

¹Australia and New Zealand
Dialysis and Transplant Registry
Adelaide

²Department of Renal Medicine
University of Queensland at
Princess Alexandra Hospital
Brisbane, Australia

³Department of Nephrology &
Transplantation Services University
of Adelaide at the Queen Elizabeth
Hospital, Adelaide

⁴Department of Nephrology
Monash Medical Centre, Clayton
Victoria, Australia

⁵Renal Department, Middlemore
Hospital, Otahuhu, Auckland
New Zealand

⁶Department of Medicine
St Vincent's Hospital, University of
Melbourne, Fitzroy, Victoria

⁷Department of Nephrology, Royal
Adelaide Hospital, Adelaide
Australia

E-mail: katherine_barracough@health.qld.gov.au

Katherine
Barracough^{1,2}

Carmel M.
Hawley^{1,2}

Stephen P.
McDonald^{1,3}

Fiona G. Brown^{1,4}

Johan B.
Rosman^{1,5}

Kathryn J.
Wiggins^{1,6}

Kym M.
Bannister^{1,7}

David W.
Johnson^{1,2}

The only available presentation of LC (FOSRENOL[®], Shire Pharmaceuticals, Basingstoke, UK) is a chewable tablet containing no excipients to aid dispersal. Tablets should be taken with or immediately after meals and should be chewed completely; intact tablets should not be swallowed [2]. The size of the lanthanum particles evident in the radiograph is consistent with that of chewed LC, as has been seen in other published reports and not been associated with gastrointestinal obstruction [3,4]. As expected, and noted by the authors, the lanthanum particles 'continued to migrate through the digestive tract'. In contrast, the case report by Kurtz (sic) *et al.* (Kongress der Gesellschaft für Nephrologie, Tübingen, Germany, 2008) cited by Muller clearly showed the presence of un-chewed tablets.

Speculation that deposition of lanthanum in the central nervous system (CNS) resulted in the confusional state draws on controversial evidence from *in vivo* studies [5,6]. Recent data from a study examining the potential for contamination of tissue samples in dietary studies of LC leads one to question the validity of this evidence [7]. In this study comparing dietary, oral gavage and intravenous administration, lanthanum was only detectable in brain tissue from rats administered LC in their diet. It appears that despite stringent efforts to limit contamination, lanthanum is still transferred to tissue samples during autopsy [7]. In another recent study, Bervoets *et al.* demonstrated no difference in the brain concentrations of lanthanum between healthy rats and those with chronic renal failure treated by oral gavage with LC for 20 weeks [8]. Levels remained around the lower limit of quantification for the assay. The results of these studies add to the weight of evidence in the literature that lanthanum does not cross the blood-brain barrier, even in the uraemic inflammatory and other disease states [8–10]. In the study by Feng *et al.*, which suggests alteration of CNS function with lanthanum treatment, changes in biochemical parameters were not dose dependent and not predictive of effects in humans as discussed in the literature [6,11].

In addition, the authors do not consider the clinical data on the effects of LC on cognitive function [12]. Altmann *et al.* found no difference in the rate of cognitive decline in dialysis patients randomized to LC or standard phosphate-binder therapy (mainly calcium based) [12]. In this study, the median plasma lanthanum level of LC-treated patients stabilized at ~0.3 (range 0.0–3.1) ng/mL. Therefore, the plasma lanthanum value of 2.13 µg/L noted by Muller *et al.* is neither 'higher than normal' compared with a population treated with LC for 2 years, nor is it associated with excessive cognitive decline. Extrapolation from *in vivo* tissue deposition data [8] based on human plasma lanthanum levels [13] is not scientifically sound and the conclusion that toxic levels of lanthanum can be reached in patients with renal failure is purely speculative, with no human or animal evidence provided.

This patient was elderly and had diffuse cerebral atrophy on CT scan. Her presenting symptoms included dizziness with falling and confusion. Infection is commonly implicated with the etiology of several conditions that cause confusion in the elderly, and therapy of the underlying condition leads to recovery [14]. Benzodiazepine use is also

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A confusional state associated with use of lanthanum carbonate in a dialysis patient: a case report

Sir,

Muller and colleagues report a case of febrile confusion and 'diverticular flare-up' with abdominal pain and speculate an association with lanthanum carbonate (LC) because discontinuation of LC treatment and initiation of antibiotic therapy led to recovery [1]. They support their argument with the radiographic detection of lanthanum particles in the gastrointestinal tract, a reduction of plasma lanthanum levels following discontinuation of treatment and a selective review of the literature. However, there is no convincing argument for an association with LC treatment.

commonly associated with confusion in the elderly. Either of these factors are plausible explanations for the confusion experienced by this patient.

In summary, this patient with known diverticular disease presented with a febrile episode that responded to antibiotic treatment. The authors noted the expected radio-opaque appearance of lanthanum in the gastrointestinal tract and plasma lanthanum levels within the range observed in pivotal clinical trials. Neither finding has been convincingly linked to the patient's presentation; therefore, there are no grounds for revising the benefit–risk profile for LC.

Conflict of interest statement. MS and RDP are employees of Shire Pharmaceuticals.

¹Global Medical Affairs
Shire Pharmaceuticals
Basingstoke, UK

²Research and Development
Shire Pharmaceuticals
Wayne, PA, USA
E-mail: msmith@shire.com

Michael D. L.
Smyth¹
Raymond D. Pratt²

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Reply

In response to Dr Smyth's letter to the editor, we would like to remind readers that lanthanum carbonate has indeed shown its efficacy, but that many safety concerns remain unsolved. We would like to draw attention to two main points brought out in our case report:

- Gastro-intestinal effects: Lanthanum has been shown to induce a number of gastrointestinal effects [1].

Patients with acute peptic ulcer, ulcerative colitis, Crohn disease or bowel obstruction were not included in the pivotal FOSRENOL(R) study, its 6-year follow-up report [2] or in Finn's work [3]. Therefore, caution should be exercised in patients with these conditions [4]. There was more withdrawal in patients treated with lanthanum mainly attributable to digestive disorders in these studies. Our patient had previous digestive disorders and therefore should be considered a high-risk patient for digestive side effects.

In our patient, the plasmatic lanthanum level was 2.13 µg/l. In the public assessment report [5], the mean concentration for long-term ingestion of 3 g lanthanum/day ranges from 0.5 to 0.6 ng/ml. There was no significant dose or time effect on treatment. Altman's study reported the same mean plasmatic value—0.3 ng/ml—but a wide range (0.0–3.1 ng/ml). More information would be required to explain this difference.

It has been shown that the tissue concentration is higher than the plasma concentration so we cannot assume that lanthanum is not nontoxic. Tissue accumulation is seen particularly in the gastro-intestinal tract, lymphoreticular system, bone, liver and spleen [5]. Recently, Davis and Jerrold reported the detection of lanthanum deposits in a mesenteric lymph node in a patient 3 years after exposure [6].

The degree of digestive absorption has not been evaluated, nor has the excretion of the unabsorbed dose of lanthanum in the faeces been demonstrated in humans [5,7].

The two FDA reviewers for market approval of lanthanum (Drs Pelayo and Olufemi [1]) made a negative recommendation because of the gastro-intestinal effects and the unknown accumulation and elimination of the product, which presented 'a real risk of malnutrition and additional injury in this population'. They stated that it can be 'unacceptably toxic'. The sponsor was in charge of providing proof on this point but was unable to do so.

- The effects on the central nervous system: a number of animal studies indicate significant brain exposure [8].

The blood–brain barrier can be damaged when there is significant inflammation, tumours, etc. and can allow selective delivery of pharmacological agents to the brain [9]. The impact of lanthanide on brain function is not insignificant [10]. It is known that when it passes the blood–brain barrier in animals, it can be toxic to the nervous system and cognition [11,12]. In healthy rats, Damment *et al.* [13] showed that the lanthanum brain concentration found is considered contamination.