Calcium–Calcitriol: A Match made in Heaven?

Calcium/calcitriol fixed-dose combinations (FDC) show significant divergence in prescription practice between endocrinologists and general physicians (GPs). In a recent study by Dutta *et al*.,[1] 53% of GPs showed a preference for calcium/calcitriol preparations compared with 0% of endocrinologists for the treatment of osteoporosis and vitamin D deficiency. While this may be decried as irrational, this practice begs a more important question—is it always irrational? If not, what could be the ideal situations for the use of these fixed drug combinations?

The reasons commonly mentioned for avoiding calcium/calcitriol FDC are:

- Cost
- Risk of hypercalcemia
- Need for monitoring serum and urine calcium
- Failure of calcitriol to improve vitamin D stores.

Each of these concerns merits a deep dive.

Cost and Convenience

However, the cost cannot be assessed in isolation and must always be assessed in relationship with benefit. The additional cost accrued by combining calcitriol and calcium may not be useful for the most common indications for which calcium is used - osteoporosis and vitamin D deficiency. However, in conditions for which calcitriol is required for management, calcium/calcitriol combination could be more beneficial and the combination can bring down the cost by up to 31.5%.

These conditions include:

1. Chronic kidney disease (CKD)
2. Hypoparathyroidism
3. Pseudo hypoparathyroidism
4. Vitamin D dependent rickets
5. Hypophosphatemic rickets/osteomalacia.

Apart from these conditions, calcitriol might also have a role in the prevention and management of steroid-induced osteoporosis.[2] Currently, there are no data available on the usage of calcium/calcitriol FDCs in these groups of patients. While it is easier to calculate the cost benefits, it is hard to put a value on the convenience of a reduced pill burden.

Risk of Hypercalcemia

The second reason stated for avoiding calcium/calcitriol combination therapy is the risk of hypercalcemia with the latter. However, this risk is determined by many factors—including the dose of calcium, dose of calcitriol, baseline dietary calcium intake, and coexisting use of cholecalciferol. Most cases of vitamin D toxicity reported in the literature are because of indiscriminate use of cholecalciferol—often as injectable therapy,[3] and most cases of hypercalcemia mediated by calcitriol are because of endogenous calcitriol production—because of ectopic expression of 1 alpha-hydroxylase by granulomatous lesions.

A study by Tilyard *et al*.[4] showed that at doses of 0.5 mcg twice daily for 3 years in patients with osteoporosis, no hypercalcemia was seen. In patients with hypoparathyroidism, no difference in bone mineral density was noted at 3 years between calcitriol and Parathyroid hormone (PTH). Although mild hypercalciuria was more common in the calcitriol group, no instances of nephrocalcinosis or hypercalcemia were noted.[5] In another study by Schaefer *et al*.,[6] the risk of hypercalcemia in dialysis patients was lower if the timing of calcitriol was shifted to night. It is important to remember that as shown by Balk *et al*.,[7] the average calcium intake in India is low (400–500 mg/day). Given the low calcium intake, high prevalence of vitamin D deficiency,[8] and a low dose of calcitriol in FDCs (0.25 mcg), the risk of hypercalcemia attributable to calcium calcitriol FDCs is likely to be low as long as the patient does not get high doses of cholecalciferol.

Need for Monitoring Serum and Urine Calcium

The need for monitoring is a direct consequence of the perceived high risk of hypercalcemia with calcitriol therapy. This high risk is largely mediated by inappropriate dosing of other drugs, such as cholecalciferol. Due to the reasons stated above, the risk of hypercalcemia is low; thus, the need for monitoring is moot. Similar considerations apply for hypercalciuria and renal calculus formation. In a study of 53 Thai women, supplementation of calcium vs calcium and calcitriol did not result in an increased risk of calcium oxalate nephrolithiasis.[9]

Failure to Improve Vitamin D Stores

A legitimate gripe with the FDCs is their failure to build-up vitamin D stores. However, this is neither a requirement nor a desirable feature in people with the impaired conversion of 25 hydroxyl vitamin D to calcitriol.

Conclusions

For most patients with osteoporosis and vitamin D deficiency, calcitriol/calcium combination therapy would increase costs without tangible benefits—as their renal 1-alpha, hydroxylation is normal.

The drug price control order (DPCO) of 2013 fixes the maximum amount that companies can charge for essential medication. The National List of Essential Medicines (NLEM) of 2015 has 376 drugs, which includes calcium. The DPCO is a double-edged sword—while it allows a reduction in prices when an expensive medication is combined with an essential

medicine (e.g., calcium with calcitriol, aspirin with a statin, etc.), the availability of such combinations also opens up the market for the costlier drugs. As Nietzsche once said, "When you look deep into the abyss, the abyss looks back into you." Paradoxically, the same mechanism that causes reduction in prices might end up costing the patient more. This is especially important as the Department of Pharmaceuticals (DoP) data show that the costly + cheap medicine combinations occupy less than 10% of the pharmaceutical market and even in those, the reduction in prices is to the tune of 20% or less. Calcium/calcitriol combination is an exception—46.5% of available preparations contain calcitriol.[10]

For those with impaired activation of vitamin D, calcium–calcitriol FDC offers both a cost and convenience advantage. Thus, wherever there is a genuine need for calcitriol therapy, calcium–calcitriol FDCs can be considered.

Owing to the nuances involved, doctors may be tempted to eschew the use of FDCs completely—however, that would be akin to throwing the baby with the bathwater. Thus, the onus of choosing the right FDC for the right patient falls on the clinician. So, loop back to the original question—is calcitriol–calcium FDC a match made in heaven or hell? It depends on the matchmaker—the prescribing clinician.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Karthik Balachandran, Adlyne R. Asirvatham, Shriraam Mahadevan

Department of Endocrinology, Sri Ramachandra Medical College and Research Institute, Porur, Chennai, Tamil Nadu, India

Address for correspondence: Prof. Shriraam Mahadevan, Department of Endocrinology, Sri Ramachandra Medical College and Research Institute, Porur, Chennai - 600 116, Tamil Nadu, India.
E-mail: mshriraam@gmail.com

References

1. Dutta D, Khandelwal D, Chittawar S, Aggarwal S, Bhattacharya S, Surana V, *et al*. Bone health clinical practice in India—Concern regarding vitamin d toxicity. US Endocrinology 2018;14:87.
2. Steroid-induced osteoporosis: How can it be avoided [editorial]. Nephrol Dial Transplant 2003;18:861.
3. Kaur P, Mishra SK, Mithal A. Vitamin D toxicity resulting from overzealous correction of vitamin D deficiency. Clin Endocrinol 2015;83:327-31.
4. Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. New Engl J Med 1992;326:357-62.
5. Winer KK, Ko CW, Reynolds JC, Dowdy K, Keil M, Peterson D, *et al*. Long-term treatment of hypoparathyroidism: A randomized controlled study comparing parathyroid hormone-(1–34) versus calcitriol and calcium. J Clin Endocrinol Metab 2003;88:4214-20.
6. Schaefer K, Umlauf E, von Herrath D. Reduced risk of hypercalcemia for hemodialysis patients by administering calcitriol at night. Am J Kidney Dis 1992;19:460-4.
7. Balk EM, Adam GP, Langberg VN, Earley A, Clark P, Ebeling PR, *et al*. Global dietary calcium intake among adults: A systematic review. Osteoporos Int 2017;28:3315-24.
8. G R, Gupta A. Vitamin D deficiency in India: Prevalence, causalities and interventions. Nutrients 2014;6:729-75.
9. Domrongkitchaiporn S, Ongphiphadhanakul B, Stitchantrakul W, Piaseu N, Chansirikam S, Puavilai G, *et al*. Risk of calcium oxalate nephrolithiasis after calcium or combined calcium and calcitriol supplementation in postmenopausal women. Osteoporos Int 2000;11:486-92.
10. Lhamo Y, Chugh PK, Tripathi CD. Vitamin D supplements in the Indian market. Indian J Pharm Sci 2016;78:41-7.

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_583_19

How to cite this article: Balachandran K, Asirvatham AR, Mahadevan S. Calcium-calcitriol: A match made in heaven? Indian J Endocr Metab 2019;23:649-50.