

Lanthanum Carbonate - A New Attractive Therapy in Management of Uncontrolled Hyperoxaluria

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Letter

In 1842, Golding Bird was the first to describe hyperoxaluria as “a condition, which leads to the formation of a particular kidney stone”. Nowadays, hyperoxaluria is a well-known major lithogenic risk factor for nephrocalcinosis and nephrolithiasis and within these clinical settings is considered as important as hypercalciuria [1]. Primary hyperoxaluria is a rare inherited disease caused by mutations in genes involved in the oxalate metabolism which leads to excessive endogenous oxalate synthesis resulting in increased plasma oxalate levels and hyperoxaluria. Worldwide epidemiological data indicate a progressive increase in secondary hyperoxaluria, which is an oxalate homeostasis disorder mainly related to pathologically increased intestinal oxalate absorption or excessive dietary oxalate load [2].

Obviously, hyperoxaluria not only needs to be considered as a major determinant of recurrent calcium oxalate nephrolithiasis but also as a toxic factor responsible for acute and/or chronic tubulointerstitial kidney injury (crystal nephropathy). Hyperoxaluria even under normal urinary calcium excretion generates a supersaturation of calcium oxalate forming whewellite (calcium oxalate monohydrate) crystals in the urine. These crystals are insoluble in water and therefore easily aggregate in the tubular lumen. Retention of these crystals in the intratubular lumen induces tubular epithelial cell injury and interstitial inflammation through NLRP3-mediated IL-1 β secretion [3], which in-turn favors adhesion of whewellite crystals to the tubular epithelium resulting in intratubular or interstitial nephrocalcinosis. This vicious circle, especially in a state of uncontrolled hyperoxaluria, incites chronic NALP3-mediated inflammation and progressive renal dysfunction.

The primary goal of hyperoxaluria management consists in the prevention of whewellite crystal formation/precipitation and ensuing kidney stone formation. Unfortunately, all current therapeutic strategies often fail in their effectiveness and compliance which makes that calcium oxalate stone recurrence is still common and indicates the urgent need for new efficient therapeutic interventions.

Lanthanum carbonate (LC) emerged as an attractive drug for the management of uncontrolled hyperoxaluria at the 19th « Necker’s hospital clinico-biological confrontations on urinary stones » in Paris last year (Figure 1). Lanthanum carbonate is a calcium-free, non-resin-based phosphate binder, which is prescribed for the management of hyperphosphatemia in patients with end-stage renal disease since 2004 [4]. Importantly, the bioavailability of an oral dose of LC is extremely low (~0.001%) and is not influenced by pH, intestinal inflammation or microflora modifications during enteropathies. Lanthanum undergoes transcellular transport in the liver and is excreted by the hepatobiliary system mainly in the feces (80%). Renal clearance accounts for only 1.7% of the total plasma clearance of lanthanum. LC is neither

a substrate nor an inhibitor of cytochrome P450 enzymes. There is no evidence that LC interferes with the absorption of vitamin D or any other fat-soluble vitamin. Clinical studies evaluating the efficacy, tolerability and long-term safety of LC monotherapy have consistently reported that the compound is well tolerated, with no evidence of adverse safety outcomes in bone, gastrointestinal tract, liver or central nervous system [4].

The rationale for the use of lanthanum carbonate (LC) in patients with hyperoxaluria is based on findings from *in vitro* and *in vivo* studies [5]. *In vitro*, lanthanum binds oxalate anions under the formation of insoluble lanthanum-oxalate complexes across the entire pH range in the gastrointestinal tract. Recently, in a rat model of hyperoxaluria

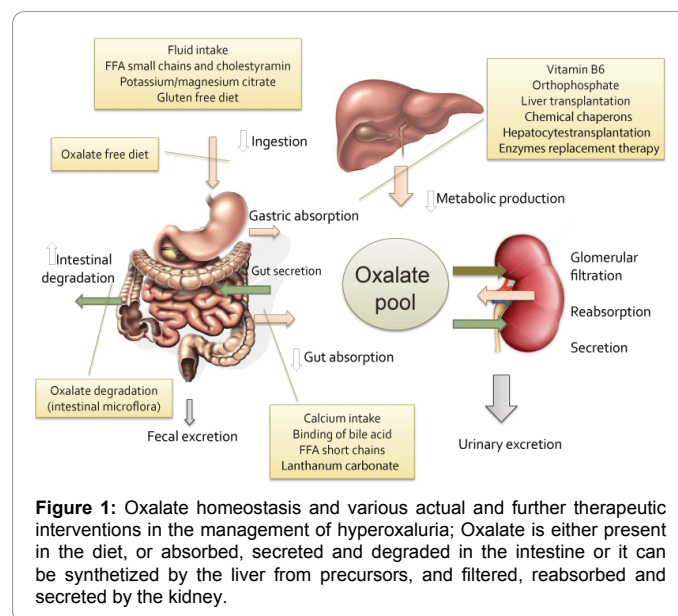


Figure 1: Oxalate homeostasis and various actual and further therapeutic interventions in the management of hyperoxaluria; Oxalate is either present in the diet, or absorbed, secreted and degraded in the intestine or it can be synthesized by the liver from precursors, and filtered, reabsorbed and secreted by the kidney.

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(male Sprague-Dawley), oral administration of LC significantly reduced the serum oxalate concentration, oxaluria, the formation of calcium oxalate crystals and nephrocalcinosis [6,7].

In view of the above, LC provides interesting perspectives for the medical management of uncontrolled hyperoxaluria, especially in patients presenting with enteric hyperoxaluria (and also in the case of primary hyperoxaluria where the oxalate-lanthanum ions complexes formation could increase the outgoing flow of oxalate from serum to intestine, thus helping to reduce oxalemia and the amount of oxalate delivered to the kidney). Indeed, being a phosphate binder, LC is an attractive therapy with potential benefit for preventing intratubular calcium phosphate precipitation also. Further clinical studies need to be done to evaluate usefulness of LC as a therapeutic strategy to control hyperoxaluria in human.

Conflict of interests

Authors have no conflict of interests to disclose

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