9. Pérez-García R, Alcázar R. El dializador en el año 2017; mucho más que una membrana. Nefrología. 2018;38:4–7, http://dx.doi.org/10.1016/j.nefro.2017.08.003.

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Letter to the Editor

New information on phosphate binder interactions with vitamin K☆

Nueva información sobre interacciones de captores de fósforo con la vitamina K

Dear Editor,

We recently published an editorial in the journal NEFROLOGÍA to draw attention to a little known aspect of phosphate binders, specifically their potential pharmacological interactions.[1] In this article, we underlined that sevelamer can reduce the absorption of fat-soluble vitamins D, E and K and folic acid (according to the summary of product characteristics), although with debatable clinical impact. These data from the summary of product characteristics were obtained from experimental pre-clinical studies in rats and dogs and *in vitro* studies.

In recent years, the distinction between vitamin K_1 (phylloquinone or phytomenadione) and vitamins K_2 (menaquinones) has been emphasised and, in the nephrology community, these vitamins have gained importance as it has been recognised that vitamin K deficiency is very common in kidney patients, in particular those on renal replacement therapy.[2] This vitamin K deficiency would limit the post-translational activation by carboxylation and phosphorylation of multiple proteins related to the inhibition of vascular calcification (**K**-alcification) (osteocalcin, Bone-Gla protein, Matrix-Gla protein [MGP], among other vitamin K-dependent proteins), in addition to their effects on the classic coagulation pathways (**K**-oagulation).[2] Therefore, as vitamin K is an important cofactor for the activation of these proteins, its deficiency produces an increase in inactive forms (dephosphorylated-uncarboxylated),[2] with vitamin K_2 being the preferred cofactor for the carboxylation of MGP (tissue inhibitor of vascular calcification).[3] In this way, very recent studies (included in Figure 1 of the publication) have underlined that sevelamer (just like sucroferric oxyhydroxide [SOH] and in contrast to lanthanum carbonate) did not seem to have interactions with vitamin K_2.[3] This information comes from the publication by Neradova et al.[3] in which it was reported that SOH and sevelamer did not bind to vitamin K_2 *in vitro*, both in the presence and in the absence of phosphate in the solution.

However, a subsequent study in patients with chronic kidney disease (CKD) (on haemodialysis, peritoneal dialysis and transplant patients)[4] has analysed the impact of phosphate binders on vitamin K status in humans for the first time. These authors measured dephosphorylated-uncarboxylated MGP (inactive MGP), with a validated and standardised technique that better reflects vitamin K status than "simple" measurement of uncarboxylated MGP.[5] This study demonstrated an association between monotherapy with sevelamer and higher levels of dephosphorylated-uncarboxylated MGP (inactive) after adjusting for age, gender and use of vitamin K, suggesting a possible worsening of vitamin K status with this phosphate binder, with the potential negative impact on vascular calcification progression in these patients.[6] However, as we have pointed out previously, these interactions with vitamins have a debatable clinical impact. For example, no significant interactions have been reported in any of the summary of product characteristics for sevelamer, lanthanum or SOH (in healthy volunteers at least) with warfarin (vitamin K antagonist, with acenocoumarol being our normal equiv-

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alent). Furthermore, several studies and/or meta-analyses report (although not uniformly) an attenuation in the progression of vascular/valvular calcification and improvements in survival on dialysis with the use of non-calcium chelating agents in general and sevelamer (for which the greatest and most extensive experience is available), in particular.[7–9]

Given the growing awareness acquired with the frequent use of vitamin K antagonists such as anticoagulants in patients with CKD, the potential use of vitamin K in kidney patients[10] and/or the emergence, with possible advantages, of the novel oral anticoagulants (NOACs),[10] independent of vitamin K, we believe it is relevant to highlight that this new information could be clinically relevant in the choice of phosphate binders, the concomitant prescription with acenocoumarol and, indeed, it should also be taken into account in the design and assessment of both current and future clinical studies.

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Conflicts of interest

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REFERENCES

1. Bover J, Navarro-González JF, Arenas MD, Torregrosa V, Tamargo Menéndez J, de Francisco AL, et al. Interacciones farmacológicas de los captores del fósforo. Nefrologia. 2018;38:573–8.
2. Schurgers LJ, Barreto DV, Barreto FC, Liabeuf S, Renard C, Magdeleyns EJ, et al. The circulating inactive form of matrix gla protein is a surrogate marker for vascular calcification in chronic kidney disease: a preliminary report. Clin J Am Soc Nephrol. 2010;5:568–75.
3. Neradova A, Schumacher SP, Hubeek I, Lux P, Schurgers LJ, Vervloet MG. Phosphate binders affect vitamin K concentration by undesired binding, an in vitro study. BMC Nephrol. 2017;18:149.
4. Jansz TT, Neradova A, van Ballegooijen AJ, Verhaar MC, Vervloet MG, Schurgers LJ, et al. The role of kidney transplantation and phosphate binder use in vitamin K status. PLOS ONE. 2018;13:e0203157.
5. Cranenburg EC, Koos R, Schurgers LJ, Magdeleyns EJ, Schoonbrood TH, Landewé RB, et al. Characterisation and potential diagnostic value of circulating matrix Gla protein (MGP) species. Thromb Haemost. 2010;104:811–22.
6. Bover J, Ureña-Torres P, Górriz JL, Lloret MJ, da Silva I, Ruiz-García C, et al. Cardiovascular calcifications in chronic kidney disease: potential therapeutic implications. Nefrologia. 2016;36:597–608.
7. Wang C, Liu X, Zhou Y, Li S, Chen Y, Wang Y, et al. New conclusions regarding comparison of sevelamer and calcium-based phosphate binders in coronary-artery calcification for dialysis patients: a meta-analysis of randomized controlled trials. PLOS ONE. 2015;10:e0133938.
8. Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet. 2013;382:1268–77.
9. Spoendlin J, Paik JM, Tsacogianis T, Kim SC, Schneeweiss S, Desai RJ. Cardiovascular outcomes of calcium-free vs calcium-based phosphate binders in patients 65 years or older with end-stage renal disease requiring hemodialysis. JAMA Intern Med. 2019;179:741–9.
10. Stamellou E, Floege J. Novel oral anticoagulants in patients with chronic kidney disease and atrial fibrillation. Nephrol Dial Transplant. 2018;33:1683–9, http://dx.doi.org/10.1093/ndt/gfx322.

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