Should cinacalcet be used in patients who are not on dialysis?

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The available information about cinacalcet indicates that it still should not be used in stages 3-4 CKD patients. It effectively reduces PTH but the decrease in serum calcium and the increase in serum phosphorus observed are non-desirable not fully understood effects which require further investigation.

MAIN TEXT

Despite the benefits observed in stage 5 CKD patients, the use of cinacalcet in earlier stages of CKD is still not approved and it is a highly controversial subject. Recently, the first long-term randomized, double-blind, placebo-controlled study on the efficacy and safety of cinacalcet in stages 3 and 4 CKD patients has been published[1]. The study showed that cinacalcet reduced the mean serum iPTH by 43.1% after 32 weeks of treatment. At the same time, cinacalcet led to an 8.9% decrease in serum calcium, a 21.4% increase in serum phosphorus and 14% decrease in urinary phosphorus excretion. The reduction of serum PTH and calcium are in keeping with the results observed after 5 years using cinacalcet in hemodialysis patients. On the contrary, changes in serum phosphorous observed in CKD patients not receiving dialysis, almost mirror the changes observed in stage 5 CKD patients.

Let us review the pathophysiological and clinical implications of the observed changes in the CKD-MBD biochemical parameters in patients not receiving dialysis. Hypocalcemia has been associated with both decreased[2] and increased mortality in hemodialysis patients[3]. In the study by Chonchol et al, serum calcium was 1 mg/dL lower in the cinacalcet than in the placebo group after 32 weeks despite the former consuming higher amounts of f vitamin D sterols. Serum calcium in the cinacalcet group was within the range of values associated with a higher risk of mortality[3]. We could argue the reduction in serum calcium is not the most relevant clinical problem because it could be corrected by increasing the use of vitamin D sterols and calcium supplements even in a greater proportion than in the study of Chonchol et al[1], where only 46% of patients in the cinacalcet group received vitamin D sterols compared with 25% in the placebo group, despite the decrease in serum calcium levels observed in patients treated with cinacalcet

The modulation of the response of the CaSR to cinacalcet in the different tissues is beyond our control. However, under the influence of cinacalcet, CaSR increases its sensitivity to calcium hence “sensing” low calcium just as if it was normal calcium; this is clearly beneficial for the parathyroid glands, but the same is not true for the kidneys where cinacalcet promoted a non-desirable increase in calcium excretion. It is likely that the cinacalcet-induced increase of CaSR sensitivity in the kidneys “perceives” low calcium as if it was normal calcium and, as a result, there is a non-desirable and

unnecessary high urinary excretion of calcium (50-60% higher than the baseline value in the paper by Chonchol et al), despite serum calcium, levels being low, making the CaSR kidney response to cinacalcet inappropriate and inconvenient.

The scenario became even more complex when we analyse cinacalcet-induced hyperphosphatemia which is probably the most worrisome concern about the use of this drug in the management of stages 3-4 CKD patients. Several studies have implicated serum phosphorus as one of the main factors responsible for vascular calcification and the strongest negative independent factor associated with survival[4]. Therefore, the hyperphosphatemic effect observed when administering cinacalcet to stages 3-4 CKD patients, –even with mean values in the high-normal range- ,represents a clear non-desirable effect which may have a negative impact in other CKD-MBD constellations such as vascular calcification and mortality. On the contrary, cinacalcet can be beneficial in CKD 3-4 kidney transplanted patients in whom the cinacalcet reduction in the PTH-induced phosphaturia and the consequent retention of phosphorus may counterbalance the frequently observed PTH-dependent reduction in serum phosphorus due to the persisting parathyroid gland hyperplasia.

Other important issue that needs clarification is the existence of other possible mechanisms implicated in both hyperphosphatemia and the decreased urinary phosphorus excretion observed with cinacalcet in stages 3-4 CKD patients. It is likely that phosphorus changes in serum and urine are not only PTH-dependent effects of cinacalcet. A similar reduction in serum PTH levels has been shown in stages 3-4 CKD patients receiving paricalcitol with no significant increases in serum phosphorus or decreases in urinary phosphorus excretion compared with placebo[5]. In addition, the greater phosphaturia observed in those patients treated with VDRAs could be explained by increments in FGF-23 induced by the VDRAs themselves[6].

Unfortunately, in the study of Chonchol et al, they did not mention serum FGF-23 values; they quoted only serum 25(OH)D3 but not calcitriol levels, and thus we cannot evaluate the effect of cinacalcet on FGF-23. However, recent results from kidney transplanted cinacalcet-treated patients showed decreases in serum FGF 23 values[7]. If this were also the case in non-kidney transplanted CKD 3-4 cinacalcet treated patients, we could hypothesized that the decrease in urinary phosphorus excretion observed in the study of Chonchol et al, could have been partly driven by the reduction of FGF- 23 and calcitriol.

As explained before, there exits other options such as VDRAs to manage secondary hyperparathyroidism at all stages, including stages 3 and 4 CKD, which are likely to present additional benefits beyond CKD-MBD control, as recently shown in patients receiving dialysis[8]. Calcitriol and alfacalcidol, the most used VDRAs, effectively suppress PTH in stages 2-5 CKD patients, but unfortunately they frequently induce

hypercalcemia and hyperphosphatemia. Other VDRAs, show a better profile not only on calcium and phosphorous, but also on proteinuria[9]. Hence, if VDRAs, are a well accepted, safe and efficacious strategy for the management of secondary hyperparathyroidism in stages 3-4 CKD patients, should cinacalcet be also used or discarded?

The study from Chonchol et al.[1] in CKD patients not receiving dialysis was designed to assess efficacy and safety but not other possible non-skeletal effects, like vascular calcifications or mortality. Thus, we do not know if cinacalcet may have other long-term clinically relevant effects apart from the discussed changes in the CKD-MBD biochemical parameters. The CaSR is widely distributed throughout the human body and, like VDR, it is present not only in tissues involved in calcium homeostasis but also in other tissues. A recent study has shown that the CaSR is functionally expressed in human arteries and it could reduce the phosphate-induced calcification process by protecting the vessels from calcification[10]. In addition, experimental and clinical studies have shown that cinacalcet may prevent or attenuate parathyroid hyperplasia[11], an area where the VDRAs have only achieved marginal results.

In summary, the available information about cinacalcet indicates that it still should not be used in stages 3-4 CKD patients. The decrease in serum calcium and the increase in serum phosphorus are non-desirable not fully understood effects which require further investigation. Nevertheless, cinacalcet may have other long-term clinical effects of interest, thus; it is necessary to wait for the results of the long-term studies in progress in order to reassess the potential use of cinacalcet in stages 3-4 CKD patients.

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