Original Article

A randomized trial comparing 1.25 mmol/l calcium dialysate to 1.75 mmol/l calcium dialysate in CAPD patients

D. W. Johnson[1], R. J. Rigby[1], H. D. McIntyre[2], A. Brown[1] and J. Freeman[1]

[1]Department of Nephrology, Princess Alexandra Hospital and [2]Department of Endocrinology, Mater Misericordiae Hospital, Brisbane, Australia

Abstract

Background. Effective control of hyperparathyroidism and renal osteodystrophy in CAPD patients requires a combination of calcitriol and calcium carbonate ($CaCO_3$), but is frequently limited by hypercalcaemia. Reducing dialysate calcium (Ca) concentration may overcome this problem, but had not been examined in a controlled trial.

Methods. 45 stable CAPD patients were randomly assigned in a prospective, double-blind trial to either a study group (1.25 mmol/l Ca dialysate) or a control group (1.75 mmol/l Ca dialysate) for 12 months. Clinical, biochemical and radiological parameters of secondary hyperparathyroidism were followed.

Results. Twenty-three patients did not complete the study due to death (9), transplantation (7) or conversion to haemodialysis (7). Eleven patients in each group completed the study. Mean serum Ca, phosphate, ionized Ca, aluminium, alkaline phosphatase (AP), and bone mineral density (BMD) Z-scores did not differ significantly at any time within or between the two groups. Severe hypercalcaemia was more common in the control group (11 vs. 2, $P = 0.027$). Mean serum intact parathyroid hormone (PTH) and osteocalcin (OCN) initially rose in the study group relative to controls at 3 months (40 ± 7 vs 12 ± 3 pmol/l, $P = 0.004$, and 33 ± 5 vs 15 ± 2 µg/l, $P = 0.002$ respectively), but were not sustained. Median weekly dosages of calcitriol and daily dosages of $CaCO_3$ increased significantly in the study group (0 µg to 1 µg $P = 0.014$ and 1260 mg to 2520 mg $P = 0.002$ respectively), but not in the control group. Supplementary aluminium hydroxide ($Al(OH)_3$) was required for phosphate control in both study ($n = 5$) and control patients ($n = 4$).

Conclusions. Lowering dialysate calcium concentration reduced the frequency of severe hypercalcaemia and allowed prescription of larger quantities of calcitriol and $CaCO_3$. However, in this study it offered no advantage in terms of $Al(OH)_3$ requirement, while bone mass density did and may have initially exacerbated secondary hyperparathyroidism not change.

Key words: bone mineral density; calcitriol; calcium; calcium carbonate; hyperparathyroidism; peritoneal dialysis solutions

Introduction

Calcium carbonate ($CaCO_3$) has emerged as a first-line treatment for uraemic hyperphosphataemia due to the concerns regarding aluminium toxicity with $Al(OH)_3$ [1], and to the demonstrated superiority of $CaCO_3$ over $Al(OH)_3$ in retarding progression of renal osteodystrophy [2]. Unfortunately optimal phosphate control is frequently not possible with $CaCO_3$ alone due to the occurrence of dose-limiting hypercalcaemia in 35–56% of CAPD patients [3,4]. An attractive strategy for preventing hypercalcaemia while allowing the phosphate-binding benefits of $CaCO_3$ is to reduce the calcium content of peritoneal dialysate from the standard level of 1.75 mmol/l to 1.25 mmol/l.

Small preliminary studies have suggested that the use of low-calcium dialysate (LCD), when compared with the use of standard calcium dialysate (SCD), results in fewer hypercalcaemic episodes, prescription of larger doses of $CaCO_3$ and the opportunity to avoid aluminium salts [5–9]. The effects of LCD on the skeleton, however, are uncertain. Moreover, there are also disturbing reports that LCD possibly exacerbates secondary hyperparathyroidism [8,10,11]. The rise in parathyroid hormone (PTH) levels have been attributed to the net calcium efflux into the LCD [11], and could conceivably have been prevented by the use of calcitriol, which inhibits PTH release both directly and via increased gastrointestinal absorption of calcium [12]. Unfortunately there have been no randomized controlled trials comparing LCD to SCD in patients who were treated with both $CaCO_3$ and calcitriol.

The aim of our study was to prospectively investigate the effects of LCD versus SCD over a 12-month period on (i) serum biochemistries; (ii) total and regional

Correspondence and offprint requests to: Dr Russell Rigby, Department of Nephrology, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, Queensland, Australia. 4102.

bone mineral densities; and (iii) dosages of calcitriol, $CaCO_3$, and $Al(OH)_3$.

Subjects and methods

Patients

Forty-five stable CAPD patients (19 males and 26 females) gave informed consent to participate in the study. All patients had been free of peritonitis for at least 1 month prior to study entry and had dialysed using three or four 2-litre exchanges per day of SCD (Baxter Healthcare, Australia). Demographic data are presented in Table 1.

$CaCO_3$ was prescribed as the primary phosphate binder in all patients, while eleven (LCD group five, SCD group six) also received $Al(OH)_3$. Nine patients (LCD group four, SCD group five) were already receiving calcitriol because of elevated serum PTH levels (above 20 pmol/l). All patients were advised to continue on their usual diet of 1.2 g/kg/day of protein, 1 g/day of phosphate and 0.4 g/day of calcium.

Study design

The 45 patients were randomly assigned to receive LCD or continue on SCD for a period of 12 months. Observers and treating physicians were blinded to the calcium content of their patients' peritoneal dialysates. Serum biochemistries (see Methods below) were evaluated 3-monthly and when clinically indicated. Total and regional BMDs were assessed at baseline and at 12 months.

Prescribed dosages of $CaCO_3$, $Al(OH)_3$ and calcitriol were recorded at baseline and at 12 months. Adjustments in the dosages of these medications during the course of the study were left to the clinical discretion of the attending physician. The intended goal was to maintain ionized calcium between 1.25 and 1.35 mmol/l and serum phosphate below 1.8 mmol/l.

Episodes of significant hypercalcaemia were also recorded. These were defined as sufficient serum calcium elevations to warrant reduction of $CaCO_3$ and/or calcitriol in the clinical opinion of the attending physician.

Methods

A BM/Hitachi 737 analyser (Boehringer Mannhein) was used to measure serum levels of phosphate, magnesium and

total calcium. Total calcium levels were corrected for serum albumin according to the formula:
Corrected Ca (mmol/l) = Total Ca (mmol/l) + 0.02 × [40 − serum albumin (g/l)]

Ionized calcium was determined using an ion-selective (Radiometer ICA2) electrode. Serum aluminium was measured using flameless atomic absorption spectrophotometry (Perkin-Elmer model 4100ZL with Zeeman correction). Intact PTH was measured by a two-site immunoradiometric assay (N-tact PTH IRMA, Incstar Corporation, Stillwater, Minnesota, USA, interassay coefficient of variation (CV) 3.7%, intra-assay CV 2.0%). Serum OCN was quantified by radioimmunoassay (CIS Bio International, obtained through Australian Radioisotopes, Australia, interassay CV 3.9%, intra-assay CV 2.7%).

Total body and regional BMDs were determined according to the principle of dual-energy X-ray absorptiometry (DEXA) (Lunar DPX.L bone densitometer with Software Version 1.3, Wisconsin, USA). The BMD Z-score for each patient was calculated by initially determining the difference between their BMD and the mean BMD of a corresponding age- and sex-matched normal (reference) population [13]. This difference was then divided by the standard deviation of BMDs of the reference population.

Statistical analysis

Results are expressed as mean ± standard error of the mean or as 5, 25, 50, 75, 95 centile Tukey box plots. Hypercalcaemic episodes and medication dosages are expressed as median (25th–75th percentile), since the values did not follow a normal distribution as determined by the Kolmogorov–Smirnov test. Paired and unpaired t tests were used to compare data with a normal distribution. Nonparametric analyses of paired and unpaired data were performed using the Wilcoxon signed rank test and Mann–Whitney rank sum test respectively. Differences in serial biochemical measurements were assessed by one-way analysis of variance for repeated measures (ANOVAR) and all pairwise multiple comparisons were made using the Student–Newman–Keuls method. Fisher's exact test was used to compare proportions.

Data analysis was performed using the software package, Sigmastat version 1.01 (Jandel Scientific, USA). The 0.05 level of significance was used for all analyses.

Table 1. Characteristics of the 11 patients in each group who completed the study and of the 23 patients who did not complete the study

Patient characteristics	LCD (n=11)	SCD (n=11)	Drop-outs (n=23)
Male vs Female (n)	5 vs 6	3 vs 8	11 vs 12
Age (years)[a]	59.8±3.1	60.2±2.8	58.7±2.5
Body mass index[a]	24.92±1.10	26.96±1.60	23.98±0.83
CRF duration (years)[a]	8.1±1.7	5.0±0.7	7.5±1.20
CAPD duration (years)[a]	2.3±0.7	1.6±0.4	2.4±0.38
Previous fractures (n)	2	3	2
Previous hypercalcaemia (n)	4	5	5
Previous parathyroidectomy (n)	1	3	4
Diabetes (n)	2	2	4
Previous steroids (n)	2	2	2

[a] Values are mean ± SEM. The groups did not differ with respect to the above patient characteristics.
LCD = low calcium dialysate group. SCD = standard calcium dialysate group.

Results

Patients were followed for 12 months. Twenty-three patients were excluded from the result analysis due to failure to complete the study because of death ($n=9$), transplantation ($n=7$) or conversion to haemodialysis (mostly related to refractory Tenckhoff catheter infections) ($n=7$). There were no differences between the two groups with respect to the occurrence of death, transplantation or conversion to haemodialysis. Results of serum biochemistries, BMDs and medication dosages recorded in patients prior to their exclusion did not significantly differ from non-excluded patients within their original randomisation group. Moreover, there were no statistically significant differences found between those who completed the study and those who did not with respect to the patient characteristics shown in Table 1. The eleven patients who remained in each of the two groups at the end of the 12-month study period were also well matched for these patient characteristics. Of the 45 patients who commenced the study, nine patients randomized to receive LCD experienced 12 episodes of peritonitis in 12 months, compared with eight patients in the SCD group who experienced 11 episodes ($P=$not significant).

(i) Serum biochemistry

No significant differences were found between baseline and subsequent values of mean total corrected calcium, ionized calcium or phosphate within each group or between the two groups at any time point (Figure 1). Ionized calcium was at the upper limit of normal throughout the study. Two patients in the LCD group experienced one significant hypercalcaemic episode each, whereas seven patients in the SCD group experi-
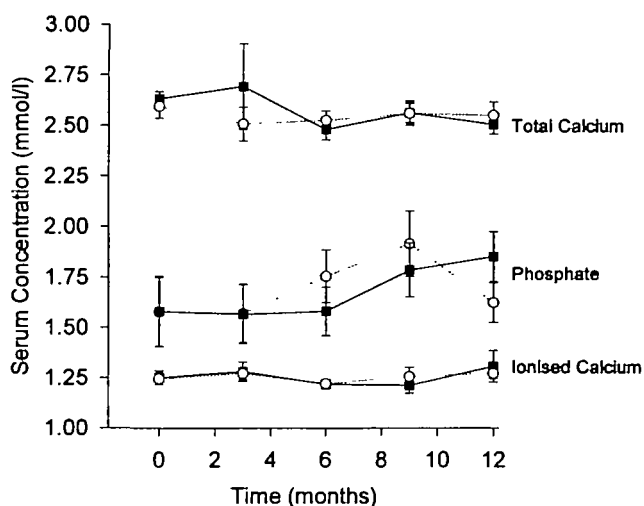
enced eleven episodes of hypercalcaemia ($P=0.027$). All hypercalcaemic episodes responded promptly to a reduction or cessation of $CaCO_3$ and/or calcitriol therapy. Mean serum aluminium levels were below 1.25 mmol/l throughout the entire study and did not differ significantly between the groups or over time.

Serum PTH tended to initially rise in the first 6 months in the LCD group from 33 ± 8 pmol/l to 41 ± 8 pmol/l, but no significant differences were noted at any time point relative to baseline using ANOVAR ($P=0.70$) (Figure 2). PTH levels were slightly lower in the SCD group than the LCD group at the start of the study (19 ± 7 pmol/l vs 33 ± 8 pmol/l, $P=0.20$), but again, no significant differences were noted at any time point relative to baseline using ANOVAR ($P=0.52$). At the 3-month and 6-month intervals, mean PTH levels were significantly higher in the LCD patients compared with SCD patients ($P=0.004$ and $P=0.016$ respectively). No significant differences were detected between the two groups in the last six months of the study.

Results for serum OCN parallelled those of serum PTH (Figure 2).

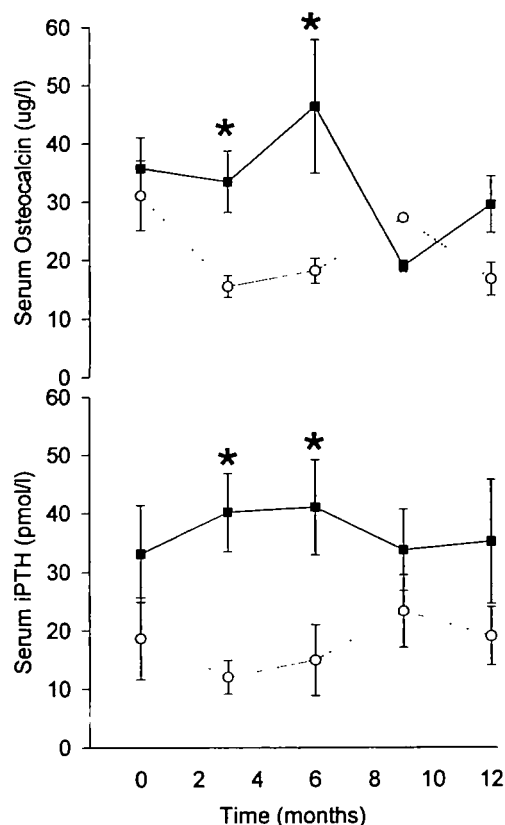No differences were noted in serum AP between or within the two groups throughout the study.

Fig. 1. Mean ($\pm$SEM) serum corrected total calcium, phosphate and ionized calcium in the low-calcium dialysate group (closed figures connected by solid lines, $n=11$) and the standard calcium dialysate group (open figures connected by dotted lines, $n=11$), over 12 months.

Fig. 2. Mean ($\pm$SEM) serum intact PTH (lower graph) and osteocalcin (upper graph) levels in the low calcium dialysate group (filled squares connected by solid lines, $n=11$) and the standard calcium dialysate group (open circles connected by dotted lines, $n=11$), over 12 months. *$P<0.05$.

(ii) Bone mineral density measurements

Z-scores for total and regional BMDs did not differ between the two groups at the end of the 12-month study and did not differ when compared with baseline values (Figure 3).

(iii) Phosphate binders and calcitriol

Medication non-compliance, defined as omission of two or more doses of a prescribed medication per week, were noted in two patients in each of the two groups (18%). Dietary non-compliance, as assessed by routine 3-monthly dietitian reviews was limited to the patients who were non-compliant with medications. Target calcium and phosphate levels were generally achieved in the remaining patients within each group.

Median dosages of $CaCO_3$ in the two groups were not significantly different at the start of the study. Although there was a progressive, but insignificant fall in median daily dosage in the SCD group from 2520 mg (1260–3340 mg) to 1260 mg (1260–2520 mg) over the 12-month period ($P = 0.275$), the median daily oral dose of $CaCO_3$ increased significantly in the LCD group from 1260 g (315–1260 g) to 2520 g (2520–3340 g) ($P = 0.002$). $CaCO_3$ dosages were significantly higher in the LCD group than the SCD group at the end of the study ($P = 0.023$).

Similarly, median weekly calcitriol dosages did not change significantly in the SCD group from 0 µg (0–0.50 µg) at baseline to 0.50 µg (0–0.88 µg) at 12 months ($P = 0.125$), but rose significantly in the LCD group from 0 µg (0–0.38 µg) to 1 µg (0.25–2.00 µg) ($P = 0.014$). Calcitriol doses tended to be higher in the LCD group than the SCD group at the 12 month mark, but did not reach statistical significance ($P = 0.231$). The number of patients receiving calcitriol at the start and end of the study increased from four to
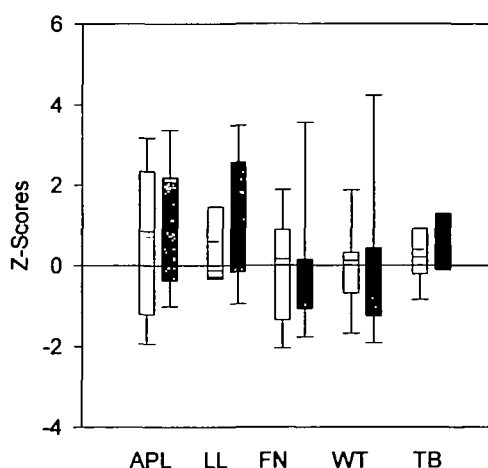

Fig. 3. 5, 25, 50, 75, 95 centile Tukey box plots of Z scores for total and regional bone mineral densities in the low calcium dialysate group (open boxes, $n = 11$) and the standard calcium dialysate group (hatched boxes, $n = 11$), after 12 months. APL, anteroposterior lumbar spine; LL, lateral lumbar spine; FN, femoral neck; WT, Ward's triangle; TB, total body.

nine in the LCD group ($P = 0.08$) and from five to seven in the SCD group ($P = 0.64$).

Four patients in the SCD group and five patients in the LCD group required $Al(OH)_3$ in addition to $CaCO_3$ for phosphate control. Eight of these patients received 1800 mg per day, while one patient in the SCD group required 5400 mg per day to achieve optimal phosphate control. Dosages did not differ over time between the two groups or within each group. Patient numbers, however, were too small to avoid type II (beta) statistical error.

Discussion

In this study, LCD, compared with SCD, resulted in considerably fewer hypercalcaemic episodes, larger attained dosages of $CaCO_3$ and calcitriol, and initially higher levels of PTH and OCN during the first 6 months. No significant differences were noted with respect to serum phosphate control, serum aluminium levels, $Al(OH)_3$ dosages or total and regional BMDs.

Small final numbers, due to the well-known high drop-out rate of CAPD, limited the statistical power of analyses, (particularly of subgroups), although important and significant differences were still found between the LCD and SCD groups as a whole. Potential sampling bias due to the exclusion of drop-outs does not seem likely, given that the frequencies of different exclusion events did not differ between LCD and SCD groups and that inclusion of the results obtained from the excluded patients prior to their cessation of CAPD did not alter result outcomes. Furthermore, patients in the LCD, SCD and exclusion groups did not differ significantly with respect to the baseline characteristics shown in Table 1, although there were slightly higher starting PTH levels in the LCD group and slightly more previously parathyroidectomized patients in the SCD group.

The major advantage of LCD demonstrated by this study was a reduction in episodes of clinically significant hypercalcaemia. This result supports the findings of previous studies [10,15].

The use of LCD further permitted the administration of larger doses of both $CaCO_3$ and calcitriol without significant changes in serum or ionized calcium. Previous studies have demonstrated identical findings for either $CaCO_3$ alone [7,8,14] or calcitriol alone [9,12,16], but no prior study has prospectively compared LCD with SCD in patients taking *both* agents. The results of this study are therefore particularly pertinent to routine clinical practice, where patients are more likely to receive a combination of these medications rather than one or the other.

The combination of $CaCO_3$ and calcitriol for the first time in our trial may also explain important differences found between our results and those of previous studies. Unlike most other studies, which have found a decreased reliance on $Al(OH)_3$ with LCD [7,8,14,15], we observed no change in the ingestion of $Al(OH)_3$. This may have been because of the

small numbers of patients in each group. Alternatively, the additional inclusion of calcitriol could have preserved the need for Al(OH)$_3$ with LCD, by increasing calcium absorption (thereby limiting the maximum dose of CaCO$_3$ that could be used), and by increasing oral phosphate absorption (thereby increasing the total dose of phosphate binders required for satisfactory phosphate control). The latter postulate was supported by the finding that phosphate control was equivalent in both groups, despite the use of larger total doses of phosphate binders in the LCD group.

Control of hyperparathyroidism on LCD in our study also differed somewhat from that reported in other trials. Hutchinson *et al.* [17] found that PTH levels fell significantly during the first 6 months in their LCD group relative to their SCD group, although this was probably explained by a significant and marked early fall in serum phosphate levels in the former. Martis *et al.* [7] on the other hand found no significant change in PTH levels following switching 13 patients from SCD to LCD. Most studies, however, have mirrored our findings of an early rise in PTH after conversion to LCD, despite stable serum levels of ionized calcium, phosphate and aluminium [5,8,11,15]. Kawanashi *et al.* [11] argued that the PTH rise was due to a small initial fall in free calcium after conversion to LCD. This excited PTH secretion, which in turn stimulated bone mobilization of calcium and returned the serum free calcium towards baseline. The difference in our study was that the PTH rise was unsustained and returned towards baseline after the first 6 months. This was temporally associated with an overall increase in calcitriol dosage. Since calcitriol is more potent than CaCO$_3$ in suppressing PTH at equivalent serum calcium concentrations [20] and since the incorporation of calcitriol into the study design was unique to our trial, it is tempting to speculate that this agent was responsible for counteracting the PTH rise seen with LCD.

Serum OCN, a specific marker of neo-osteogenesis, tended to parallel the changes seen in PTH in patients on LCD. Although no significant changes were seen in Z-scores for total and regional BMDs after 12 months, the results of our study suggest that lowering dialysis fluid calcium does not have beneficial skeletal consequences and may even be potentially deleterious. There have been no other studies of LCD involving bone densitometry or OCN measurements. Only one prior study looked at the effect of LCD on bone histomorphometry and found no significant change after 12 months [17]. Clearly, longer term studies are required to determine the precise metabolic impact of lowered dialysate calcium on the skeleton.

In conclusion, in this study of 22 patients over a 12-month period, the usage of 1.25 mmol/l calcium dialysate (LCD), in conjunction with CaCO$_3$ and calcitriol, offered no advantage over 1.75 mmol/l calcium dialysate (SCD) in terms of phosphate control or requirements for aluminium compounds. The main advantage of lowering dialysis fluid calcium was avoidance of clinically significant episodes of hypercalcaemia

due to CaCO$_3$ and/or calcitriol administration. The main potential disadvantage was exacerbation of secondary hyperparathyroidism, which was curbed by maximal use of CaCO$_3$ and by close supervision of serum PTH with appropriate addition or increase of calcitriol dosage in response to PTH increases. It would appear then that the risk : benefit ratio clearly favours SCD for non-compliant patients and LCD for patients in whom hypercalcaemia is problematic. Until more is known about the long-term skeletal sequelae of LCD, the remaining bulk of CAPD patients should probably be treated initially with SCD and then changed over to LCD if hypercalcaemia occurs with suboptimal doses of calcitriol and/or CaCO$_3$.

References

1. Wills MR, Savory J. Aluminium poisoning: dialysis encephalopathy, osteomalacia and anaemia. *Lancet* 1983; 2: 29–34
2. Jespersen B, Jensen J, Nielsen H *et al.* Comparison of calcium carbonate and aluminium hydroxide as phosphate binders on biochemical bone markers, PTH(1-84), and bone mineral content in dialysis patients. *Nephrol Dial Transplant* 1991; 6: 98–104
3. Slingeneyer A, Laroche B, Loupi E *et al.* Calcium concentration in PD dialysate must be lowered. Exclusive use of calcium carbonate as a phosphate binder. *Perit Dial Int* 1992; 12 [Suppl 2]: S161
4. Cunningham J, Sawyer N, Altmann P *et al.* Mineral metabolism in CAPD patients treated with calcium carbonate and step-wise reduction of dialysate calcium. *Kidney Int* 1992; 141: 455
5. Honkanen E, Gronhagen-Riska C, Kala AR. CAPD with low calcium (2.5 mEq/l) dialysate (LCD) and calcium carbonate. *Perit Dial Int* 1992; 12[Suppl 1]: 127
6. Kafka J, Spry LA. Retrospective comparison of patients converted to low calcium solution. *Perit Dial Int, XII Annual* 1992; 12[Suppl 1]: 143
7. Martis L, Zimmerman SW, Delmez JA *et al.* Dianeal 2.5 mEq/l calcium and calcium carbonate in CAPD. *Perit Dial Int, XII Annual* 1992; 12[Suppl 1]: 139
8. Piraino B, Perlmutter JA, Holley JL, Johnston JR, Bernadini J. The use of dialysate containing 2.5 mEq/l calcium in peritoneal dialysis patients. *Perit Dial Int* 1992; 12: 75–76
9. Kawanashi H, Tsuchiya T, Namba S *et al.* Clinical application of low calcium peritoneal dialysate. *ASAIO Trans* 1991; 37: M404–M406
10. Rotellar C, Kinsel V, Goggins M *et al.* Does low-calcium dialysate accelerate secondary hyperparathyroidism in continuous ambulatory peritoneal dialysis patients? *Perit Dial Int* 1993; 13[Suppl 2]: S471–S472
11. Kawanashi H, Takahashi N, Namba S *et al.* Clinical effects of low calcium CAPD dialysate (Ca 2.3 mEq/l) and its problems. *Perit Dial Int* 1992; 12[Suppl 1]: 131
12. Banalagay E, Bernadini J, Holley J, Chen T, Piraino B. A randomised trial comparing 2.5 mEq/l calcium dialysate and calcitriol to 3.5 mEq/l calcium dialysate in patients on peritoneal dialysis. *Adv Perit Dial* 1993; 9: 280–283
13. Lunar Corporation. Appendix C: Comparison to reference population. In: *Lunar DPX-L Technical Manual*. Madison, Wisconsin: 1991; C.1–C.9
14. Hutchinson AJ, Gokal R. Towards tailored dialysis fluids in CAPD—The role of reduced calcium and magnesium in dialysis fluids. *Perit Dial Int* 1992; 12: 199–203
15. Carozzi S, Nasini MG, Santoni O, Pietrucci A. Low- and high-turnover bone disease in continuous ambulatory peritoneal dialysis: effects of low-Ca^{++} peritoneal dialysis solution. *Perit Dial Int* 1993; 13[Suppl 2]: S473–S475
16. Hamdy NAT, Boletis J, Charlesworth D *et al.* Low calcium

dialysate increases the tolerance to vitamin D in peritoneal dialysis. *Contrib Nephrol* 1991; 89: 190–198

17. Hutchinson AJ, Freemont AJ, Boulton HF, Gokal R. Low-calcium dialysis fluid and oral calcium carbonate in CAPD. A method of controlling hyperphosphataemia whilst minimising

aluminium exposure and hypercalcaemia. *Nephrol Dial Transplant* 1992; 7: 1219–1225

18. Delmez JA. Calcitriol and secondary hyperparathyroidism in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 1993; 13: 95–97