Chronic kidney disease: network meta-analysis compares the effectiveness of calcium-based and non-calcium-based phosphate binders

A network meta-analysis that included 28 studies (n=8,335) found that calcium-based phosphate binders increased mortality compared with sevelamer, with an absolute mortality increase of 43 per 1,000 people treated. This network meta-analysis did not consider the cost effectiveness and relative safety of the different phosphate binders and there were some limitations. It is difficult to say whether the difference in mortality is related to harmful effects of calcium-based binders or beneficial effects of sevelamer. The NICE guideline on hyperphosphataemia in chronic kidney disease recommends calcium acetate as the first-line phosphate binder in adults with stage 4 or 5 CKD, with calcium carbonate an option for people who find calcium acetate unpalatable or intolerable. Non-calcium-based phosphate binders are recommended in certain circumstances, for example if hypercalcaemia develops.

Overview and current advice

Chronic kidney disease (CKD) describes abnormal kidney function and/or structure. It is common and often exists together with other conditions, such as cardiovascular disease and diabetes. Hyperphosphataemia can occur as kidney dysfunction advances because of insufficient filtering of phosphate from the blood. High serum phosphate levels can directly and indirectly increase parathyroid hormone secretion, leading to the development of secondary hyperparathyroidism. Left untreated, secondary hyperparathyroidism increases morbidity and mortality and may lead to renal bone disease, with people experiencing bone and muscular pain, increased incidence of fracture, abnormalities of bone and joint morphology, and vascular and soft tissue calcification.

The NICE guideline on chronic kidney disease (stage 4 or 5): management of hyperphosphataemia recommends that adults should be offered calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management. If calcium acetate is not tolerated or not palatable consider calcium carbonate.

The guideline makes recommendations on the use of non-calcium-based phosphate binders as second-line therapy:

For adults with stage 4 or 5 CKD who are not on dialysis and who are taking a calcium-based phosphate binder:

- consider switching to a non-calcium-based binder if calcium-based phosphate binders are not tolerated
• consider either combining with, or switching to, a non-calcium-based binder if hypercalcaemia develops, or if serum parathyroid hormone levels are low.

For adults with stage 5 CKD who are on dialysis and remain hyperphosphataemic despite adherence to the maximum recommended or tolerated dose of calcium-based phosphate binder, consider either combining with, or switching to, a non-calcium-based binder.

For adults with stage 5 CKD who are on dialysis and who are taking a calcium-based binder, if serum phosphate is controlled by the current diet and phosphate binder regimen but:
• serum calcium goes above the upper limit of normal, or
• serum parathyroid hormone levels are low,
consider either combining with, or switching to, sevelamer hydrochloride or lanthanum carbonate, having taken into account other causes of raised calcium.

The NICE pathway on chronic kidney disease brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

Although the different types of phosphate binder have been compared to each other in randomised trials and meta-analyses, uncertainty remains about which treatment option is the most effective at lowering mortality and cardiovascular complications, and whether phosphate binders are better than placebo. A 2013 meta-analysis by Jamal et al. compared calcium-based and non-calcium-based phosphate binders, suggesting a slightly lower risk of all-cause mortality in people receiving non-calcium-based binders (absolute risk reduction 2.8%). However this review has several limitations, which are discussed in the Medicines Evidence Commentary – Chronic kidney disease: calcium-based versus non-calcium-based phosphate binders.

A new network meta-analysis served to update the review by Jamal et al. and provide estimates for the effect of the individual phosphate binders. The results of this are discussed below.

New evidence

A systematic review and network meta-analysis by Sekercioglu et al. compared the effectiveness of different phosphate binders in adults only. A conventional meta-analysis was also carried out to compare the effectiveness of calcium-based phosphate binders with non-calcium-based phosphate binders. The review included randomised controlled trials (RCTs) with moderate or worse CKD (eGFR<60ml/min/1.73m^2) who were on dialysis and not on dialysis. The studies included calcium-based phosphate binders (calcium acetate, calcium carbonate and calcium citrate) and non-calcium-based phosphate binders (sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, sucroferric oxyhydroxide and ferric citrate). Studies reported one of the following outcomes: all-cause mortality, cardiovascular mortality and hospitalisation for any cause. Studies were required to have a minimum of 4 weeks follow-up.

A total of 28 studies were included in the review (n=8,335), the mean age of participants ranged from 47 to 69 years. All-cause mortality was reported in 25/28 studies, and 7/28 studies included non-dialysis patients. The overall quality of the evidence for all-cause mortality was reported to be low or moderate (assessed using GRADE).

Results from the network-meta-analysis suggested higher all-cause mortality with calcium-based phosphate binders compared with sevelamer (risk ratio [RR] 1.89, 95% confidence interval [CI] 1.02 to 3.50, 10 studies). With a baseline mortality of 23% over a year this relative effect translates into an absolute mortality increase with calcium of 43 per 1000 (95% CI 23 to 80 more). There was no statistically significant difference in all-cause mortality for calcium-based binders compared with lanthanum (RR 1.17, 95% CI 0.96 to 1.43, 4 studies).
Results of the conventional meta-analysis showed an increase in all-cause mortality with calcium-based binders compared with non-calcium-based binders (RR 1.76, 95% CI 1.21 to 2.56, 15 studies). Conventional meta-analysis found no statistically significant difference in cardiovascular mortality for calcium-based binders compared with non-calcium-based binders (RR 2.54, 95% CI 0.67 to 9.62, 5 studies). No significant difference in hospitalisation was observed for calcium-based binders compared with non-calcium-based binders (RR 1.28, 95% CI 0.94 to 1.74, 3 studies).

Commentary

Commentary provided by Dr Indranil Dasgupta, Consultant Nephrologist, Heart of England NHS Foundation Trust. Dr Dasgupta was a member of the Guideline Development Group for the NICE clinical guideline on hyperphosphataemia in chronic kidney disease.

Chronic kidney disease bone mineral disorder has been linked to adverse health outcomes including mortality. The systematic review by Sekercioglu et al.2 used conventional and network meta-analyses of RCTs to explore the association between the use of various phosphate binders and all-cause mortality, cardiovascular mortality, and hospitalisation. Consistent with the results of a previous meta-analysis1, this study demonstrated significantly higher all-cause mortality associated with the use of calcium-based binders compared with non-calcium-based binders. Specifically, there was higher all-cause mortality with calcium based binders compared with sevelamer (RR 1.89, 95% CI, 1.02 to 3.50) on network meta-analysis. The evidence was of moderate quality. There was no statistically significant difference in cardiovascular mortality or hospitalisation between the two types of binders. By the authors’ own admission, it is difficult to say whether the difference in mortality is related to harmful effects of calcium-based binders or beneficial effects of sevelamer, and ‘should ideally be informed by trials of non-calcium-based phosphate binders versus placebo, no treatment, or a phosphorus restricted diet’.

Coincidentally, another recent network meta-analysis of randomised controlled trials of phosphate binders addresses this issue. The meta-analysis by Palmer et al.3 shows that none of the phosphate binders, either calcium or non-calcium based, reduce all-cause mortality when compared with placebo. They have also found that all-cause mortality is lower with sevelamer compared with calcium-based binders. However, this beneficial effect of sevelamer appears to be driven by a single study4; the difference in all-cause mortality was no longer significant after removing this study from the analysis. On the other hand, this was one of the few longer term studies (24 months) in the two meta-analyses. The results of these two meta-analyses indicate there is need for trials of sufficient power and duration to answer whether phosphate binders reduce mortality and if they do, whether there is a difference between different types of binders in this respect.

One criticism of both of these and previous meta-analyses, is that both calcium acetate and calcium carbonate have been considered together as calcium-based binders and compared with non-calcium-based binders. We know that calcium carbonate contains much higher elemental calcium than calcium acetate and as such its use is associated with a higher calcium load. Multiple treatment comparisons, performed as part of NICE hyperphosphataemia guideline development, looking at efficacy of phosphate binders at various time points (3, 6, 12 months) show calcium acetate to be as effective as any other binder. The health economic model that informed the decision making of NICE guideline development group reflected a probable survival benefit for people taking non-calcium-based phosphate binders; however, the extra benefit came at too great an expense. The incremental cost effectiveness ratio for sevelamer was approximately £90,000 per quality adjusted life year (QALY) compared to around £8,000 per QALY for calcium acetate when used as a first-line phosphate binder. The NICE guideline on chronic kidney disease (stage 4 or 5): management of hyperphosphataemia recommended use of calcium acetate as first line treatment. Admittedly, some of the recent data were not available at the time of publication of the NICE guideline. Despite this, until sevelamer is available
at a comparable price to calcium acetate, it would be difficult to justify using it as a first line phosphate binder in the NHS.

Declaration of interests:
Dr Indranil Dasgupta is currently Chief Investigator for a GSK multi-centre clinical trial and a member of the expert advisory board for Velphoro (sucroferric oxyhydroxide, a non-calcium containing phosphate binder), Vifor Fresenius Medical Care Renal Pharma UK Ltd (2016).

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References

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