PRE-TREATMENT OF DAIRY AND BREAST MILK WITH SEVELAMER HYDROCHLORIDE AND SEVELAMER CARBONATE TO REDUCE PHOSPHATE

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♦ **Introduction:** Young children and infants with chronic kidney disease are at increased risk of hyperphosphatemia because of high intake of dairy products. Hyperphosphatemia leads to metastatic calcifications and an increased risk of cardiovascular complications. Sevelamer is an effective phosphate binder, but for children it has important practical disadvantages: it clogs enteral feeding tubes and can cause gastrointestinal complaints. Pre-treatment of dairy products to reduce their phosphate content might solve those problems.

♦ **Methods:** Sevelamer hydrochloride and sevelamer carbonate were suspended in various dairy products (cow's milk, breast milk, baby formula, and tube-feeding formula). Each product was tested with varying concentrations of sevelamer. After suspension, each sample was stored for 10 minutes, allowing the sevelamer to precipitate. The supernatant was decanted and analyzed for pH and for phosphate, calcium, magnesium, potassium, sodium, and chloride content.

♦ **Results:** We observed a significant decrease in the phosphate content of all tested products. With sevelamer hydrochloride, the phosphate reduction was 48% – 91% in the various products, and with sevelamer carbonate, it was 22% – 87%. The highest effectiveness was found in breast milk. A pH increase was found in all products. With sevelamer hydrochloride, a significant increase in chloride occurred. Notably, a significant decrease in calcium content (–75%) was observed in treated breast milk.

♦ **Conclusions:** Pretreatment of a variety of dairy products with either sevelamer hydrochloride or sevelamer carbonate effectively reduced their phosphate content and might avoid troublesome ingestion of sevelamer in children. The change in pH with sevelamer hydrochloride was remarkable, reflecting buffering mechanisms. The reduction in the calcium content of breast milk is a potential concern and should be carefully considered and monitored during clinical use of sevelamer.

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Patients with renal failure have disturbed bone metabolism. Phosphate retention, decreased synthesis of calcitriol, and loss of calcium occur with declining renal function. As an initial adaptive response, fibroblast growth factor-23 and, later, parathyroid hormone increase to maintain adequate calcium and phosphate levels, but hyperphosphatemia generally occurs as the glomerular filtration rate decreases from chronic kidney disease stage 3a (45 – 59 mL/min/1.73 m²) to 3b (30 – 44 mL/min/1.73 m²) (1,2).

With hyperphosphatemia, hyperparathyroid hormone further progresses and, with treatment of hyperphosphatemia, hypercalcemia often develops as well. Hyperphosphatemia and an elevated Ca×P product both predispose to metastatic calcifications and directly correlate with mortality risk in adults (3). In children with chronic kidney disease, increased phosphate and an increased Ca×P product respectively correlate with arterial stiffness and increased intima media thickness of the carotid artery (4). To treat hyperphosphatemia, oral phosphate binders are almost always necessary in addition to dietary phosphate restriction and, eventually, dialysis.

Several different phosphate binders have been used so far. The early aluminium-containing phosphate binders have been abandoned because of associations with toxic aluminium accumulation in the body (5,6). With the lanthanum-containing phosphate binders, deposition leading to toxicity has been shown in animal studies as well (7,8). Although intestinal absorption of lanthanum is very low in healthy volunteers (9), safety in pediatric patients remains unclear, and

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further studies are warranted. The frequently used calcium salts have the disadvantage of also causing hypercalcemia, associated with vascular alterations and calcification (10,11).

A novel promising iron-based phosphate binder called SBR759 was recently introduced, but studies are still in the preliminary phase (12).

Sevelamer is a polymeric ion-exchange phosphate binder, available as sevelamer hydrochloride and, more recently, also as sevelamer "carbonate." Technically, sevelamer carbonate is not an accurate name, because the resin exists only as a mix of the free amine and bicarbonate forms—the carbonate form being too unstable, except in very alkaline conditions (13). In the present study, we followed convention and used the name "sevelamer carbonate" per the product monograph.

Compared with sevelamer hydrochloride, sevelamer carbonate has shown equivalent phosphate control and lowering of Ca $\times$ P product. With sevelamer carbonate, a significant rise in serum bicarbonate is seen as well; sevelamer hydrochloride results in equal or decreased serum bicarbonate (14–18).

In young pediatric renal patients, who are often dependent on nutrition in liquid forms, sevelamer use has important disadvantages: sevelamer hydrochloride and sevelamer carbonate both cause clogging of feeding tubes because of the hydrogel that is formed with fluids. Gastrointestinal complaints have also been described after oral administration (19). If sevelamer were to be added to phosphate-rich soluble foods such as tube-feeding formula, baby formula, or milk and then decanted, those problems might be solved.

In an earlier published study, sevelamer hydrochloride was successfully added to breast milk (20). The goal of the present study was to evaluate the effects of the addition of sevelamer hydrochloride and sevelamer carbonate on the composition of various dietary formulae and breast milk. To be able to use this technique in patients, it is necessary to understand its effectiveness in relation to the reduction of phosphate content and to evaluate any chemical interactions and effects on other minerals.

METHODS

Sevelamer hydrochloride and sevelamer carbonate were both suspended in several dairy products: semi-skimmed cow's milk, standard baby formula (Nutrilon: Nutricia, Schiphol, Netherlands), standard tube-feeding formula (Frebini: Fresenius Kabi, Runcorn, UK), and breast milk. (For specifications of the formulae, see Table 1.)

TABLE 1
Baseline Constituents in Baby Formula and
Tube-Feeding Formula

Constituent	Formula type ^a	
	Nutrilon 1 ^b	Frebini ^c
Phosphate (mmol/L)	7.7	16.1
Calcium (mmol/L)	11.2	15.0
Chloride (mmol/L)	12.1	28.0
pH	Not described	Not described

^a Average values given by the manufacturer; may vary with the protein source.

^b Nutricia, Schiphol, Netherlands.

^c Fresenius Kabi, Runcorn, UK.

SEVELAMER

For sevelamer hydrochloride, 800 mg Renagel tablets (Genzyme Europe, Naarden, Netherlands) were used. These oval, film-coated, compressed tablets contain 800 mg sevelamer hydrochloride on an anhydrous basis. Sevelamer hydrochloride is a polyallylamine hydrochloride (a polymeric phosphate binder developed for oral administration). Sevelamer hydrochloride is hydrophilic, but not soluble in water. It binds phosphate using a combination of anionic and hydrogen binding (18).

For sevelamer carbonate, either 800 mg Renvela tablets (Genzyme Europe) or 800 mg Renvela powder (one third of a 2400 mg sachet, measured using a weigh scale) were used. The oval, film-coated tablets contain 800 mg sevelamer carbonate on an anhydrous basis. Sevelamer carbonate has the same polymeric structure as sevelamer hydrochloride, with carbonate replacing chloride as the counter-ion (21).

GENERAL PROCEDURE

Tablets or powder were added to samples of the dairy products, which were then firmly stirred or shaken until the sevelamer was visibly suspended. In the experiments, it took 5 – 10 minutes for whole tablets to dissolve completely. When tablets were cut into pieces or suspended in 10 mL of hot water and then well stirred, they dissolved within 1 – 3 minutes.

The resulting suspensions were stored for 10 minutes to allow the sevelamer to precipitate with phosphate. The supernatant was collected and analyzed. Previous experiments by Ferrara *et al.* (20), looking at the timing for pre-treating breast milk with sevelamer hydrochloride, had showed that the maximal decrease in phosphate content occurred within 5 – 10 minutes after mixing

(a)

(b)

Figure 1 — Mean percentage change in phosphate, calcium, chloride, and pH for (a) semi-skimmed cow's milk (50 mL) with 800 mg sevelamer hydrochloride (Renagel: Genzyme Europe, Naarden, Netherlands) or with 800 mg sevelamer carbonate (Renvela: Genzyme Europe); and for (b) breast milk (50 mL) with 800 mg sevelamer hydrochloride or with 800 mg sevelamer carbonate. Values are the mean of 3 samples each.

and that the sevelamer precipitated as a hydrogel at the bottom of the cup.

Phosphate, total calcium, magnesium, potassium, sodium, chloride, and pH in the dairy products were determined before and after the addition of each sevelamer dose. Experiments were performed at every dose level for all the formulae and for both types of sevelamer. All experiments were repeated at least 3 times each for all 50-mL dosages and at least 2 times each for the other dosages. For sevelamer carbonate, only the lowest concentration of 400 mL was not tested.

MEASUREMENT METHODS

For all experiments, a practical "kitchen" approach was used. After suspension, the precipitation of phosphate with sevelamer was allowed to occur for 10 minutes, showing a clear precipitated layer, and then decantation was performed. Centrifuging of the decanted milk was necessary

to eliminate excess fat, otherwise the equipment might be damaged and not be able to accurately measure the samples [centrifuging occurred for 10 minutes at 14 000 rpm (Mikro 24-48R: Hettich, Tuttlingen, Germany)]. Precipitated sevelamer was not observed in the samples after centrifuging, indicating that the decantation had worked well and that truly decanted fluid was analyzed.

Phosphate, total calcium, and magnesium were measured using a spectrophotometric method. Sodium, potassium, and chloride were measured using a potentiometric method. All minerals were measured using an Aeroset chemical analyzer (Abbott Laboratories, Abbott Park, IL, USA). The pH was measured using a glass electrode containing a constant buffer (PHM220: Radiometer, Copenhagen, Denmark).

Using the supernatant, three series of experiments were performed:

- First, a dose-response curve for each product was sought using a fixed dose of sevelamer hydrochloride against an increasing volume of each dairy product. These measurements were subsequently performed with sevelamer carbonate and compared with those using sevelamer hydrochloride.
- Second, measurements after mixing and precipitation with sevelamer hydrochloride were taken at a variety of temperatures: refrigeration (4°C), room temperature (20°C), and near-boiling (80°C – 90°C). Because no effect on any of the electrolytes was seen across the temperatures tested, these experiments were not repeated with sevelamer carbonate.
- Finally, because of an observed time-dependent effect on pH in the treated samples, pH was measured over time from 0 to 120 minutes after treatment with sevelamer hydrochloride and sevelamer carbonate.

DATA ANALYSIS

To be able to compare the various dairy products, results are reported as the mean percentage change for each analyte. For each dairy product, absolute values for one representative sample are also given. Independent t-tests were used to compare the various dairy products and to compare sevelamer hydrochloride with sevelamer carbonate treatment. Paired t-tests were used to compare samples before and after treatment.

RESULTS

OVERVIEW RESULTS FOR THE VARIOUS DAIRY PRODUCTS

Tables 2 and 3 set out the absolute concentrations and mean percentage changes in phosphate, calcium, chloride,

TABLE 2
Absolute Results of One Representative Sample^a and Mean Percentage Change in All Samples
Before and After Treatment with Sevelamer Hydrochloride^b

Constituent	Cow's milk		Breast milk		Baby formula		Tube-feeding formula	
	Before	After	Before	After	Before	After	Before	After
Phosphate (mmol/L)	19.9	10.7	1.7	0.2	3.6	1.0	10.4	4.9
Mean percentage change		-48% ^c		-91% ^c		-76% ^c		-53% ^d
Calcium (mmol/L)	25.6	20.8	3.9	1.0	8.5	7.4	12.1	10.7
Mean percentage change		-18% ^d		-75% ^c		-13% ^e		-13% ^e
Chloride (mmol/L)	31.6	60.2	13.0	22.8	16.8	37.2	32.6	48.5
Mean percentage change		+92% ^c		+63% ^e		+122% ^c		+49% ^d
pH	6.7	8.6	6.8	7.8	7.1	8.7	6.8	8.8
Mean percentage change		+28% ^c		+15% ^e		+15% ^c		+30% ^d

^a 50 mL.

^b 800 mg.

^c $p < 0.001$ by paired t-test.

^d $p < 0.01$ by paired t-test.

^e $p < 0.05$ by paired t-test.

TABLE 3
Absolute Results of One Representative Sample^a and Mean Percentage Change in All Samples
Before and After Treatment with Sevelamer Carbonate^b

Constituent	Cow's milk		Breast milk		Baby formula		Tube-feeding formula	
	Before	After	Before	After	Before	After	Before	After
Phosphate (mmol/L)	20.0	15.7	1.8	0.2	3.0	0.9	14.0	10.5
Mean percentage change		-22% ^c		-87% ^d		-69% ^e		-25% ^c
Calcium (mmol/L)	30.0	23.8	3.6	0.9	6.5	4.7	13.0	12.3
Mean percentage change		-21% ^d		-77% ^d		-27% ^c		-6%
Chloride (mmol/L)	30.0	31.0	12.5	12.0	16.0	16.0	28.0	29.5
Mean percentage change		+3%		-4%		0%		+5%
pH	6.7	9.2	6.7	8.7	7.0	9.5	6.9	9.0
Mean percentage change		+38% ^c		+29% ^e		+37% ^d		+30% ^c

^a 50 mL.

^b 800 mg.

^c $p < 0.05$ by paired t-test.

^d $p < 0.01$ by paired t-test.

^e $p < 0.001$ by paired t-test.

and pH before and after treatment with sevelamer hydrochloride and sevelamer carbonate respectively. Figure 1(a,b) gives an overview of the mean percentage change in phosphate for breast milk and semi-skimmed cow's milk. For all the experiments, 800 mg sevelamer was suspended in 50 mL dairy product. The choice of 50-mL samples was made to evaluate the maximal effect of sevelamer.

For all dairy products, a significant reduction in phosphate and a significant rise in pH were seen with both sevelamer hydrochloride and sevelamer carbonate. For all dairy products, a significant rise in chloride was seen with sevelamer hydrochloride. For breast milk, a highly significant reduction in calcium that was smaller or absent in the other dairy products was seen with both sevelamer

hydrochloride and sevelamer carbonate. No differences in potassium and sodium were found before and after treatment. A small decrease in magnesium, varying from 5% to 25%, was observed after treatment.

After suspension, no significant differences were found between products treated with sevelamer carbonate tablets and with sevelamer carbonate powder. No differences were found at the different temperatures. All samples were tasted by the same observer before and after treatment with sevelamer hydrochloride and sevelamer carbonate. No differences in taste were observed.

DOSE-RESPONSE RESULTS

Dose-dependency for phosphate was evident, as shown for cow's milk in Figure 2(a). Comparable curves were seen with the baby and tube-feeding formulae (results not shown). Compared with sevelamer carbonate, sevelamer hydrochloride showed somewhat higher efficacy at all concentrations. The effect was most pronounced in cow's milk. The initial phosphate concentration was significantly lower in breast milk than in other products. At lower doses, sevelamer hydrochloride and sevelamer carbonate both showed more efficacy in breast milk than in other dairy products, probably because of the lower initial phosphate concentration with more abundance of sevelamer [Figure 3(a)]. Figures 2(b) and 3(b) show the dose-response effect for calcium. A dose-response effect was observed for pH as well. A dose-response effect for chloride was found only with sevelamer hydrochloride.

DIFFERENCES BETWEEN SEVELAMER HYDROCHLORIDE AND SEVELAMER CARBONATE

The largest difference between sevelamer hydrochloride and sevelamer carbonate was the evident rise in chloride for all dairy products with sevelamer hydrochloride. No change in chloride occurred with sevelamer carbonate. For cow's milk and the tube-feeding formula, the decrease in phosphate was significantly less with sevelamer carbonate. The same trend was seen with breast milk and baby formula, but the differences were not statistically significant.

DIFFERENCES BETWEEN DAIRY PRODUCTS

A significantly better decrease in phosphate was achieved in breast milk and baby formula than in cow's milk and tube-feeding formula. A much larger decrease in calcium was also observed in breast milk than in the other dairy products. Another difference between breast

FOOD PRE-TREATED WITH SEVELAMER TO REDUCE PHOSPHATE

(a)

(b)

Figure 2 — Decrease in (a) phosphate (mmol/L) and (b) calcium (mmol/L) for skimmed cow's milk after treatment with sevelamer hydrochloride (Renagel: Genzyme Europe, Naarden, Netherlands) or sevelamer carbonate (Renvela: Genzyme Europe). Values are the dose-response course of 2 representative samples.

milk and the other dairy products was the observed rise in pH, which was significantly less in breast milk, especially with the use of sevelamer hydrochloride. A remarkable observation concerning the rise in pH was that, over time, the pH of breast milk treated with sevelamer hydrochloride declined again, almost to pre-treatment values. This time-dependency was not shown for any of the other tested dairy products.

DISCUSSION

In the present study, we treated semi-skimmed cow's milk, breast milk, baby formula, and tube-feeding formula with sevelamer hydrochloride and sevelamer carbonate to investigate whether phosphate would be effectively reduced and what the possible effects on other minerals and pH might be. With the highest dose of sevelamer hydrochloride, the mean observed reduction in phosphate was 48% – 91% for the various

Figure 3 — Decrease in (a) phosphate (mmol/L) and (b) calcium (mmol/L) for breast milk after treatment with sevelamer hydrochloride (Renagel: Genzyme Europe, Naarden, Netherlands) or sevelamer carbonate (Renvela: Genzyme Europe). Values are the dose-response course of 2 representative samples.

dairy products, and with the highest dose of sevelamer carbonate, the mean reduction in phosphate was 22% – 87% for the various dairy products. The most important other effects were a distinct rise in chloride with sevelamer hydrochloride and a rise in pH with both sevelamer hydrochloride and sevelamer carbonate. The calcium content declined in all samples, with the largest decline occurring in breast milk.

For sevelamer carbonate, the pH rise was expected and can be explained by the bicarbonate ions being exchanged. However, for sevelamer hydrochloride, we found a surprisingly significant increase in pH as well, together with a rise in chloride.

From previous studies in patients, acidosis might be expected with sevelamer hydrochloride (17,18,22). Sevelamer hydrochloride is a quaternary amine anion exchange resin with a non-absorbed polymer chain having covalently linked amino groups. Approximately 40% of those groups consist of amine hydrochloride.

According to Brezina *et al.* (23), hydrochloride molecules from sevelamer are exchanged in the human gastrointestinal tract with monovalent phosphate, bicarbonate, and bile salts. According to Wrong and Harland (24), acidosis might also develop because of the exchange of chloride with short-chain fatty acid anions present in the gastrointestinal tract. These proposed mechanisms point to an increase in chloride and development of metabolic acidosis.

Given the results of the present study, the increase in chloride ions can be explained by the above-mentioned mechanisms; we assume that the exchange occurs mostly with divalent phosphate anions in the pH range of milk (25). Further, chloride might also exchange with other anions, explaining the observed rise in chloride.

The *in vitro* pH increase of the decanted milk must be caused by a release of base or by binding or loss of acid in the reaction of dairy products with sevelamer hydrochloride during precipitation. A suspension of sevelamer hydrochloride in distilled water did not change the pH of the distilled water, and so the pH rise has to be explained by the interaction of sevelamer with substances in the milk. An alkaline load is likely to have been released because of the molecular interaction of proteins in the milk, especially caseins. The casein content of cow's milk represents 80% of the milk proteins. Most of the casein proteins exist as colloidal particles known as casein micelles. Calcium and phosphate are present as $\text{Ca}_3[\text{PO}_4]_2$. As described earlier, the exchange of chloride with phosphate occurs mainly with the divalent phosphate anion H_2PO_4^- , meaning that, during the precipitation of sevelamer with phosphate in skimmed cow's milk at pH 6.7, about 20 mEq H^+ ions will be bound by interaction with sevelamer hydrochloride. In addition, the interaction with proteins can alter their spatial structure and consequently affect proton exchange. In the decanted milk, base release has to occur, resulting in the formation of bicarbonate and the slow formation of CO_2 . The exact effect of the pH increase could theoretically be determined only by measuring the course of pH change in the stomach after feeding milk and after feeding decanted milk, which is ethically undesirable. However, the expectation would be that the buffering capacity of the stomach is more than sufficient to compensate for the observed pH effect. Food with a higher pH is commonly consumed, as are large supplements of sodium bicarbonate (2 – 20 mmol/kg daily in tubular acidosis), which are not harmful, and prolonged administration of large doses of sodium bicarbonate have previously been shown to be safe in humans (26).

Pretreatment of formula or breast milk has been performed before to reduce dietary intake of phosphate or potassium and to avoid the practical disadvantages or potential side effects of taking the medication. For potassium, Bunchman *et al.* (27) found that sodium polystyrene sulfonate effectively reduced the potassium content in several formulae. However, sodium increased disproportionately, and calcium and magnesium decreased. Schröder *et al.* (28) pretreated four different formulae with calcium polystyrene sulfonate. They effectively reduced the potassium content 50% without an important increase of sodium, similar to the Bunchman *et al.* results.

For phosphate reduction, calcium acetate has been used to pretreat milk for reduction of phosphate content (29), but no effect on phosphate was seen; meanwhile, the calcium content in the formula increased by a factor of up to 3. The formula also developed an unpleasant sour taste with the addition of increasing amounts of calcium acetate. It is likely that the phosphate contained in the casein micelles in milk cannot be reached by calcium acetate, but only by interaction with sevelamer. The only study using sevelamer to reduce phosphate content was performed by Ferrara *et al.* (20), who used breast milk and added sevelamer hydrochloride. In their study, the additional of 806 mg sevelamer to 180 mL breast milk effectively reduced the phosphate content by 80%, which is comparable with our results in the present study.

Ferrara *et al.* found no change in pH, which differs from the finding of a pH rise in the present study. A potential explanation is that, in breast milk, the pH declines again with time to almost the original value. Ferrara's group measured pH after 1 hour. The reason that pH declines with time after the initial rise in breast milk might be a result of the relatively small buffering capacity of breast milk, with its lower casein content. If bicarbonate continues to escape in small amounts via CO₂, the pH of the breast milk will be affected over time because of the small buffering capacity.

In the study by Ferrara *et al.*, chloride was not measured. The reduction in calcium that we found was also observed by Ferrara's group. We showed that this reduction in calcium is dose-dependent, with the reduction in calcium being as high as 75% when 800 mg sevelamer hydrochloride or sevelamer carbonate are added to 50 mL breast milk. This calcium reduction is considerable and could theoretically affect normal bone metabolism. Serum calcium, alkaline phosphatase, and parathormone should therefore be carefully monitored.

A few differences were observed between the various dairy products. The highest effectiveness of sevelamer was seen with breast milk, in which it produced a relatively large decrease in calcium and a less pronounced

rise in pH. Those findings might be a result of the lower total phosphate and calcium content in breast milk compared with other dairy products (especially semi-skimmed cow's milk and tube-feeding formula), with a relative excess of sevelamer. Another observed difference was the somewhat lower effectiveness of sevelamer carbonate compared with sevelamer hydrochloride in dairy products with the highest total phosphate content (semi-skimmed cow's milk and tube-feeding formula). A difference in effectiveness between sevelamer carbonate and sevelamer hydrochloride has not been reported in clinical use in patients. Differences in the affinity of sevelamer carbonate ions in dairy products, with less exchange of bicarbonate ions with divalent phosphate, might play a role.

An important limitation of the present study for practical use is the individual variance in dairy products, which makes it impossible to give exact values for the changes in minerals and pH for every product. Only the mean percentage results can therefore be extrapolated to other countries and settings. Pre-treated dairy products and breast milk might vary in their phosphate content because of different feeding patterns—variances that are inevitable—but the proportionate decrease in phosphate would be expected to be comparable.

CONCLUSIONS

Effective phosphate reduction was achieved with the use of both sevelamer hydrochloride and sevelamer carbonate to pretreat various dairy products, the highest effectiveness being seen in breast milk. A dose of 800 mg sevelamer hydrochloride is effective for up to 400 mL breast milk (phosphate decrease exceeding 85% at all dosages). For sevelamer carbonate in breast milk, the same pattern was seen. A dose of 800 mg sevelamer hydrochloride is effective for 100 mL semi-skimmed cow's milk, tube-feeding formula, and baby formula (phosphate decreases of 42%, 48%, and 68% in 100 mL respectively). Sevelamer carbonate is less effective for semi-skimmed cow's milk and tube-feeding formula (phosphate decrease of less than 30% at all dosages). The observed pH rise is not expected to be clinically important. The decrease in calcium has to be taken into account; calcium values should be monitored closely, especially in patients receiving pretreated breast milk.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

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