Lanthanum carbonate—new data on parathyroid hormone control without liver damage

Mario Cozzolino and Diego Brancaccio

Renal Division, University of Milan, S. Paolo Hospital, Milan, Italy

Keywords: chronic kidney disease; lanthanum carbonate; phosphate; phosphate binders; secondary hyperparathyroidism

Recent investigations have provided conclusive evidence that abnormalities in mineral and bone metabolism are associated with increased cardiovascular (CV) morbidity and mortality in chronic kidney disease (CKD) patients [1,2]. In fact, elevated serum phosphate (P) levels play an important role in the pathogenesis of secondary hyperparathyroidism (SHPT) [3]. Recent studies have shown the molecular mechanisms by which P may regulate parathyroid (PT) function. Within 2 weeks after 5/6 nephrectomy (Nx) in rats, uraemia-induced mitotic activity is further enhanced by high dietary P, but prevented by P-restriction [4,5]. In contrast to the mitogenic effects of hyperphosphataemia, low dietary P appears to counteract the proliferative signals induced by uraemia, thus preventing PT cell replication and consequently, the increase in PT gland size [6,7]. Moreover, the regulation of PTH mRNA by P has been found to occur post-transcriptionally through binding of PT cytosolic proteins to the 3'-untranslated region (UTR) and in particular to the terminal 60 nucleotides of PTH-mRNA [8].

Hyperphosphataemia not only induces SHPT, but also plays a major role in the pathogenesis of vascular calcification (VC) in the uraemic population [9]. In fact, recent in vitro studies have shown how vascular smooth muscle cells calcify when incubated in a medium containing elevated concentrations of inorganic P [10]. Together with classical passive precipitation of calcium phosphate in soft tissues, inorganic P may cause extra-skeletal calcification directly through a real ‘ossification’ of the tunica media in the vasculature of uraemic patients [11]. Therefore, P-control represents the major challenge for any clinical nephrologist.

The classic treatment of hyperphosphataemia in CKD patients consists of either calcium- (Ca) or aluminium (Al)-based P-binders. Unfortunately, this ‘first generation’ class of therapy is not free of complications. New free-Ca and -Al P-binders, such as sevelamer hydrochloride and lanthanum carbonate, may be used to treat hyperphosphataemia and prevent both SHPT and VC in CKD.

The dream for every nephrologist is to control serum P-levels in CKD patients, using P-binders with no side effects. Can this dream become a reality?

In the manuscript that appears in this issue of NDT, Ben-Dov and collaborators [12] show the effects of lanthanum carbonate on decreasing PTH-mRNA expression, without inducing liver damage in uraemic rats. The experimental model of uraemic rats fed with a low P-diet represents the ‘ideal world’, in which, in a uraemic environment, it is possible to prevent not only PTH synthesis and secretion, but also parathyroid (PT) hyperplasia, just by controlling P.

In the present study by Ben-Dov and collaborators [12], uraemic rats treated with lanthanum carbonate behave as if they were P-restricted. In fact, both uraemic low dietary P and uraemic 3.0% lanthanum-treated rats present: (i). reduced serum P and PTH levels in contrast to hyperphosphataemia induced by high P-diet; (ii) decreased PTH-mRNA expression linked to reduced serum PTH levels, when compared with the elevations due to uraemia and further enhanced by high P-diet.

What do we know about the physiopathology of SHPT and use of P-binder?

Three groups have recently investigated the role of sevelamer hydrochloride in regulating PTH secretion...
and PT hyperplasia. First, Ksatunata and collaborators [13] compared PTH secretion between sevelamer-treated adenine-induced renal failure rats with a normal-control group, demonstrating that sevelamer significantly controls SHPT in this model of renal failure. Moreover, Nagano and collaborators [14] demonstrated that sevelamer greatly decreases serum P, Ca × P-product and PTH levels, suppressing PT gland growth and PT proliferating cell nuclear antigen (PCNA) expression, compared with 5/6 nephrectomized untreated rats. Finally, sevelamer also prevents PT hyperplasia through a reduction in PT transforming growth factor-β (TGF-β) and its receptor, epidermal growth factor receptor (EGFR), in a long-experimental model of renal failure, equally to low P restriction [15]. In Figure 1, we describe the different hypothetical effects of sevelamer and lanthanum on the pathogenesis of secondary hyperparathyroidism. At this time, further investigation is necessary to demonstrate the direct role of a P-binder on either PTH synthesis or PT hyperplasia, independently by P-control.

The second important result described in Ben-Dov’s paper [12] is that lanthanum carbonate can reverse SHPT-reducing serum P-levels in uraemic rats with no evidence of hepatic toxicity.

When we think of the potential side effects of lanthanum carbonate, should we consider liver ‘toxicity’, ‘deposition’, ‘accumulation’ or ‘handling’?

This question has recently caused a profound scientific debate in the nephrology community. Probably the correct answer is in this statement by Paracelus (1493–1541): ‘All substances are poisons: there is none which is not a poison. The right dose differentiates a poison from a remedy’.

Two recent studies investigated lanthanum deposition in the liver in experimental models of chronic renal failure. First, Lacour and collaborators [16] showed that in both 5/6 Nx and adenine-treated rats, liver lanthanum concentration increased in lanthanum-receiving animals compared with uraemic untreated rats. Second, Slatopolsky and collaborators [17] confirmed that uraemic rats treated with lanthanum carbonate had a greater (100-fold increase) accumulation of lanthanum that increased in a time-dependent manner. These two studies opened the debate: (i) Have control measurements for contamination been performed during rat handling, blood and urine collection, to avoid contamination with exogenous lanthanum [18]? (ii) Why are liver weights, in lanthanum carbonate-treated uraemic rats, reduced only when corrected by femoral length, but not when normalized using body weight [19]? (iii) What might happen in a long-term liver lanthanum exposure experimental model (78 weeks)? Will a steady-state condition be reached, with a small enhancement of liver lanthanum concentration [20]?

In conclusion, the manuscript by Ben-Dov and collaborators [12] confirmed that lanthanum deposited in uraemic rat liver, as recently demonstrated [21], but without detecting elevations on plasma transaminase and cholestatic enzyme activities, as already demonstrated in dialysis patients treated for 3 years with lanthanum carbonate [22]. Furthermore, liver magnetic resonance did not demonstrate abnormalities; liver weights were similar in each experimental condition, and light microscopy did not show any signs of lanthanum-induced hepatic toxicity.

We believe that this manuscript will stimulate further investigation to address the possible direct role of lanthanum carbonate on PTH synthesis, independently by P-control. The near future should give us mounting evidence of new approaches on P and PTH suppression in CKD patients.

Conflict of interest statement. None declared.


References

The link between mechanical stretch and glucose metabolism—a conceptual advance in understanding diabetic (and non diabetic?) renal disease

Luigi Gnudi and Giancarlo Viberti

Cardiovascular Division, King's College London School of Medicine, Guy's Hospital, London, UK

Keywords: diabetes; facilitative glucose transporter-1; hypertension; TGF-β1

Diabetic nephropathy—a tale of two hits?

Diabetic kidney disease is today the most common cause of end-stage renal failure in many countries of the world and the number of diabetic patients in need of renal replacement therapy has increased over the last two decades [1]. Haemodynamic forces are major contributors to the development of renal damage in diabetes [2] and in other chronic glomerulopathies characterized by increased intraglomerular capillary pressure [3].