Sevelamer

Introduction

The kidneys are the main regulators of phosphate balance; 90% of the daily filtered load of phosphate (6–8g) is reabsorbed in the proximal tubule via co-transport with sodium. As chronic kidney disease (CKD) progresses, phosphate retention occurs leading to elevated serum phosphate levels (hyperphosphataemia). This is an important contributor to the clinical entity known as CKD mineral and bone disorder. Hyperphosphataemia has also been recognised as an independent risk factor for the increase in cardiovascular disease in those with CKD. Although the exact mechanisms are unclear, in addition to contributing to the process of vascular calcification, hyperphosphataemia is associated with non-atherosclerotic arterial calcification, increased arterial stiffness and left ventricular hypertrophy, each being an independent risk factor for death. Disrupted phosphorus homeostasis occurs during the early stages of CKD, but only becomes biochemically evident at CKD stages 4 and 5 (eGFR <30ml/min/1.73m²).

Phosphate binders came into clinical use in the 1970s and were mainly calcium and aluminium containing compounds. Hypercalcaemia, particularly in those individuals with tertiary hyperparathyroidism, was exacerbated by calcium containing compounds increasing the calcium load. This led to the development of non-calcium containing phosphate binders which became available in the late 1990s. Two sevelamer compounds are licensed for use in the UK – sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela). Both are licensed for the treatment of hyperphosphataemia in patients on haemodialysis and peritoneal dialysis, but the latter is also licensed for the treatment of patients with CKD and not on dialysis who have a serum phosphate level of 1.78mmol/L or more.

Pharmacology

Figure 1 outlines the pharmacological action of sevelamer hydrochloride. It is a polymer of cross-linked polyallylamine, a large molecule consisting of repeated subunits with molecular weight of 10¹⁶ Daltons. Taken orally it is not absorbed from the gut and binds phosphate in exchange for chloride, most optimally at a pH of 7.0. Phosphate binds to
amino groups of the sevelamer HCl molecule replacing chloride ions that are then released as hydrochloric acid. Some studies have shown an association between the use of sevelamer HCl in dialysis patients and exacerbation of metabolic acidosis but it is rarely seen in clinical practice. This effect seems to be related to the release of hydrochloric acid in the gut and to the binding of short chain fatty acids in the large intestine. In the carbonate form of the drug, chloride ions in amino groups have been replaced by bicarbonate, thus reducing the potential to exacerbate metabolic acidosis.

Both sevelamer compounds are non-selective anion exchangers and therefore may bind with other anions as they transit through the intestine. By this mechanism sevelamer binds with bile acids and reduces LDL cholesterol. It may also bind lipophilic drugs such as immunosuppressants and the fat soluble vitamins D, E and K and affects the pharmacokinetics of drugs having enterohepatic circulation.

When compared to other phosphate lowering agents, sevelamer has a lower phosphate-binding capacity per gram of substance (e.g. relative binding capacities: sevelamer = 0.75, calcium carbonate/acetate = 1, and lanthanum carbonate = 2). Therefore most patients require increased doses of sevelamer which may have an impact on adherence to treatment. There is a significant increase in the risk of gastrointestinal adverse events with sevelamer compared with calcium salts. The mild metabolic acidosis that may accompany sevelamer HCl usage can be managed by increasing bicarbonate concentration in the dialysis solution or by use of the sevelamer carbonate formulation.

**Trials of safety and efficacy**

Although attempts were made to show that once daily sevelamer carbonate was as good as three times daily sevelamer HCl, this was found not to be the case and both molecules need multiple daily dosing for comparable efficacy and safety.1 Sevelamer HCl was shown to be more efficacious than calcium carbonate in an open-labelled, 24-month, randomised clinical trial.2 This study had limitations, including recruitment of only 466 patients, but it showed sevelamer treated patients experiencing lower cardiovascular mortality compared with patients treated with calcium carbonate (HR 0.99; 95% CI 0.95–0.99; p<0.001). Sevelamer carbonate has been demonstrated to effectively lower phosphate levels and reduce progression of coronary calcification in hyperphosphataemic CKD stages 3–5 not yet established on haemodialysis.3 The evidence for the cardiovascular benefit of phosphate binders is not completely established because most studies are small, open-labelled and have wide heterogeneity. However, improved mortality for non-calcium containing phosphate binders, including both sevelamer molecules and in patients who are on haemodialysis or pre-dialysis, is implied by a large systematic review.4 In this review, an analysis of 11 randomised trials (4622 patients) reporting an outcome of mortality showed that patients assigned to non-calcium based binders had a 22% reduction in all-cause mortality compared with those assigned to calcium based phosphate binders (risk ratio 0.78, 95% CI 0.61–0.98). Although this review included trials suggesting attenuation of the progression of coronary calcification in patients with CKD, it has been criticised for not including a large negative trial (2013 patients), for having a small study effect and for the quality of the studies included.5

**Specific evidence for use in diabetes**

Diabetes remains the most common cause of end stage renal disease and CKD. Individuals with diabetes make up a large proportion of the study populations in which sevelamer has been shown to be efficacious in lowering phosphate. In a randomised, open-label, crossover study comparing sevelamer carbonate with calcium carbonate in 20 patients with type 2 diabetes and CKD not on haemodialysis for two months with a one-week wash out period in between, there was improvement in HbA1c of -0.67% (95% CI -1.25; -0.1; p<0.02) when on sevelamer compared to calcium carbonate.6 The mechanism whereby sevelamer lowers HbA1c may be due to increased bile acids reaching the ileum with subsequent increase in GLP-1 release. There was also an improvement in triglycerides, total cholesterol and FGF-23 levels all independent of phosphate levels. FGF-23 in addition to parathyroid hormone is known to rise early in the development of CKD and may represent a potential early target for intervention.

**Discussion**

High phosphate levels in CKD are associated with poor cardiovascular outcomes, so it seems reasonable to use phosphate binders to lower and maintain optimum phosphate levels despite the evidence of benefit not being completely certain. Non-calcium containing compounds are often used to avoid hypercalcaemia, with or without tertiary hyperthyroidism which can be problematic. Sevelamer has the advantage of not accumulating in the body and has equivalent efficacy of phosphate control when compared with alternative agents. Current NICE guidance recommends consideration of non-calcium containing compounds in patients with CKD stages 4–5 and hypercalcaemia. The link between sevelamer use and improved cardiovascular outcomes, perhaps as a result of improving markers of cardiovascular disease including HbA1c, is of interest and further research is needed.

**Declaration of interests**

There are no conflicts of interest declared.

**References**

References are available online at www.practicaldiabetes.com.
**References**


