The need for contamination control in studies on lanthanum biodisposition

To the Editor: Whereas published data on the biodisposition of lanthanum should be welcomed, those reported by Lacour et al [1] give cause for concern. Concentrations of lanthanum in plasma for control samples were of the order of 400 ng/mL, and values were not significantly elevated in rats given lanthanum carbonate. In independent studies we, and others, have obtained background levels 1000 to 10,000 times lower and routinely differentiate plasma from control and lanthanum-treated groups (see Fig. 1) [2]. In dialysis patients treated with recommended doses of Fosrenol®, steady state plasma concentrations are <1 ng/mL [3] (see also Prescribing Information), 400 times lower than in the placebo samples in the Lacour et al [1] rat study. These results strongly suggest contamination of analytical samples with lanthanum from the animals’ environment.

It is well known that trace/ultratrace element determinations are subject to potential analyte contamination at all stages in the sampling/analytical process and, in our experience with lanthanum, stringent precautions must be taken to avoid contamination. Lanthanum’s low oral bioavailability (0.0007% in rats) results in excretion of almost all the dose via feces into the animal’s environment, contaminating skin and fur. This situation demands rigorous contamination control measures when handling animals, during blood and urine collection, and at autopsy, to avoid the transfer of exogenous lanthanum into analytical samples. The potential problems of contamination in rodent studies, especially dietary studies, have recently attracted strong interest from drug regulatory authorities, leading to issuance of new draft guidelines on the conduct of animal safety studies [4].

Cameron McLeod, Alan Cox, and Neil Bramall
Sheffield, United Kingdom

Correspondence to Professor Cameron McLeod, Centre for Analytical Sciences, University of Sheffield, S3 7HF, United Kingdom.
E-mail: c.w.mcleod@sheffield.ac.uk

© 2005 by the International Society of Nephrology

Fig. 1. Plasma lanthanum concentrations in rats given a single oral dose of lanthanum carbonate (1500 mg/kg) or vehicle (control) by gavage. Values are mean ± SD; N = 6; LLoQ (lower limit of quantification) = 0.05 ng/mL; values <LLoQ reported as 0.05 ng/mL. Manuscript in preparation.

REFERENCES
4. EMEA/CPMP/SWP/1094/04, COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP): Draft guideline on the evaluation of control samples for toxicokinetic parameters in toxicology studies: Checking for contamination with the test substance, March 25, 2004

Reply from the Author

We thank McLeod et al for having drawn attention to an error in Figure 3A of our article published in a recent issue of Kidney International [1]. The unit of plasma lanthanum has been erroneously indicated as ‘μg/mL’ when in fact it should read ‘μg/L,’ as shown by the scan of a randomly selected original laboratory sheet of the lanthanum determinations done in our study (Fig. 1). We sent an erratum to the Editors earlier this month when we became aware of this regrettable typographic error. The erratum was published in the July 2005 issue.

We agree that every possible precaution should be taken to avoid contamination of plasma and tissue samples by trace elements when given in large amounts to experimental animals or man. It is true that in our study,
Lanthanum pharmacokinetics: Are rat data misleading?

To the Editor: On the basis of higher urine lanthanum recoveries in uremic rats, Lacour et al [1] conclude there are “important differences in the pharmacokinetics of lanthanum in chronic renal failure.” This seems not to be the case in man. Indeed, in a series of Phase I studies carried out to support the development of Fosrenol®, plasma concentration versus time profiles, and pharmacokinetic parameters (C_{max}, AUC_{0−t}, t_{1/2,abs}, and t_{1/2,elim}) were similar in healthy subjects and dialysis patients (see Fig. 1, p. 2908) [2], excluding a significant role of the kidney in the elimination of lanthanum and suggesting little influence of end-stage renal disease (ESRD) on systemic bioavailability. It is possible that higher absorption and, hence, higher portal plasma and liver lanthanum concentrations may occur in renal failure without affecting systemic plasma profiles, but no data are available on this at the present time.

Sample contamination may have influenced the Lacour et al [1] rat data, as plasma lanthanum concentrations in the controls in this study were extremely high compared to other studies [3]. Inevitably, there is contact between urine, feces, and spilled diet in standard rodent metabolism cages and, hence, an opportunity exists for the high concentrations of lanthanum present in diet and feces to transfer to urine. The extent of contamination will be proportional to the volume of urine washing over cage surfaces and, as Lacour et al [1] highlight, urine volume was markedly elevated in the uremic groups. Such contamination is a common source of error in rat excretion studies, particularly when poorly absorbed drugs, present at very low concentrations (nmol/L) in body tissues and fluids, are administered via the diet [4]. The potential for contamination can be reduced by controlled gavage of the drug directly into the stomach of the rats.

PATRICK C. D’HAES, GEERT J. BEHETS, MARC E. DE BROE, and STEPHEN J.P. DAMMENT
Antwerp, Belgium, and Basingstoke, United Kingdom

Correspondence to Patrick C. D’Haes, Faculty of Medicine, Antwerp University, B-2610 Wilrijk, Antwerp, Belgium.
E-mail: patrick.dhaes@ua.ac.be

REFERENCES

Bernard Lacour and Tilman Drüeke
Paris, France

Correspondence to Tilman B. Drüeke, INSERM U507, Service de Néphrologie, Paris, France.
E-mail: drueke@necker.fr

REFERENCES