

Advance Access publication 9 April 2008

Correction of metabolic acidosis after conversion from sevelamer hydrochloride to lanthanum carbonate

Sir,

We recently introduced lanthanum carbonate as an alternative phosphate binder to sevelamer hydrochloride in patients with elevated serum calcium. Lanthanum carbonate has a higher affinity for phosphate than sevelamer HCl, so fewer lanthanum carbonate tablets are required to achieve the same phosphate control. To reduce the pill burden in patients on high doses of sevelamer HCl, a policy of converting patients who were prescribed 8–12 sevelamer per day, and patients currently on 6 sevelamer per day but in need of a dose increase, to 3×750 mg lanthanum carbonate per day was established. Conversions were made at the discretion of the doctor, so that well-controlled patients were less likely to switch.

In October 2007, 60 haemodialysis patients converted according to the above criteria. Of these, 13 patients who disliked or were intolerant of lanthanum carbonate reverted to sevelamer HCl within 3 months. Forty-seven patients (68% male, median age 47 years, range 21–79) continued to take lanthanum carbonate.

Several studies have suggested that sevelamer HCl contributes to metabolic acidosis [1,2], while lanthanum carbonate would be expected to have an antacid effect. A comparison of the median of three routine (monthly) predialysis serum bicarbonate and phosphate measurements immediately before and after conversion for each patient showed an increase in serum bicarbonate from a mean of 20.3 ± 2.3 to 22.2 ± 2.4 mmol/l ($P < 0.0001$, paired *t*-test), see Figure 1. There was no wash-out period for these patients, so it is not clear whether the change in bicarbonate was due to the discontinuation of sevelamer or the initiation of lanthanum carbonate. It is noteworthy that the increase in bicarbonate was significantly lower in the 15 patients that were prescribed 6 sevelamer per day prior to the conversion (0.7 ± 1.9 versus 2.3 ± 2.6 mmol/l, $P = 0.04$, unpaired *t*-test). This is in keeping with previous data suggesting that the degree of acidosis is related to the dose of sevelamer [2].

Phosphate levels were unchanged (mean before and after conversion 2.02 ± 0.53 and 1.97 ± 0.50 mmol/l, respectively). At the time of this analysis, the dose of lanthanum had not been titrated. Phosphate levels increased by an average of 0.25 mmol/l in the six patients who were on the maximum dose of sevelamer, suggesting that patients taking more than 9 sevelamer per day should convert to the maximum recommended dose of lanthanum carbonate (3×1 g/day).

Our data are purely observational and no attempt was made to control or monitor adherence to the prescribed medications. Whilst a more rigorously controlled study might have shown a larger effect, the observed increase in bicarbonate is clinically significant and may be beneficial as this patient group has a tendency to develop metabolic acidosis.

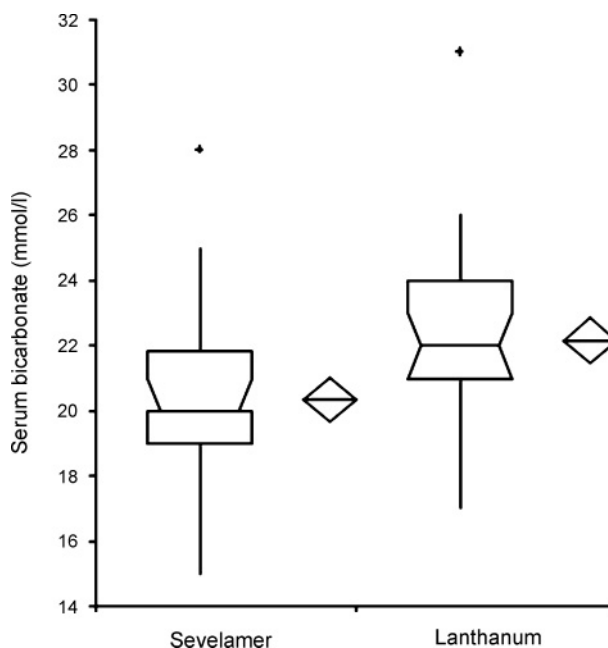


Fig. 1. Serum bicarbonate levels for 47 patients before and after conversion from sevelamer hydrochloride to lanthanum carbonate. The notches in the box plot indicate the 95% confidence interval in the median level; the diamonds indicate the 95% CI for the mean.

Conflict of interest statement. None declared.

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doi: 10.1093/ndtplus/sfn034

Advance Access publication 7 April 2008

Impact of cetuximab conventional dosing on cetuximab-induced magnesium concentration under haemodialysis in head and neck cancer

Sir,

Cetuximab-induced hypomagnesaemia is a concern in 50% of patients with normal renal function, including 15% of chronic kidney disease (CKD) stages 3–4 [1]. Cetuximab, a 150 kDa anti-EGFR (epidermal growth factor) monoclonal antibody (MAb), has been approved for the treatment of locally advanced cancer of the head and neck (LACHN) [2]

but data in patients undergoing chronic dialysis are scarce. It may be assumed that the risk for electrolyte disorders increases under dialysis with the use of cetuximab.

A 55-year-old Caucasian man on home haemodialysis presented with unresectable LASCCHN (locally advanced squamous cell cancer of the head and neck). End-stage renal disease (ESRD) resulted from polycystic kidney disease (PKD). Baseline blood abnormalities included haemoglobin (8.9 g/dl) and fibrinogen (6.9 g/l). Magnesium (0.87 mmol/l; 0.7–1) and calcium (2.33 mmol/l; 2.10–2.55) levels were normal. The dialysate contained sodium 103 mmol/l, potassium 2 mmol/l, calcium 1.5 mmol/l, bicarbonates 35 mmol/l and no magnesium. Cetuximab was given at a loading dose of 400 mg/m² followed by seven weekly doses of 250 mg/m². Electrolyte counts, including magnesium levels (0.84–0.99 mmol/l), remained normal from the initiation of treatment to Week 20. Complete tumour response was achieved 2 months following completion of treatment.

Cetuximab-induced hypomagnesaemia is associated with age, baseline magnesium concentration and prolongation of treatment [1]. The EGFR is normally localized to the basolateral surface of renal epithelial cells lining collecting tubules. EGFR mislocalization to the apical surface in PKD is accompanied by EGFR increased protein level and tyrosine kinase activity. Cetuximab-induced inappropriate urinary excretion may result from EGFR overexpression in Henle's ascending loop, where 70% of magnesium is passively reabsorbed, due to an MAb-specific phenomenon. The other 30% is reabsorbed by one half by the proximal and distal tubules. Inadequate EGFR stimulation results in insufficient activation of the epithelial magnesium channel protein TRPM6 and thereby magnesium loss [3,4]. There are no data on hypomagnesaemia after cetuximab in ESRD patients. In patients on renal replacement therapy, magnesium homeostasis no longer occurs through the kidney and ESRD patients are more likely to develop hypermagnesaemia due to a lack of renal excretion in cases of excessive magnesium levels. Due to the mechanism described for cetuximab-induced hypomagnesaemia, which occurs through deregulation of renal magnesium

reabsorption, it is unlikely to be observed in patients with damaged kidneys, i.e. in haemodialysis patients. As a result, we believe that, in haemodialysis patients, the risk for cetuximab-induced hypomagnesaemia is very low.

An important implication for the practicing oncologist was that conventional cetuximab dosing might be used in haemodialysis patients. Since haemodialysis patients now have a better life expectancy and MAb have limited toxicity, we suggest that haemodialysis patients should not be denied optimal treatment on the sole basis of their renal replacement. Translational research is needed to elucidate the mechanisms of MAb-induced electrolyte disorders at the level of the normal and damaged kidneys.

Conflict of interest statement. None declared.

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doi: 10.1093/ndtplus/sfn039