

Original Article

Length of interdialytic interval influences serum calcium and phosphorus concentrations

Mhairi K. Sigrist¹, Lisa Devlin¹, Maarten W. Taal¹, Richard J. Fluck¹ and Christopher W. McIntyre^{1,2}

¹Department of Renal Medicine, Derby City General Hospital, Derby and ²Centre for Integrated Systems Biology and Medicine, University of Nottingham, UK

Abstract

Background. Higher levels of serum phosphorus and calcium are associated with increased haemodialysis (HD) patient mortality. Both of these factors act synergistically to promote vascular smooth muscle differentiation to an osteoblast-like phenotype and subsequent vascular calcification. The aim of this study was to investigate the influence of interdialytic interval on serum levels, as well as the influence of oral calcium-based phosphate binder load on the magnitude of the observed differences.

Methods. We studied 100 patients undergoing HD three times per week, over a 2 week period. Haemoglobin, albumin, calcium and phosphate were measured pre-dialysis before each HD session. Oral phosphate binder usage was recorded. All patients were treated with dialysate containing 1.25 mEq/l calcium.

Results. Both mean serum phosphate and calcium were higher after the long interdialytic interval (1.59 ± 0.05 vs 1.45 ± 0.04 mmol/l, $P = 0.0005$, and 2.46 ± 0.03 vs 2.4 ± 0.02 mmol/l, $P = 0.001$, for serum phosphate and uncorrected calcium, respectively). There were no significant differences in haemoglobin or serum albumin, indicating that variable dilution from an increased hydration status in the long interdialytic interval was unlikely to contribute to these observed differences. A total of 74 patients were treated with calcium-containing binders and 26 patients with sevelamer. Patients on sevelamer did not exhibit the observed cyclical increase in serum calcium seen in patients on calcium-containing binders (mean difference in serum calcium 0.09 ± 0.01 mmol/l in the calcium-treated group vs 0.01 ± 0.01 mmol/l in the sevelamer-treated patients, $P = 0.0004$). The increase in serum calcium after the long interval as compared with the short interval was proportional

to the daily amount of the oral calcium-containing binder load ingested ($r = 0.63$, $P < 0.0001$).

Conclusion. Cyclical differences in interdialytic interval and overall exposure to both dietary phosphate and oral calcium load influence serum levels. This may have consequences for registry reporting, therapy modulation and potentially the pathogenesis of accelerated vascular calcification seen in HD patients.

Keywords: interdialytic interval; calcium carbonate; sevelamer; phosphate; vascular calcification; haemodialysis

Introduction

In recent years, there has been an increasing realization of the critical role that control of serum phosphorus, calcium and calcium/phosphorous product plays in determining clinical outcomes in chronic haemodialysis (HD) patients [1,2]. Mineral monitoring and control is a mandatory part of routine patient care and associated appropriate registry data collection processes.

Elevated levels of serum phosphorus and calcium (even within normocalcaemia) appear to have a synergistic effect [3] on both ectopic ossification and patient mortality in observational clinical studies [1] and recent *in vitro* studies of vascular smooth muscle cell phenotypic change and mineralization [4,5].

HD is conventionally performed three times a week. This is a result of convention, patient acceptability, resource limitations and a robust evidence base to suggest that such a strategy is associated with an acceptable degree of patient survival (rather than representing an optimal schedule). This therefore introduces a degree of asymmetry into the patient's treatment week, with one longer interdialytic interval (72 h) compared with two shorter ones (48 h). This asymmetry may be of significance when considering

Correspondence and offprint requests to: Dr C. McIntyre, Department of Renal Medicine, Derby City General Hospital, Uttoxeter Rd, Derby DE22 3NE, UK.
Email: Chris.McIntyre@derbyhospitals.nhs.uk

serum mineral concentrations and their consequences. The longer interval allows a protracted time to ingest phosphate-containing foods, potentially influenced by variable appetite due to fluctuating uraemia and the burden of HD-related symptoms. Furthermore, there is also an asymmetrical period between dialysis with respect to exposure to dietary calcium, and in particular calcium-based phosphate binders. Variability in levels in serum mineral concentration would have important implications for the timing of blood taking, to ensure consistency in monitoring patients, registry reporting and modulation of therapies concerning mineral control. In addition, cyclical fluctuations in serum calcium and phosphorus might have a role to play in the accelerated and severe vascular calcification characteristic of HD patients [6].

The aims of this study were to investigate whether or not the differing interdialytic intervals influenced serum mineral concentrations and if the type and dose of phosphate binder used contributed to any observed differences.

Patients and methods

We studied 100 patients. All had been established on HD for at least 6 months. All patients were receiving three sessions of at least 4 h duration per week (maximum 5 h per session). Dialysis was performed using Hospal Integra (Mirandola, Italy) monitors and low flux polysulfone dialysers (1.5–2.0 m², LOPS 15-20[®], Braun Medical Ltd, Sheffield, UK). All patients were dialysed using a 1.25 mEq/l calcium-containing dialysate.

Patients enrolled were on only one form of phosphate binder. Seventy-four patients were receiving calcium carbonate (Calcichew, Shire Pharmaceuticals) and 26 patients were receiving sevelamer (Renagel, Genzyme Pharmaceuticals). All patients had been on the same binder and vitamin D medication for at least 4 weeks prior to the study. No changes occurred during the 2 week sampling period. Patients were receiving regular input from a renal dietician. Advice was given to limit their dietary phosphate intake. This was individualized, however, to allow maintenance of a daily protein intake of 1 g/kg body weight. Instructions were given to distribute oral phosphate-binding medication according to the size and phosphorus content of the meal, with the aim to deliver 50% of the daily dose with the main meal (where such eating habits existed).

Bloods were sampled pre-dialysis prior to each treatment session over a 2 week period. Blood was taken from the arterial supply to the dialyser into lithium heparin and EDTA tubes, and biochemical analysis was performed on a multichannel autoanalyser (albumin measured using the bromocresol purple method and used to correct serum calcium concentration). Serum calcium, phosphorus, albumin and haemoglobin were measured and values taken before the dialysis after the long interdialytic interval and compared with values obtained from both of the preceding dialysis sessions after the short interdialytic intervals.

Appropriate ethical approval had been granted by South Derbyshire Local Research Ethics Committee, and all patients provided written consent.

Statistical method

All data were entered into Excel spread sheets. Statistical analysis was performed using the Prism v3.0 software package. Values are expressed as mean \pm SEM [95% confidence intervals (CIs) of the mean], unless otherwise stated. *P*-values of <0.05 were considered to be significant. All data were tested for normal distribution and data were compared using *t*-tests (paired as appropriate). Correlation plots were subsequently analysed by linear regression. The coefficient of determination was calculated from the Pearson correlation.

Results

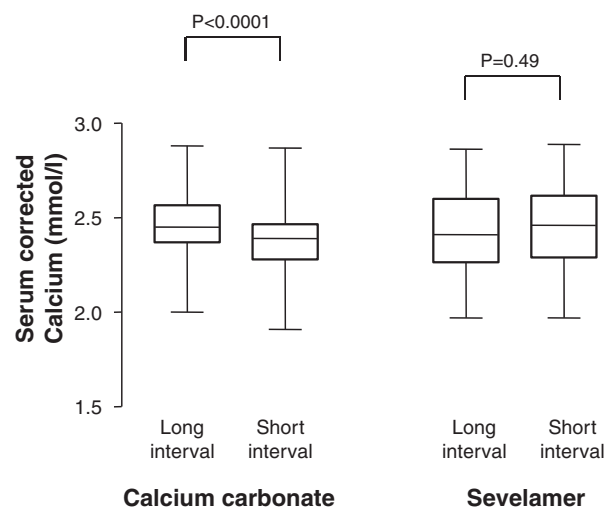
Mean serum phosphate was ~ 0.15 mmol/l higher in the same patients when assessed after the long interdialytic period, as compared with the short interdialytic period. Corrected serum calcium was also higher by ~ 0.07 mmol/l for the same comparison, and calcium and phosphorus product by ~ 0.35 mmol/l². These differences were of similar magnitude and statistical significance regardless of which of the short interdialytic periods was used for comparison (data summarized in Table 1). The higher level of serum phosphate seen after the long interdialytic interval was a consistent finding in most patients, with 88% of patients having a higher serum phosphate than in both the subsequent short interdialytic intervals (98% higher than at least one short interval). The coefficients of variation were slightly higher for both serum phosphate and serum calcium levels after the long interval as compared with the short interdialytic interval (9.8 and 8.4%, respectively, for the long and short interdialytic interval for calcium, and 28 and 25%, respectively, for the long and short interdialytic interval for phosphate). There were no differences throughout the dialysis week in either haemoglobin or albumin concentration, making it unlikely that variable fluid state and haemodilution was a significant factor. Serum bicarbonate prior to dialysis was also similar after the long interdialytic period compared with the shorter period (23.1 ± 0.5 and 24 ± 0.51 mmol/l, *P* = 0.24 respectively).

The percentage of patients with hypercalcaemia (>2.6 mmol/l) was higher when measured after the long interval than in the same group of patients measured after the short interval (23 vs 12%). Likewise, a higher percentage of patients displayed inadequate control of serum phosphorus (>1.8 mmol/l) when assessed after the long interval as compared with the short interdialytic intervals (35 vs 14%).

The difference in serum calcium between the long and short interdialytic intervals was entirely accounted for by the patients receiving calcium carbonate [mean increase 0.09 ± 0.01 mmol/l (95% CI 0.05–0.17), *P* = 0.0004]. This difference was not seen in patients treated with sevelamer (mean difference 0.01 ± 0.01 mmol/l (95% CI 0.04–0.03) *P* = 0.52]. The overall levels of serum calcium and differences between patients on calcium carbonate and sevelamer are summarized in Figure 1. In patients treated with

Table 1. Summary of blood results for the patient group as a whole ($n = 100$), comparing mean values for the long and short interdialytic period (95% CIs given in parentheses)

	Long interdialytic interval	Short interdialytic interval	P-value
Corrected serum calcium (mmol/l)	2.46 ± 0.03 (2.4–2.5)	2.4 ± 0.02 (2.35–2.46); 2.39 ± 0.02 (2.36–2.44)	0.001; 0.0005
Serum phosphate (mmol/l)	1.59 ± 0.05 (1.5–1.7)	1.45 ± 0.04 (1.37–1.55); 1.43 ± 0.03 (1.35–1.5)	0.0005; 0.0005
Calcium × phosphate product (mmol/l ²)	3.88 ± 0.15 (3.57–4.19)	3.54 ± 0.14 (3.26–3.80); 3.53 ± 0.14 (3.25–3.77)	0.0004; 0.0004
Serum albumin (g/l)	34.7 ± 0.51 (33.7–35.7)	34.65 ± 0.60 (33.4–35.8); 34.9 ± 0.50 (33.5–34.9)	0.75; 0.63
Haemoglobin (mg/dl)	11.63 ± 0.22 (11.2–12.1)	11.77 ± 0.26 (11.2–12.3); 11.59 ± 0.32 (11.1–12.4)	0.24; 0.37

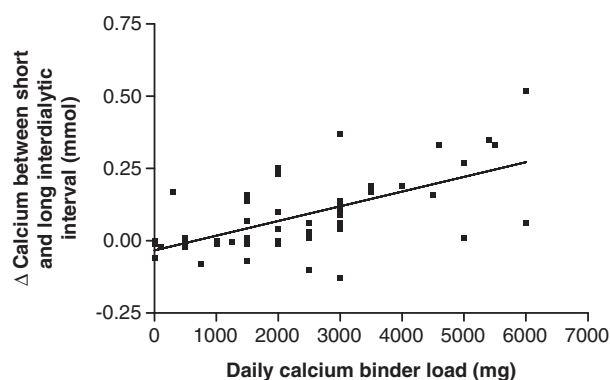
**Fig. 1.** Box and whisker plots demonstrating higher levels of serum corrected calcium after the long interdialytic interval compared with the short intervals in patients treated with calcium carbonate ($n = 76$, $P < 0.0001$), but no difference in patients treated with sevelamer ($n = 24$, $P = 0.49$).

calcium carbonate, the magnitude of the increase in serum corrected calcium seen after the long interdialytic interval was directly proportional to the prescribed daily dose of calcium ($r = 0.63$, $P < 0.0001$) (see Figure 2). There were no significant differences between serum phosphate levels in patients treated with calcium carbonate or sevelamer (1.56 ± 0.04 and 1.61 ± 0.05 mmol/l, respectively, $P = 0.36$). Furthermore, differences in serum calcium concentration were not attributable to serum phosphate levels. There was no relationship between these variables ($r^2 = 0.02$, $P = 0.23$) during the long interdialytic interval.

Discussion

This study demonstrates for the first time that the length of the interdialytic interval influences serum mineral concentration. Furthermore, the higher levels in serum corrected calcium seen after the long interdialytic period are seen only in patients treated with calcium carbonate; the magnitude of this difference is proportional to the dose of calcium.

The consistently higher level of serum phosphorus seen after the longer interval has not been reported

**Fig. 2.** Linear relationship between the difference in serum calcium between the long and short interdialytic interval and the daily prescribed intake of phosphate binder in patients treated with calcium carbonate ($r = 0.63$, $P < 0.0001$, $n = 74$).

previously. Marked variation in serum phosphorus levels has been reported in one small study, but not related to the dialysis week [7]. The differences in consumption suggest that appetite is not a relative problem in this period, and measures to encourage the redistribution of oral phosphate binder load in response to intake are only partially effective at best. The longer interval between additional phosphate removal on dialysis might be expected to be associated with the observed differences in serum phosphate level. It is important to note, however, that formal assessment of phosphate balance was not a feature of this study, and cannot be implied from the changes in serum phosphate concentration.

The relatively higher levels in serum corrected calcium seen during the same period have also not been reported before. This does not appear to be due to the higher level of hydration after the longer period, as one would expect that values would therefore be lower for that segment of the week. In addition, there were no observed changes in either haemoglobin or albumin concentration when comparing long and short intervals (both sensitive to haemodilution). The degree of variability in serum levels of both calcium and phosphate was increased slightly in the long interdialytic interval, with the variation unsurprisingly being much greater for serum calcium compared with phosphate (due to tighter homeostatic control). The similarity in pre-dialysis serum bicarbonate concentration for the long and short interdialytic interval

makes a significant influence of variable clearance on the observed differences less likely.

The higher proportions of patients identified as having suboptimal control of calcium and phosphorus, if assessed after the long interval, suggests that consistency when samples are taken is important for data recording, measurement of performance by registry statistics and modulation of therapy concerned with mineral balance.

The use of calcium carbonate as a phosphate binder is well recognized to be associated with hypercalcaemic episodes [8]. We have demonstrated that it is also responsible for periodically higher serum corrected calcium levels after the long interdialytic interval, and that the degree in elevation is directly proportional to the amount of calcium-containing phosphate binder prescribed. The correlation may have been improved if we were able to record accurately the amount actually taken, rather than that merely prescribed. Sevelamer is an effective phosphate binder, known to be associated with lower serum corrected calcium and fewer hypercalcaemic events [8]. We have demonstrated that use of this agent also avoids this variation in serum corrected calcium during the HD treatment week. An increased appreciation that serum calcium values of >2.38 mmol/l, but still within normocalcaemia, are associated with an increased relative risk of death may make this observation increasingly important [2]. Patients treated with sevelamer, however, did not have lower pre-dialysis serum calcium levels than those treated with calcium carbonate. This is unsurprising as the patients on sevelamer were largely selected by previous clinical response to calcium-based phosphate binders and vitamin D as being more likely to be hypercalcaemic. Even given that propensity, treatment with sevelamer still resulted in reduction in the cyclical increase in serum calcium concentration seen in patients treated with calcium carbonate.

The cyclical increase in calcium and phosphorus (and product) that patients treated with HD (and in particular with calcium carbonate) are subject to may also be important in the pathophysiology of accelerated vascular calcification characteristically seen in this group of patients [9]. Elevated levels of calcium and phosphate are known to have a synergistic effect on both vascular calcification and survival. Recent data concerning the dual effect of elevated extracellular calcium and phosphorus levels on vascular smooth muscle cell osteoblast-like phenotypic transformation and subsequent mineralization (via effects via PIT-1, transmembrane sodium/phosphate transporter) suggest a potential pathophysiological mechanism for this [4,5]. Patients undergoing peritoneal dialysis (PD) are not exposed to this phenomenon, and indeed we have recently presented data in abstract form comparing HD and PD patients [10], showing reduced

levels of peripheral vascular calcification in PD patients despite similar exposure to calcium, hyperparathyroidism, vascular co-morbidity and time on dialysis. Quotidian HD might also offer benefits in this respect, but at present data are only available on improved phosphate control and reduced need for binders in this group of patients [11].

In conclusion, cyclical differences in interdialytic interval and overall exposure to both dietary phosphate and oral calcium load influence serum levels. This may have consequences for registry reporting, therapy modulation and potentially the pathogenesis of accelerated vascular calcification seen in HD patients.

Conflict of interest statement. None declared.

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