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Original Article

Influence of pH and phosphate concentration on the phosphate binding capacity of five contemporary binders. An in vitro study

STEFAN P SCHUMACHER,[1] LEON J SCHURGERS,[2] MARC G VERVLOET[3,4] AND AEGIDA NERADOVA[3]

Departments of [1]Cardiology, and [3]Nephrology, VU University Medical Center, and [4]Institute for Cardiovascular Research VU, ICaR-VU, Amsterdam, and [2]Department of Biochemistry, Cardiovascular Research Institute Maastricht, University Maastricht, Maastricht, The Netherlands

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Correspondence
Dr Aegida Neradova, Department of Nephrology, VU University Medical Center, De Boelelaan 1117 1081 HV Amsterdam, The Netherlands. Email: a.neradova@vumc.nl

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SUMMARY AT A GLANCE

This study assesses the efficacy of five phosphate binders in vitro, in relation to pH, phosphate concentration and exposure time. Except for calcium acetate/magnesium carbonate, all binders were more effective at lower pH, and binding by lanthanum carbonate doubled at pH 3 versus pH 6. This highlights the clinically important impact of gastric acidity on phosphate binding.

ABSTRACT:

Aim: **Hyperphosphataemia is associated with increased mortality and morbidity in end stage renal disease. Despite phosphate binder therapy, a large proportion of patients do not reach the treatment target. In five contemporary binders we explored the influence of pH and phosphate concentration on phosphate binding. This interaction could be of relevance in clinical practice.**

Methods: **Phosphate binding was quantified in vitro in 25 mL of purified water containing phosphate concentrations of 10, 15 and 20 mM and baseline pH values of 3.0 or 6.0, with a binder over 6 h. Lanthanum carbonate, calcium acetate/magnesium carbonate, sevelamer carbonate, calcium carbonate and sucroferric oxyhydroxide, 67 mg of each, were used. The experiments were performed in duplicate. The primary outcome was the difference in the amount of bound phosphate for each binder after 6 h in solutions at two different pH values. Secondary outcomes were the influence of phosphate concentration on phosphate binding, next to binding patterns and phosphate binder saturation.**

Results and Conclusion: **In this specific in vitro setting, lanthanum carbonate, sevelamer carbonate, calcium carbonate and sucroferric oxyhydroxide bound more phosphate in the solution with baseline pH of 3.0. Differences however were small except for lanthanum carbonate. Calcium acetate/magnesium carbonate was most effective in a solution with baseline pH of 6.0. All phosphate binders bound more phosphate in solutions with higher concentrations of phosphate. Sevelamer carbonate, calcium acetate/magnesium carbonate and sucroferric oxyhydroxide bound most phosphate in the first hour and reached maximum binding capacity in less than 6 h.**

Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease. The combination of CKD and cardiovascular disease increases a patient's risk of death.[1] In later stages of CKD, phosphate excretion is impaired and serum phosphate rises. Hyperphosphataemia, especially in combination with high calcium levels, is correlated with mortality and morbidity in dialysis patients.[2–4] Phosphate binders bind phosphate in the gastrointestinal (GI) tract resulting in less phosphate absorption. In spite of dietary restrictions and widespread phosphate binder use, a significant number of patients are not able to reach the target phosphate serum level.[5] There are multiple factors involved: non-compliance to the dietary restrictions and phosphate binder use,[6] bone derived phosphate and pharmacological aspects of phosphate binders. Furthermore, less acidic environment in use of proton pump inhibitors can be of influence, since lanthanum carbonate and calcium carbonate bind more phosphate in acidic surroundings.[7–9] In depth knowledge of phosphate binders, like influence of pH, different phosphate intake and binder saturation, can be of great importance for clinical decision-making. In this in vitro study we compare the difference in phosphate binding capacity in solutions at two pH levels and various phosphate concentrations for several phosphate binders.

Table 1 Different phosphate binders, manufacturer and the city and country of origin

Phosphate binder	Manufacturer	City, Country
Lanthanum carbonate hydrate (FosrenolR 750 mg sachets)	Shire Pharmaceutical	Basingstoke, United Kingdom
Calcium acetate/magnesium carbonate (OsvarenR 435 mg/235 mg film-coated tablets)	Fresenius Medical Care Nephrologica	Bad Homburg, Germany
Sevelamer carbonate (RenvelaR 2,4 g sachets)	Sanofi Europe B.V.	Naarden, Netherlands
Calcium carbonate (500 mg chewing tablets)	Fagron BV	Uitgeest, Netherlands
Sucroferric-oxyhydroxide (VelphoroR 500 mg chewing tablets)	Vifor Fresenius Medical Care Renal Pharma France	Neuilly-sur-Seine, France

METHODS

Materials

Phosphate binders used are listed in Table 1. Ammonium phosphate from Sigma-Aldrich Co. (St. Louis, MO, USA) was used for phosphate solutions. Ammonia 25% and hydrochloric acid 37% were purchased from Merck (Darmstadt, Germany) and BDH (Fontenay-sous-Bois, France) respectively and used for pH media. A Purelab Flex water purification device (Elga Labwater Global Operations/Veolia Water Solutions & Technologies, Lane End, United Kingdom) provided purified water for the phosphate solutions and pH media.

Preparation of phosphate binders, phosphate solution and pH media

Sevelamer carbonate (SC) and lanthanum carbonate (LA) were used in powder form and calcium carbonate (CC), calcium acetate/magnesium carbonate (CA/MC) and sucroferric oxyhydroxide (SOH) tablets were crushed to powder with a pestle. We measured the total weight of the commercial product, however since this weight includes substances used in manufacturing the tablet that do not contribute to the phosphate binding capacity, formula 1 was used to calculate 67 mg of the active constituent for each binder (an example of which is shown in the supplementary data, Appendix S1).

The weight of phosphate binder needed was measured by a Mettler AT250 microbalance, with a maximum deviation of 0.05 mg.

$$W = (A/P) \times 67$$

Formula 1: W = used amount of substance (mg); A = average weight (mg) of the whole supplement calculated after 10 measurements; P = amount of active phosphate binding component (mg) in the supplement mentioned on the package.

Next, 230 mg, 345 mg and 460 mg monobasic ammonium phosphate were mixed with 200 mL purified water in order to obtain 10, 15 and 20 mM phosphate solutions, respectively. pH was set at baseline values of 3.0 and 6.0 by adding hydrochloric acid 37% or ammonia 25%. Purified water and all pH media were tested and did not contain phosphate. A pH 209 m with a HI 1332 electrode of Hanna Instruments was calibrated at pH 2, 4 and 7 before each experiment. Finally, the phosphate binders were added to 25 mL of phosphate solution with baseline pH values 3.0 and 6.0 (mimicking pH conditions in the stomach and the small bowel) and phosphate concentrations 10, 15 and 20 mM. Phosphate solutions without a binder were used as control.

Set up

All phosphate solutions had a fixed temperature of 37°C and were stirred continuously. Two duplicate samples of 0.5 mL were taken from the phosphate solutions at the start of the experiment and after 5, 20, 60, 120, 180, 240, 300 and 360 min. Phosphate concentrations in μmol/L were determined by spectrophotometric assay with ammonium molybdate by Cobas 8000 analyzer from Roche Diagnostics after centrifuging the 0.5 mL samples in a Hettich Zentrifugen (5 min, 1800 rates per min and 20°C). This was performed in duplicate at the start of the experiment and after 5, 20, 60, 120, 180, 240, 300 and 360 min. Absolute phosphate binding in micromole was assessed with formula 2. During the experiment multiple samples of 1 mL were removed to assess the phosphate concentration at a certain time point. pH was measured throughout the experiments.

$$Ab = (Cb \times Vb) - (Ct \times Vt) - (Cr \times Vr)$$

Formula 2: Ab = Absolute binding (μmol), Cb = baseline concentration μmol/L, Vb = baseline volume (mL), Ct = concentration at certain time point (μmol/L), Vt volume at certain time point (mL), Cr = removed concentration (μmol/L), Vr removed volume (mL).

Statistical analysis

An independent samples *t*-test was used to compare phosphate binding after 360 min between the two different

Table 2 Phosphate binding at different pH values and phosphate concentrations

Phosphate binder	Phosphate (mM)	Start pH 3.0 Bound phosphate (μmol)	Start pH 6.0 Bound phosphate (μmol)	*P*-value
LC	10	85.7 (51.7)	45.2 (27.1)	< 0.001
	15	123.9† (48.0)	55.8 (21.6)	< 0.001
	20	131.3† (37.6)	70.5†,‡ (20.4)	0.002
CA/MC	10	145.6 (87.9)	147.7 (88.7)	0.62
	15	209.9† (81.2)	235.8† (91.5)	< 0.001
	20	208.2† (59.6)	263.2†,‡ (76.0)	0.003
SC	10	133.3 (80.4)	118.2 (70.9)	0.005
	15	200.7† (77.7)	173.3† (67.2)	0.003
	20	242.6†,‡ (69.5)	214.8†,‡ (62.1)	< 0.001
CC	10	139.8 (84.4)	124.8 (74.9)	0.014
	15	196.8† (76.2)	164.1† (63.7)	0.003
	20	209.0† (59.9)	180.9†,‡ (52.2)	0.002
SOH	10	132.8 (80.1)	126.4 (75.9)	0.15
	15	179.4† (69.4)	163.6† (63.5)	0.007
	20	203.1†,‡ (58.2)	189.0†,‡ (54.6)	0.004

The first column depicts the phosphate binders, Lanthanum carbonate (LC), mixture of calcium acetate and magnesium carbonate (CA/MC) sevelamer carbonate (SC), calcium carbonate (CC), sucroferric oxyhydroxide (SOH). The second column depicts the initial phosphate concentration. The third and fourth column represent the amount of bound phosphate in μmol (%) at initial phosphate concentration and pH 3 and 6 after 360 min. *P*-value indicates level of statistical significance of the difference between the two pH concentrations. †Significant more phosphate bound in initial phosphate concentration compared to 10 mM ($P < 0.05$). ‡Significant more phosphate bound in initial phosphate concentration compared to 15 mM ($P < 0.05$).

baseline pH settings within each phosphate binder per phosphate concentration. No formal comparison was performed between different binders because no equipotent doses were used since these are unknown. An ANOVA test was used to compare the influence of the different phosphate concentrations on absolute bound phosphate. Statistical analysis was performed using SPSS version 23.

RESULTS

Influence of pH

Table 2 depicts the amount of bound phosphate (in μmol) in solutions with different pH levels and phosphate concentrations. For all three baseline phosphate concentrations LC, SC and CC bound significantly more phosphate in a phosphate solution set to baseline pH 3.0 compared to pH 6.0. SOH also bound significantly more phosphate in a pH 3.0 phosphate solution, except in the 10 mM solution. CA/MC bound significantly more phosphate in a phosphate solution set to baseline pH 6.0, except in the 10 mM solution. Overall the absolute difference of phosphate binding between different baseline pH were modest, except for LA where the binding effect was almost doubled at lower pH. pH was measured throughout the experiment (Table S1).

Influence of phosphate concentration

Independent of phosphate binder, phosphate concentration and baseline pH value, significantly more phosphate was bound ($P < 0.01$) compared to control. The majority of binders bound more phosphate in the 15 mM and 20 mM solutions compared to the 10 mM solution, except for CA/MC at pH 3.0 where no additional phosphate was bound when the concentration in the solution increased from 15 to 20 mM. At both baseline pH values, the relative amount of bound phosphate declined for higher concentrations phosphate, except for CA/MC in the 15 mM phosphate solution compared to the 10 mM solution at baseline pH 6.0, as shown in Figure 1.

Phosphate binding over time

CA/MC, SC and SOH reached maximum binding capacity within 1 h. CC and in particular LC did not reach their maximum binding capacity within 6 h in our experiments.

DISCUSSION

Influence of pH

Our results show that the pH of a phosphate solution has a modest influence on phosphate binding for all binders except for LC, which binds considerably more phosphate in a solution with baseline pH 3.0 compared to pH 6.0. SC, CC and SOH also bound more phosphate in a phosphate solution with baseline pH 3.0 compared to pH 6.0. Clinically this may indicate a negative influence of a higher pH value on phosphate binding capacity. This has been demonstrated after ingestion of a meal, with proton pump inhibitor use, and in patients with chronic gastritis and hypochlorhydria, as frequently encountered in CKD.[7,9–14] CA/MC bound more phosphate with baseline pH 6.0 and therefore the limitations mentioned above seem to be of lesser importance for CA/MC. However, pH values in the binder solutions in all experiments increased immediately (in less than 40 min) to less acidic and even basic solutions toward the end of the experiments (340 min), due to the buffering capacity of all binders. This may have decreased the phosphate binding. Although LC is considered to be an effective phosphate binder,[15,16] recent research confirmed our in vitro data and showed better phosphate binding by LC at lower pH, in contrast to previous assumptions that LC was effective across a wide pH range.[8,15] This could explain why LC, in our experiments, bound less phosphate compared to other binders. Nevertheless, LC did bind some phosphate also at non-acidic pH. CA/MC was a strong binder at both baseline pH settings, probably due to the capacity of CA/MC to increase the pH in our experiments to favourable pH values for CA to bind phosphate.[17,18] This was comparable to pH levels in the duodenum (4–6) and terminal ileum (3–7).[19,20] SC

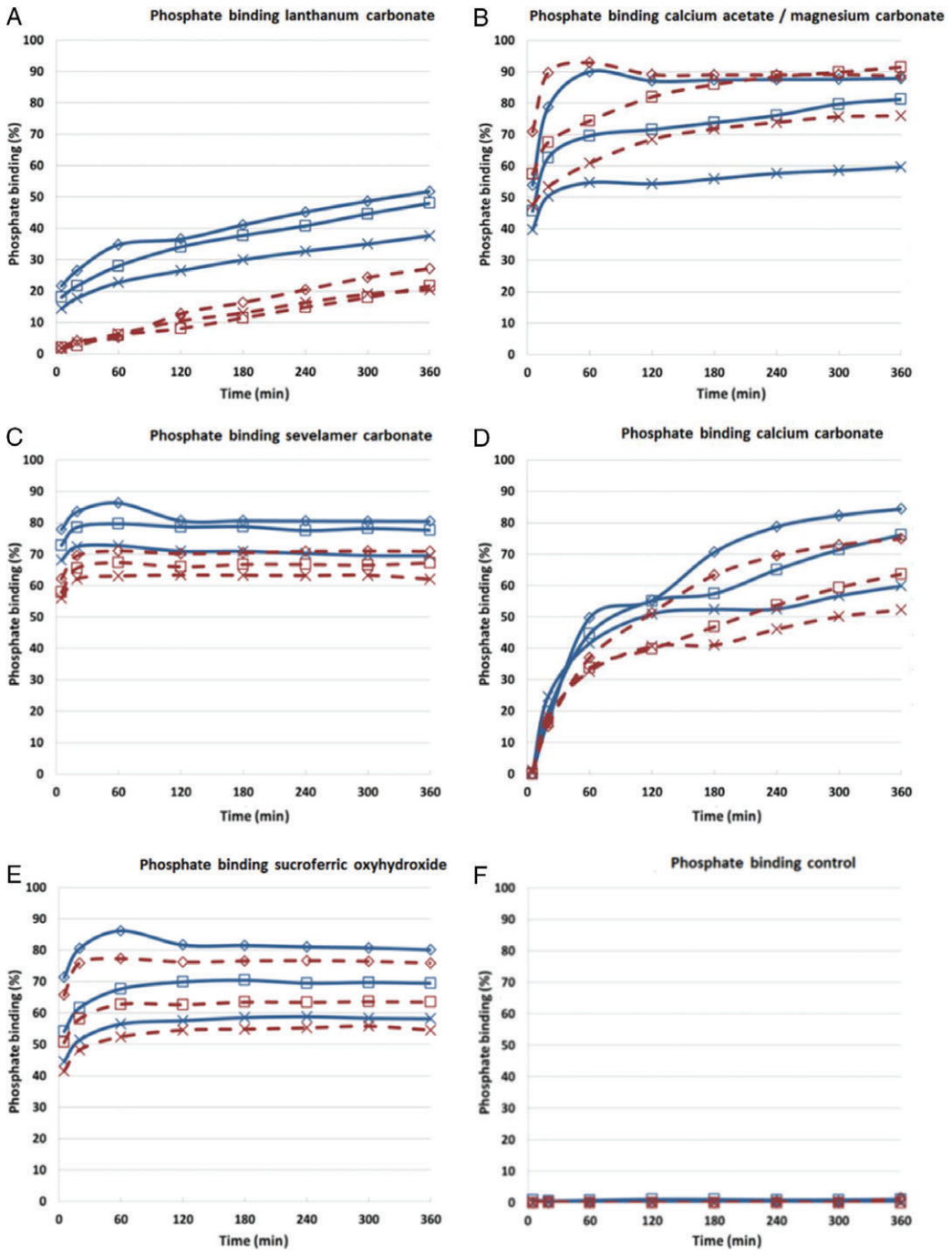

Fig. 1 Percentage phosphate binding over 6 hours of continuous stirring at 37°C for each binder and one control per baseline phosphate concentration at both pH settings. Baseline phosphate concentrations 10,15 and 20 mM and baseline pH values 3.0 and 6.,0 were used. Measurements were performed at 5,20,60,120,180,240,300 and 360 minutes. (—◇—) 10 mM/L; start pH 3.0, (—□—) 15 mM/L; start pH 3.0, (—×—) 20 mM/L; start pH 3.0, (—◇—) 10 mM/L; start pH 6.0, (—□—) 15 mM/L; start pH 6.0, and (—×—) 20 mM/L; start pH 6.0.

demonstrated statistically significant more phosphate binding in a phosphate solution with baseline pH 3.0. The pH range in the SC solution was between 5–7 most of the time in our experiment and this is in accordance with ideal pH range of 5–7.5 found in previous research for sevelamer hydrochloride (SH) which bears resemblance to SC.[15,21] However this comparison is hard to make since SH is a more acidic compound. As reported before for SH[22] more phosphate was bound by SC when initially exposed to a lower pH level. Although, in a randomized clinical trial in haemodialysis patients using SH only or SH and pantoprazole, no significant difference between phosphate levels was observed.[13]

CC bound more phosphate in acidic conditions, which is in concurrence with the previous literature,[17,23] probably

because of its optimum solubility in an acidic milieu.[7] Similar effects were demonstrated with concomitant use of pantoprazole and CC in vivo where serum phosphate was higher in the group using both CC and pantoprazole.[9]

SOH bound more phosphate in a phosphate solution with baseline pH 3.0 compared to pH 6.0, although the influence of pH seemed less compared to other phosphate binders. This may be an indication for better preservation of effective binding over the wide pH range of the GI tract as described before.[18]

Influence of phosphate concentration

Previous studies demonstrated more phosphate binding for LC and SH in contact with higher available phosphate concentrations,[8,21,24] which is in accordance with our findings. In this study, in general the absolute amount of bound phosphate increased when higher phosphate concentrations were available. However, doubling of the phosphate concentration did not lead to doubling of the phosphate binding, demonstrating that these binding processes are saturable when a fixed dose of binder is used.

Phosphate binding over time

CA/MC, SC and SOH demonstrated to be phosphate binders that bound most phosphate immediately after mixing, independent of phosphate concentration, and reached maximum binding capacity in less than 6 h. However, this again may be the consequence of relative dosing effects. Maximum binding plateau is reached later for LC and CC compared to the other binders as shown in Figure 1. In vivo, phosphate absorption mainly occurs in the small intestine, with estimated mean small intestine transit times of 3–9 h after gastric emptying. Ideally all phosphate should be bound before absorption in the small intestines can occur.[20,25] Therefore a longer duration until maximum binding capacity is reached, which has been shown in the simplistic settings of these experiments, might represent a limitation for CC and LC. However, it should be noted that transit times through the GI tract are hard to estimate in patients in clinical practice, and could be highly variable within and between patients depending on the digestive state and presence of GI tract diseases.[20,25–27]

In vitro and in vivo binding

A limitation of the current study is that the quantity of the active compound tested was based on in vitro experiments[15] and may not reflect doses prescribed in clinical practice. This is particularly the case for CC where only a small amount of elemental calcium, as the active compound was tested. These experiments do help us to understand more about the influence of the pH and phosphate concentration on phosphate binding of these binders in vivo.

However, our model lacks the complexity of the GI tract, and therefore extrapolation of our results can only be performed with great caution. In vivo, many factors induce variability in phosphate binding capacity, like distribution of phosphate binders, presence of bile salts, passage time through the stomach and intestines, the use of food additives,[28] a variable phosphate absorption even when using the same binder,[29] and a less acidic environment when proton pump inhibitors are used.[7–9]

CONCLUSION

This in vitro study with five currently available phosphate binders, including the recently approved SOH, demonstrates that pH and phosphate concentration have a modest influence on phosphate binding in all tested phosphate binders. CA/MC bound more phosphate in a phosphate solution with a baseline pH value 6.0. LA, SC, CC and SOH bound more phosphate in the solution with pH 3.0 at baseline. If extrapolated to clinical practice, these differences may be clinically meaningful, and the impact of pH could be taken into account. All phosphate binders bound more phosphate in solutions with higher concentrations of phosphate. However, doubling of the phosphate concentration did not lead to doubling of the phosphate binding. CA/MC, SC and SOH bound most phosphate within 1 h. LC and CC did not reach maximum binding after 6 h. These experiments have been conducted in an in vitro environment, so further research is warranted in vivo especially since the in vivo situation is much more complicated.

DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix S1 Formula example.

Table S1 Results of pH measurements after 40 min and 340 min in all six solutions. LC, lanthanum carbonate; CA/MC, calcium acetate/magnesium carbonate; SC, sevelamer carbonate; CC, calcium carbonate; SO, sucroferric oxyhydroxide; Co, control.