by disturbance in mineral and bone metabolism causing a multifaceted disorder that has been named CKD-mineral bone disorder (CKD-MBD) (24). Disturbances initiate in the initial stages of the CKD and aggravated with its advance. The biological changes of CKD-MBD include high PTH, decreased activated vitamin D and serum calcium, high serum phosphate and fibroblast growth factor-23 (FGF23) (24). Cinacalcet has been regarded a potential mediation to avoid cardiovascular results and death in CKD-MBD. In severe forms of the CKD-MBD disease (serum PTH >300 pg/mL), medicinal controlling needs combination therapy of vitamin D and calcimimetic agents (25).

4. Acute kidney injury

The adenine regime prompted severe acute kidney injury (AKI) matching to stage 4 CKD, with typical uremic results containing anemia, hyperphosphatemia, SHPT, and hyperkalemia. As expected, cinacalcet treatment well decreased PTH, whereas the therapy was without effect on kidney function in the adenine kind of AKI. Recently, moderate reduction of PTH with cinacalcet in the adenine-kind of CKD was addressed to weaken the endothelial-to-mesenchymal transition in kidneys that is common in atherosclerotic lesions and fibrotic disorders (10).

Lithium-prompted hypercalcemia is a CaSR syndrome that can occur in dynamically and earlier medicated patients. Endurance syndrome without regard of persistent lithium use has needed parathyroid surgery after control of hypercalcemia. It is suggested that cinacalcet can supply a substitute nonsurgical method to manage the syndrome. This may supply better long-term results in patients with hypercalcemia which surgical treatment for them is not a suitable (26).

5. Diabetic nephropathy

It is suggested cinacalcet may play a critical role in the prevention of diabetic vascular disease via the activation of nitric oxide synthase pathway. It is detected the important effect of cinacalcet in AMPK activation in ameliorating podocyte dysfunction beside its protective role in diabetic nephropathy. It is outlined an important physiologic role of calcium dependent AMPK activation in diabetic nephropathy, showing that recovery of AMPK activity by cinacalcet maintains therapeutic capability for diabetic nephropathy (5,27).

Conclusion

Calcimimetic drugs would be supposed to enhance urinary calcium excretion via PTH-dependent and PTH-independent responses that PTH-independent actions are mediated by renal CaSR. Therefore, cinacalcet can is used for different kidney diseases associated to primary and secondary hyperparathyroidism. Cinacalcet has renoprotective role especially in CKD patients receiving dialysis.

Authors' contribution

HN is the single author of the manuscript.

Conflicts of interest

This author is a researcher in Nickan Research Institute. However, the process of peer- review was no affected by his job.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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