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Letter regarding 'advisory about gadolinium calls for caution in the treatment of uremic patients with lanthanum carbonate'

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To the Editor: Aime and colleagues[1] suggest that the Food and Drug Administration (FDA) guidance on gadolinium-based contrasting agents should lead to caution in the use of lanthanum carbonate (FOSRENOL, Shire Pharmaceuticals, Basingstoke, UK). The basis for their concern is that gadolinium and lanthanum are similar physiochemically.

Gadolinium salts administered intravenously have known toxicities and thus chelates are used to limit them.[2] These are administered usually at single intravenous doses of 0.1 mmol/kg, leading to plasma gadolinium concentrations of up to 2.5 mmol/l (392.5 mg/l) at standard doses[2] and 5 mmol/l (785 mg/l) at double doses used for magnetic resonance imaging angiography. The chelates are cleared primarily by renal elimination. Thus, the half-life of gadolinium increases from 1.96 h in healthy individuals to 5.61 anzd 9.18 h in patients with chronic kidney disease stages 4 and 5, respectively.[3] Prolonged systemic exposure increases the potential for transmetalation and the release of free gadolinium. It is believed that this free gadolinium forms insoluble complexes and deposits in the skin and other organs.[4]

The exposure paradigms for gadolinium and lanthanum are completely different. Gram doses of intravenous gadolinium are 100% bioavailable, whereas oral lanthanum carbonate has a bioavailability of 0.00127%.[5] Plasma lanthanum concentrations following long-term treatment plateau at nanomolar levels of 2.5–9.7 nmol/l;[6] approximately 500,000-fold lower than for gadolinium double dosing. Furthermore, absorbed lanthanum is highly protein bound ($>99.7\%$),[5] resulting in free plasma lanthanum concentrations in the pmol/l range. Rodent toxicity studies demonstrate that skin concentrations of lanthanum are negligible (oral gavage or intravenous dosing).[7]

There are no reports of nephrogenic systemic fibrosis associated with lanthanum carbonate either in clinical trials (over 5000 patients) or in post-marketing surveillance (data on file).

The assumption that the risks of gadolinium can be extrapolated to lanthanum on the basis of proximity in the periodic table, rather than on pharmacokinetic, toxicologic, and clinical evidence, is not warranted and scientifically inappropriate.

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Response to 'Advisory about gadolinium calls for caution in the treatment of uremic patients with lanthanum carbonate'

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The biodistribution of lanthanum(III) complexes relies on their speciation (that is, the distribution among chemical species that provide coordination sites to the lanthanum(III) ions). Among the huge number of biomolecules, the speciation of lanthanum (III) complexes is determined by their relative thermodynamic stabilities.[1]

The close analogy in the coordination chemistry of lanthanum and gadolinium trivalent ions allows one to anticipate that there would be analogies in the biodistribution of the two ions in living systems. However, the administration route (oral or intravenous), the quantities involved, and the chemical differences of the forms that reach the blood (as highly thermodynamically stable chelates in the case of gadolinium or speciated among different biomolecules in the case of lanthanum arising from the orally administered carbonate) generate differences between the two protocols. Attention should be invoked to consider the complex picture made of a number of intercorrelated equilibria (that are analogous for the two ions). On the basis of the tremendous output that comes from the use of not sufficiently stable gadolinium

chelates in magnetic resonance imaging, more efforts should be devoted to characterize the *in vivo* distribution/accumulation of lanthanum upon oral administration of lanthanum carbonate.

The observation of plasma lanthanum concentrations in blood that plateau at nanomolar values does not guarantee against its deposition/accumulation outside the blood circuit. In the absence of a clear understanding of the ethiology of nephrogenic systemic fibrosis (and, in particular, of the co-causes that determine the development of the disease), it appears definitively not possible to assume the absence of risks associated to the lanthanum carbonate treatment.[2]

It is worth to note that the same concern has been expressed in the 'Guidance Document for safe MR practice' that has been recently published by the American College of Radiology: 'There are early data that suggest that elevated levels of phosphate, iron, zinc or copper or the presence of Fosrenol (lanthanum carbonate, Shire) might serve as efficient competitors for the 'attention' of the chelate molecule, so to speak, and increase the concentration of free gadolinium in the patient, which might therefore increase the potential of the patient to develop NSF' (p 13) and 'other cations such as lanthanum, now used as lanthanum carbonate (Fosrenol) for phosphorus binding in end-stage renal disease patients, could also present similar transmetallation and free gadolinium concerns…' (p 15).[3]

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A wearable hemofilter for continuous ambulatory ultrafiltration

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To the Editor: In their recent article on continuous ambulatory hemofiltration, Gura *et al.*[1] state, 'This study describes the first human use of a wearable hemofiltration device to manage fluid overload' and claim, 'This first-ever human study of a wearable hemofiltration device indicates that its application as such is feasible.' The claims of priority and novelty embedded in these statements are simply not true. Neff *et al.*[2] in 1988, Shaldon *et al.*[3] 1989, Murisasco *et al.*[4] in 1986, and Takai *et al.*[5] in 1991 have all published clinical trials involving wearable ultrafiltration devices. None were cited in the article by Gura *et al.* 'All four authors conducted clinical tests on dialysis patients and, although Gura *et al.*, discuss application to cardiovascular disease their study group was the same as in earlier investigations.' The potential of using isolated ultrafiltration in diuretic-resistant cardiac failure has also been reported and was poorly tolerated in advanced cases.[6] The published works by Neff *et al.*,[2] Shaldon *et al.*,[3] Murisasco *et al.*,[4] and Takai *et al.*[5] are not difficult to find: they will turn up in a simple PubMed search or even on Google with keywords 'wearable ultrafilter' or 'ambulatory hemofiltration.' Also, their content is highly relevant. Three of the four earlier reports describe significantly higher fluid removal rates than were reported by Gura *et al.*; the third describes clinical evaluation in patients not for 6 h (Gura *et al.*) but for 21 days (Shaldon *et al.*). In this latter case, the device was custom designed with wide bore fibers allowing the ambulatory patient to be anticoagulated with aspirin rather than by heparin. Investigators are certainly entitled to present their findings in the most favorable light. However, it is never appropriate to omit readily available earlier citations, and thereby blur the distinction between contributions of a pioneering and breakthrough nature and efforts, which merely represent ongoing evolution. The peer-review process is supposed to prevent this Plimsoll line from being crossed, but, in this case, regrettably, it failed to do so.

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Response to 'A wearable hemofilter for continuous ambulatory ultrafiltration'

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We thank Professors Shaldon and Lysaght[1] for their insightful letter. The concept of developing wearable devices for treating both patients with heart failure and