Lanthanum deposition in a dialysis patient

Richard L. Davis and Jerrold L. Abraham

Department of Pathology, Suny Upstate Medical University, Syracuse, NY 13210, USA

Correspondence and offprint requests to: Jerrold L. Abraham; E-mail: abrahamj@upstate.edu

Abstract
Lanthanum carbonate (LaCO3) is an oral phosphate binder widely used in end-stage renal disease (ESRD). Preclinical animal studies reported the highest La concentrations outside the gut to be in mesenteric lymph nodes. We observed previously unreported La deposition visible by light microscopy and confirmed by scanning electron microscopy with energy dispersive x-ray spectroscopy in a mesenteric lymph node at autopsy of a 38-year-old female ESRD patient 3 years following LaCO3 administration. Although LaCO3 is generally thought to be minimally absorbed, this demonstration suggests the need for further investigation of the extent and potential effects of such absorption.

Keywords: end-stage renal disease; lanthanum; lymph node; scanning electron microscopy/energy dispersive x-ray spectroscopy

Introduction
Lanthanum carbonate (Fosrenol®) (LaCO3) is used as an orally administered phosphate-binding agent to reduce the gastrointestinal absorption of phosphate and ameliorate hyperphosphataemia in end-stage renal disease (ESRD). It is minimally absorbed in normal individuals, but markedly increased absorption has been demonstrated in uraemic rats [1]. Plasma and bone levels of La have been seen to rise during therapeutic administration in humans, with long-term gradual mobilization from bone stores during a year after discontinuation of therapy [2]. Interestingly, La deposition at levels higher than in bone or liver has been reported in mesenteric lymph nodes of rats given oral LaCO3 (personal communication, M. Smythe, PhD, Shire corporation, 13 May 2009).

Case report
We report substantial, readily detected La deposits in a mesenteric lymph node several years after the oral ingestion of LaCO3. The patient was a 38-year-old woman with IgA nephropathy and ESRD beginning in 1996. She received a cadaveric kidney transplant in 1999, which was rejected and removed in 2003, and began peritoneal dialysis (PD) which continued through September/October 2005. She received LaCO3 (one tablet after each meal) from April through October of 2005 (most or all of which time she was on PD), then haemodialysis (HD) from September/October to early December, returning to PD in early December 2005. In

References

Received for publication: 25.5.09; Accepted in revised form: 22.6.09

doi: 10.1093/ndt/gfp364
Advance Access publication 22 July 2009

Conflict of interest statement. None declared.

Lanthanum deposition in a dialysis patient may have favoured lanthanum absorption. The remaining question is whether the tablets of lanthanum carbonate were responsible for diverticular sigmoiditis by occlusion of the diverticulum and/or irritation of the intestinal mucosa’.

doi: 10.1093/ndt/gfp364
Advance Access publication 22 July 2009
December 2005, while on PD she was exposed to gadolinium (Gd), a component of the contrast dye (Omniscan®) used for abdominal magnetic resonance imaging (MRI). Within a few days, she experienced joint pains, knee effusions and erythema around the ankles. HD was resumed 8 days following her MRI and continued for the remainder of her life. A skin biopsy resulted in a diagnosis of nephrogenic systemic fibrosis (NSF) in April 2006. She became disabled due to contractions and atrophy of her hands and feet and required hyperbaric oxygen therapy for non-healing skin lesions. She died 12 years after the onset of ESRD and 2 years following the diagnosis of NSF. An autopsy was performed and paraffin-embedded tissues of multiple organs were analysed using scanning electron microscopy/energy dispersive x-ray spectroscopy (SEM/EDS) using methodology previously reported [3]. Light microscopy of the mesenteric lymph node showed marked accumulation of pale, foamy macrophages. These macrophages contained abundant material highlighted by dark-field optics (Figure 1), and SEM/EDS confirmed these deposits to contain La and Gd, but with La being more abundant than Gd (Figure 2). Similar light microscopic features have not been seen with Gd deposition alone, and no La has been detected in other tissues from this case or any other tissues among the dozens of NSF cases our laboratory has examined using the same analytical methodology. In contrast, Gd deposits were identified in skin, skeletal muscle, dura, lung, liver, kidneys, adrenals, thyroid, parathyroids and the mesenteric lymph node in this case. Neither La nor Gd was detected in oesophagus, pancreas, spleen, thoracic lymph node or brain.

Discussion

The 15 lanthanoid elements have diverse effects on living organisms. While free Gd is toxic, the Gd chelates used in MRI studies appear to be safe for patients with normal renal function. However, there is growing consensus of a causal relationship between Gd-containing contrast agents and the development of NSF in patients with renal failure [4]. By contrast, LaCO₃ has not been associated with serious adverse effects in chronic kidney disease patients, and only bone and liver have been reported to accumulate La in humans [2,5]. The levels of La reported in human liver (0.6–2.0 µg/g wet weight) [5] are likely below the
Lanthanum deposition in a dialysis patient

Fig. 2. (A) SEM backscattered electron image of the same lymph node illustrating bright (higher atomic number) features corresponding to macrophages seen in Figure 1. (B) Representative EDS spectrum confirms the presence of La as the major component, associated with phosphorus (P) and with Gd present at lower amount in the area analysed (indicated by the ‘+’ in (A)).

detection limit of our SEM/EDS analysis (probably at least 10–100 µg/g wet weight). The detection of La deposits in a mesenteric lymph node of our patient 3 years after exposure demonstrates the potential for its deposition and long-term retention in human tissue other than bone. While it is conceivable that PD fluid contamination by La could explain our findings, the absence of detectable La deposits in all the other tissues and organs (including serosal surfaces of intra-abdominal organs) that were analysed in this case makes that unlikely. Our unique histological and microanalytical findings are consistent with animal research data, showing that La is absorbed from the gastrointestinal tract of healthy, non-dialysed rats and deposited in various tissues [1]. Since the mesenteric lymph nodes represent the most proximal clearance site from the gut, one might expect to find high concentrations of La deposition there.

Although LaCO₃ is apparently safe for patients with ESRD, there may be a need for more investigation of its potential long-term toxic effects. Prospective studies of surgical specimens obtained from patients undergoing renal transplantation or transplant removal, including mesenteric and paraaortic lymph nodes that may be within the surgical field of view could establish the extent of La deposition associated with LaCO₃ therapy and its relationship with dosage, period of exposure and other clinical parameters. Further investigation of mesenteric lymph nodes obtained at autopsy from renal failure patients would also be informative. The need for accurate and detailed documentation of LaCO₃ treatment in patients’ records cannot be overstated. While analytical methods are required to confirm the existence of La deposits, the observation by light microscopy of the novel histological features reported here could alert pathologists to this possibility. Although it is unknown at present how many NSF patients have received LaCO₃ therapy, evidence to date does not suggest that La is involved in the pathogenesis of NSF, and NSF existed prior to the marketing of LaCO₃.

Conflict of interest statement. This autopsy case was initially sent to one of us (J.L.A.) at the request of attorneys to analyse for the distribution of...
gadolinium (Gd) in the tissues. Funding from Department of Pathology, SUNY Upstate Medical University, did not influence the study or reporting of this autopsy case. Autopsy case report exempt from IRB review.

References


Received for publication: 17.6.09. Accepted in revised form: 1.7.09