Phosphate binder is not phosphate binder! Sevelamer may be different!

The nicely performed analysis of Veighey and colleagues found that micronutrient deficiencies were relatively common in a clinically stable cohort of end-stage renal disease (ESRD) patients attending high-flux haemodialysis [1] using single-point measurements of a number of trace elements. Their conclusions, however, that prescription of phosphate binders did not have an observable effect on serum micronutrient concentrations (including vitamins and trace elements) stand in contrast to repeated demonstrations of lower trace element concentrations by other investigators (as cited by the authors). Furthermore, their measurements of trace elements cannot be simply extended to vitamin levels [2].

Sevelamer hydrochloride (poly(allylamin-co-\(N^N\)-diallyl-1,3-diamino-2-hydroxypropan) is a non-absorbable, cationic, polymeric ion-exchange resin with a relatively low selectivity for phosphate. In vitro studies demonstrated binding of folate to sevelamer [3], and pre-clinical studies found that sevelamer hydrochloride decreased serum folic acid levels in experimental animals [2].

We prospectively determined serum folic acid concentrations in 34 hyperphosphataemic ESRD patients treated with high-flux haemodialysis or haemodiafiltration, receiving folic acid supplementation (Dreisavit containing 0.16 mg folate per day, Gry Pharma Germany). While a switch from calcium carbonate to lanthanum carbonate (\(L, n = 15\)) was not associated with measurable differences in serum folate levels at 6 or 12 months of lanthanum administration, the introduction of sevelamer (\(S, n = 19\)) as phosphate binder resulted in a sustained reduction of serum folic acid levels, an increase in mean erythrocyte cell volume (MCV) and a higher need for erythropoietin to maintain target concentrations (Table 1). Four patients developed macrocytic anaemia (MCV > 100 fL) due to folic acid deficiency (serum folate concentrations <2.7 ng/mL). These findings could not be explained by seasonal variations of ‘dietary’ folate intake or acute illness inducing malnutrition or differences in non-adherence to folate-containing drugs [adherence rates were 60% (L) vs. 53% (S)]. Our observations are in agreement with short-term data that sevelamer may reduce serum folic levels after 6 weeks [2] or 3 months of administration [4].

Sevelamer may contribute to folic acid deficiency in aged high-flux haemodialysis patients with poor dietary intake and poor adherence to folic acid supplementations [5]. There is a need for regular monitoring of serum folic acid levels, at least in subgroups of patients at risk for folic acid deficiency, as recommended by the manufacturer of Renagel in the package insert.

Conflict of interest statement. None declared.

Table 1. Serum folate levels in anaemic patients on phosphate binders

<table>
<thead>
<tr>
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<th>Lanthanum (1.5 ± 0.5 g/day)</th>
<th>Sevelamer (2.8 ± 0.8 g/day)</th>
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<tr>
<td></td>
<td>Baseline 6 months 12 months</td>
<td>Baseline 6 months 12 months</td>
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<tr>
<td>Serum folate (ng/mL)</td>
<td>10 ± 4 9 ± 5 11 ± 5 12 ± 5</td>
<td>8 ± 4* 8 ± 3*</td>
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<tr>
<td>Transferrin saturation (%)</td>
<td>27 ± 3 29 ± 4 27 ± 4 28 ± 5</td>
<td>26 ± 7 29 ± 5</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>89 ± 3 90 ± 3 88 ± 2 90 ± 4</td>
<td>99 ± 4* 98 ± 6*</td>
</tr>
<tr>
<td>rHuEPO (IU/kg/week)</td>
<td>48 ± 9 52 ± 7 50 ± 8 52 ± 9</td>
<td>75 ± 14* 68 ± 15*</td>
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<tr>
<td>Hb (g/dL)</td>
<td>10.7 ± 0.3 11.0 ± 0.5 10.8 ± 0.5</td>
<td>10.8 ± 0.6 10.7 ± 0.7 10.6 ± 0.7</td>
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*P < 0.05 vs. baseline (calcium carbonate).

Phosphate retention occurs as patients develop progressive chronic kidney disease, and healthy patients achieving recommended nutritional targets typically require oral phosphate binders to limit phosphate absorption [1]. We were prompted to measure trace elements following a case of severe copper deficiency in a patient following gastric bypass surgery for morbid obesity [2], and in vitro studies have suggested that ion-exchange resins, including sevelamer, can potentially bind trace metals, including copper and zinc. Although some patients had trace element levels below the normal reference, this did not appear to be associated with phosphate binder prescription [3], but rather to dietary intake and recent or concurrent illnesses. Although the dialysis prescription [4] and modality [5] have been reported to impact on serum calcium and phosphate, the data to date do not suggest any significant clearance of water-soluble vitamins by different dialysis modalities, provided that patients have an adequate diet [6]. However, Schiff and Lang have now questioned whether the prescription of the ion-exchange phosphate binder, sevelamer hydrochloride, can bind water-soluble vitamins, so reducing gastrointestinal absorption and resulting in clinically apparent vitamin deficiency.

Conflict of interest statement. None declared.

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2. Rounis E, Laing CM, Davenport A. Acute neurological presentation due to copper deficiency in a haemodialysis patient following gastric bypass surgery. Clin Nephrol 2010; In press

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Varicella-zoster virus meningoencephalitis without skin lesions in a paediatric kidney recipient

Sir,
We have read with great interest the exceptional case reported by Jantsch et al. concerning a case of lethal varicella-zoster virus (VZV) reactivation without skin lesions following renal transplantation [1]. Recently, we treated an 11-year-old girl for VZV meningoencephalitis without skin lesions.

At age 5, she was diagnosed with nephrotic syndrome related to diffuse mesangial sclerosis. Despite immunosuppressive therapy with steroids and oral cyclosporine, end-stage renal disease occurred within 6 months. At age 7, after an 8-month haemodialysis period, she received a kidney transplant. Maintenance immunosuppression consisted of mycophenolate mofetil, tacrolimus and low-dose steroids on alternate days.

Despite a typical VZV eruption occurring at age 3, the patient was negative for VZV IgG and IgM before transplantation. VZV vaccination was not performed during the haemodialysis period. Three years after renal transplantation, she developed a typical VZV eruption without organ involvement. She was successfully treated with oral valacyclovir.

Four years after renal transplantation, at age 11, she was referred to our unit for febrile somnolence. On physical examination, meningsism was present, and Glasgow score was 10. There was no other physical sign and especially no skin lesions. Cerebral CT scan was normal. Spinal fluid examination displayed hypercellularity (90 cells/mm3; 93% of lymphocytes) with elevated protein concentration (0.99 g/L) and normal level of glucose. Bacterial and fungal cultures and testing for toxoplasmosis and Cryptococcus infection were negative. Viral DNA analysis was negative for herpes simplex viruses 1 and 2, enterovirus, cytomegalovirus, Epstein–Barr virus, and human herpes virus 6, but positive for VZV. Serum VZV IgG and IgM were both negative. Electroencephalogram displayed typical features of encephalitis. Diagnosis of VZV meningoencephalitis was considered, and intravenous (IV) acyclovir (500 mg/m² TID) was started. She also received two doses of specific anti-VZV human antibodies (Varitect®). Her condition improved within 3 days, and acyclovir was stopped after 10 days. On discharge, physical examination was normal.

In paediatric kidney recipients, VZV reactivation is a rare feature, mostly described in the first year after transplantation [2]. Our report is the first case of VZV meningoencephalitis without skin lesions in a paediatric kidney recipient.