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Influence of dialysate Ca concentrations on the therapeutic effects of etelcalcetide with concomitant drugs in patients with secondary hyperparathyroidism

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Abstract

Aim: Secondary hyperparathyroidism (SHPT), a complication of haemodialysis, is commonly treated with calcimimetics. The impact of dialysates containing different calcium (Ca) concentrations on clinical efficacy of calcimimetics are unclear. We examined whether dialysate Ca concentrations influence the efficacy and dosing of etelcalcetide with concomitant drugs.

Methods: We performed post hoc analyses of a 52-week, open-label, multicentre study of etelcalcetide in Japanese SHPT patients to determine whether dialysate Ca influences the therapeutic effects of etelcalcetide with concomitant drugs. We evaluated the differences in serum intact parathyroid hormone (iPTH), corrected Ca (cCa) and phosphate levels among three dialysate Ca concentration groups (2.5, 2.75 or 3.0 mEq/L Ca). Tartrate-resistant acid phosphatase 5b (TRACP-5b) and bone alkaline phosphatase (BAP) levels were also compared. Since the dialysate Ca concentration may influence dose adjustment, we assessed the etelcalcetide and concomitant drug doses.

Results: There were no clinically meaningful differences in iPTH, cCa and phosphate levels among the 2.5, 2.75 and 3.0 mEq/L groups (n = 34, 64 and 35, respectively) over 52 weeks. At Week 52, more than 82%, 71% and 67% of patients had iPTH, cCa and phosphate levels within target ranges (60-240 pg/mL, 8.4-10.0 mg/dL and 3.5-6.0 mg/dL, respectively) across the three groups. TRACP-5b and BAP levels decreased by Week 52 regardless of dialysate Ca. Changes in etelcalcetide and concomitant drug doses were generally similar in each group.

Conclusion: The efficacy and dosing of etelcalcetide with concomitant drugs were essentially unaffected by the dialysate Ca concentration. Patients showed improvements in bone hypermetabolism during treatment.

SUMMARY AT A GLANCE

This is a small observational study of the effect of dialysate calcium concentrations on etelcalcetide with concomitant drugs in secondary hyperparathyroidism. No statistically significant differences were found between the different dialysate calcium groups suggesting that calcium concentrations in the dialysate do not modulate the effect of etelcalcetide.

KEYWORDS

bone metabolism, calcimimetics, calcium dialysate, etelcalcetide, secondary hyperparathyroidism

Secondary hyperparathyroidism (SHPT) is a potentially serious complication of haemodialysis in patients with chronic kidney disease (CKD). SHPT is generally characterised by progressive parathyroid hyperplasia and excessive release of parathyroid hormone (PTH).[1,2] Elevated PTH increases bone resorption and disrupts calcium (Ca)-phosphate (P) homeostasis, leading to other complications like vascular calcification, and increased risk of death.[3,4] Therefore, it is important to maintain serum PTH levels within an appropriate range in patients with SHPT.

Ca homeostasis and PTH secretion are regulated via extracellular Ca acting on calcium-sensing receptors expressed on parathyroid cells, representing a key therapeutic target for controlling PTH secretion. Several calcimimetics have been developed to lower PTH levels and are recommended for the treatment of SHPT in the kidney disease improving global outcomes (KDIGO)[5] and Japan Society for Dialysis Therapy[6] guidelines. The first calcimimetic to be approved for the treatment of SHPT was cinacalcet, which lowered serum PTH levels and improved Ca-P homeostasis in clinical trials.[7,8] In 2016 and 2017, etelcalcetide, a second-generation calcimimetic, was approved. Etelcalcetide is an intravenous peptide calcimimetic that can be administered at the end of each haemodialysis session with good adherence.[9,10] However, calcimimetics may increase the risk of hypocalcaemia, so increasing the dose of vitamin D and/or calcium carbonate, decreasing the dose of calcimimetics, and changing the dialysate Ca concentration may be necessary.

Ca is an essential component of the dialysis solution, and dialysate Ca concentrations range from 2.5 to 3.0 mEq/L. It has been reported that the dialysate Ca concentration may influence PTH levels.[11] Moreover, the dialysate Ca concentration may have potential short- and long-term consequences, in that lower concentrations may increase the risk of hypocalcaemia and higher concentrations may contribute to vascular pathology.[12,13] Therefore, it is important to investigate whether the dialysate Ca concentration influences the clinical efficacy of calcimimetics, which may cause excessive reductions in serum Ca when using a dialysate with a low Ca concentration, and hence increase the severity of SHPT with compensatory increases in the doses of concomitant drugs used to control Ca in SHPT patients.

We performed post hoc analyses of a 52-week multicentre study in Japanese patients with SHPT[14] in order to investigate whether the dialysate Ca concentration influences the therapeutic efficacy of comprehensive treatment comprising etelcalcetide with concomitant drugs. A single-patient dialysate delivery system (SPDDS) is widely used in countries other than Japan and is considered the global standard for dialysis treatment. This makes it possible to change dialysate types and use different Ca concentrations for individual patients. By contrast, almost all facilities in Japan use a central dialysate delivery system and the type of dialysate is seldom changed in individual patients. Therefore, patients generally receive the same dialysate for the life of treatment. Accordingly, this allowed us to compare the therapeutic efficacy and dosing of etelcalcetide with concomitant drugs among three groups of patients according to the dialysate Ca concentration used. Finally, we assessed whether the dialysate Ca concentration had an impact on the safety of etelcalcetide in terms of the frequency of patients with low serum Ca concentrations.

1 | METHODS

The design of this 52-week, multicentre, open-label study is described in more detail in previous reports.[14,15] Here, we report post hoc analyses, which were performed to investigate whether the dialysate Ca concentration influences the therapeutic efficacy of etelcalcetide.

1.1 | Ethics

The study was performed in accordance with the Declaration of Helsinki and International Council on Harmonization-Good Clinical Practice guidelines, and was approved by institutional review boards at all participating centres.[14] The study was registered on the Japan Pharmaceutical Information Center database (JapicCTI-142665).

1.2 | Patients

As previously described,[14] Japanese CKD patients with SHPT aged ≥20 years on three-times-weekly haemodialysis for ≥90 days if their serum iPTH was >240 pg/mL were eligible for this study. Although patients receiving acetate-free citrate dialysate (Carbostar; Ajinomoto Pharmaceuticals Co., Ltd., Tokyo, Japan) were enrolled in the study, these patients were excluded from the present analysis because of the Ca chelating effects of citric acid contained in this dialysate.

1.3 | Dosing of etelcalcetide and concomitant drugs

Patients treated with cinacalcet entered a washout period of ≥28 days prior to starting treatment with etelcalcetide. Patients were treated with etelcalcetide three-times-weekly for 52 weeks at an initial dose was 5 mg, which was adjusted within the range of 2.5-15 mg to achieve serum iPTH of 60-240 pg/mL. This PTH target range was set according to the Japanese Society for Dialysis Therapy guidelines for CKD-mineral and bone disease,[6] which is lower than that suggested in the KDIGO guidelines (2-9 × the upper limit of normal).[5] The etelcalcetide dose was increased if the patient met all of the dose escalation criteria and the investigator believed there was no problem with safety or tolerability (Table S1). Administration of etelcalcetide was discontinued in patients with serum cCa <7.5 mg/dL, serum cCa >11.5 mg/dL or serum P P>7.0 mg/dL, at two consecutive timepoints with an interval of ≥1 week between measurements (discontinuation criteria). Administration of etelcalcetide was interrupted in patients with serum cCa <7.5 mg/dL before dialysis (interruption criterion). Active vitamin D preparations, Ca preparations and Ca-containing or Ca-free P-binders were permitted, and their doses could be adjusted as appropriate (Table S1). All patients received dialysates with Ca concentrations of 2.5, 2.75 or 3.0 mEq/L for the entire study period. The type of dialysate could be switched during the study providing the Ca concentration was unchanged.

1.4 | Assays and endpoints

Endpoints assessed in this analysis included clinical efficacy markers (iPTH, corrected Ca [cCa] and P), bone biomarkers (tartrate-resistant acid phosphatase 5b [TRACP-5b] and bone alkaline phosphatase [BAP]) and the doses of therapeutic agents (etelcalcetide, vitamin D preparations and P binders).

The clinical efficacy markers and bone biomarkers were analysed by SRL (Tokyo, Japan) using established assays. Serum iPTH was measured using an electrochemiluminescence immunoassay (Elecsys; Roche Diagnostics, Tokyo, Japan) (normal range 10-65 pg/mL). TRACP-5b was measured using an enzyme immunoassay (Osteolinks TRAP-5b; Nittobo Medical, Fukushima, Japan) (normal range, male 170-590 mU/dL, female [young adult mean] 120-420 mU/ dL). BAP was measured by chemiluminescence enzyme immunoassay (Access Ostase; Beckman Coulter, Tokyo, Japan) (normal range, male 3.7-20.9 lg/L, female before menopause 2.9-14.5 lg/L, female after menopause 3.8-22.6 lg/L). Ca and P were measured using standard laboratory tests.

As an index of safety, we determined whether the dialysate Ca concentration had an impact on the proportion of patients with low cCa concentrations (<8.4 or <7.5 mg/mL) at any time during treatment.

1.5 | Statistical analyses

The patients were divided into three groups according to the dialysate Ca concentration (2.5, 2.75 or 3.0 mEq/L). All statistical analyses were performed using global tests for comparisons among the three dialysate Ca concentration groups. Baseline characteristics were compared among the three groups by analysis of variance (ANOVA) or Fisher's exact test. Mixed-model repeated measures (MMRM) analysis was performed to compare the changes in clinical efficacy markers (iPTH, cCa and P), bone biomarkers (TRACP-5b and BAP) and doses of etelcalcetide, vitamin D preparations and P-binders among the three groups. For each analysis, the following explanatory variables were included in the model: baseline value as a covariate, treatment group and time as fixed effects, and an interaction term between treatment group and time. The residual maximum likelihood estimation method was used with an unstructured covariance structure or the Toeplitz method if the model does not converge. The Kenward-Roger method was used to calculate the degrees of freedom. P values for the fixed effect of treatment group were determined by the MMRM analyses. In all analyses, a value of $P < .05$ was considered statistically significant. Data analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

2 | RESULTS

2.1 | Patients

Of 191 patients enrolled in the study, 133 were included in the present analyses. Overall, 34, 64 and 35 patients received dialysates with Ca concentrations of 2.5, 2.75 and 3.0 mEq/L, respectively, throughout the study period. The other 58 patients were excluded from this analysis because they received acetate-free citrate dialysate at least once. One patient dropped out without receiving etelcalcetide; this patient was in the 2.75 mEq/L group and all results are presented for 63 patients, except for the patient demographics, which includes all 64 patients. Baseline characteristics of the three groups are presented in Table 1. There were no significant differences in baseline characteristics, except for the maximum dose of cinacalcet used prior to enrollment and a slight albeit non-significant imbalance in proportions of males and females among the three groups. The baseline characteristics of patients who received acetate-free citrate dialysate are shown in Table S2; their characteristics were similar to those of the three analysed groups.

TABLE 1 Patient characteristics

	Dialysate Ca concentration			
	2.5 mEq/L (n = 34)	2.75 mEq/L (n = 64)	3.0 mEq/L[a] (n = 35)	*P*-value
Sex				
Male	27 (79.4)	38 (59.4)	26 (74.3)	0.0979[b]
Female	7 (20.6)	26 (40.6)	9 (25.7)	
Age (years)	56.8 ± 9.5	58.9 ± 12.3	58.6 ± 9.3	0.6409[c]
Weight (kg)	61.6 ± 10.0	59.8 ± 15.8	65.2 ± 13.5	0.1865[c]
Duration of dialysis				
All patients	11.6 ± 7.4	11.3 ± 7.5	10.0 ± 6.5	0.5869[c]
<5 years	8 (23.5)	14 (21.9)	11 (31.4)	0.8589[b]
5 to <10 years	8 (23.5)	13 (20.3)	5 (14.3)	
10 to <20 years	13 (38.2)	30 (46.9)	16 (45.7)	
≥20 years	5 (14.7)	7 (10.9)	3 (8.6)	
Previous use of cinacalcet	23 (67.6)	40 (62.5)	21 (60.0)	0.7992[b]
Maximum dose used (mg/day)	56.5 ± 24.1	40.0 ± 21.8	48.1 ± 28.2	0.0349[c]
Concomitant therapies				
Active vitamin D preparations	32 (94.1)	54 (84.4)	29 (82.9)	0.3294[b]
Ca preparations	0 (0.0)	2 (3.1)	1 (2.9)	0.8013[b]
Ca-free or Ca-containing P binders	34 (100.0)	58 (90.6)	34 (97.1)	0.1597[b]
Serum iPTH (pg/mL)[d]	525.4 ± 289.3	499.8 ± 302.2	403.7 ± 157.8	0.1293[c]
Serum cCa (mg/dL)[d]	9.4 ± 0.6	9.5 ± 0.7	9.4 ± 0.6	0.3399[c]
Serum P (mg/dL)[d]	5.9 ± 1.2	5.9 ± 1.6	5.7 ± 1.0	0.6887[c]
cCa × P (mg²/dL²)[d]	55.3 ± 12.3	56.3 ± 15.0	53.2 ± 10.2	0.5364[c]
TRACP-5b (mU/dL)[d]	846.1 ± 413.8	876.8 ± 454.2	738.1 ± 342.2	0.2836[c]
BAP (lg/L)[d]	20.4 ± 13.2	20.0 ± 12.7	17.8 ± 10.2	0.6140[c]
1,25(OH)2D (pg/mL)[d]	9.9 ± 6.0	10.1 ± 5.4	11.7 ± 8.1	0.4208[c]

Note: Results are expressed as number (%) of patients or mean ± SD.

Abbreviations: 1,25(OH)2D, 1,25-dihydroxycholecalciferol; BAP, bone alkaline phosphatase; Ca, calcium; cCa, corrected calcium; iPTH, intact parathyroid hormone; P, phosphate; TRACP-5b, tartrate-resistant acid phosphatase 5b.

[a]Excludes acetate-free citrate dialysate.

[b]Fisher's exact test.

[c]Analysis of variance.

[d]Data obtained for baseline measurements from 190 patients (full analysis set [FAS]).

2.2 | Efficacy markers

Figure 1 shows the changes in iPTH, cCa and P levels in each group over the 52-week study period. Although the serum iPTH levels tended to track lower in the 3.0 mEq/L group than in the other two groups (Figure 1A) due to lower baseline levels, there were no significant differences among the three groups during the study. The percentage of patients with serum iPTH levels within the target level (60-240 pg/mL) increased progressively during the study; at Week 52, the target was met by 82.1%, 82.8% and 93.5% of patients in the 2.5, 2.75 and 3.0 mEq/L groups, respectively (Figure 1A, D).

The cCa and P levels (Figure 1B, C) decreased in all three groups over time and were not significantly different among the three groups at any time-point. The mean cCa and P levels were consistently below the baseline levels throughout the 52-week treatment period, and were within their respective control targets of 8.4-10.0 mg/dL (for cCa) and 3.5-6.0 mg/dL (for P). The percentages of subjects with cCa and P levels within the target at Week 52 were 71.4%, 75.9% and 93.5% for cCa, and 78.6%, 67.2% and 67.7% for P, in the 2.5, 2.75 and 3.0 mEq/L groups, respectively (Figure 1E, F).

The frequency of hypocalcaemia, defined as either <8.4 or <7.4 mg/mL, was comparable in each group and was not increased in patients in the lowest dialysate Ca concentration group (Table 2).

2.3 | Bone biomarkers

Figure 2 shows the levels of TRACP-5b as a biomarker of bone resorption and BAP as a biomarker of bone formation at each time-point. As indicated in Figure 2A, TRACP-5b levels decreased rapidly in each group. BAP levels showed a transient increase followed by a
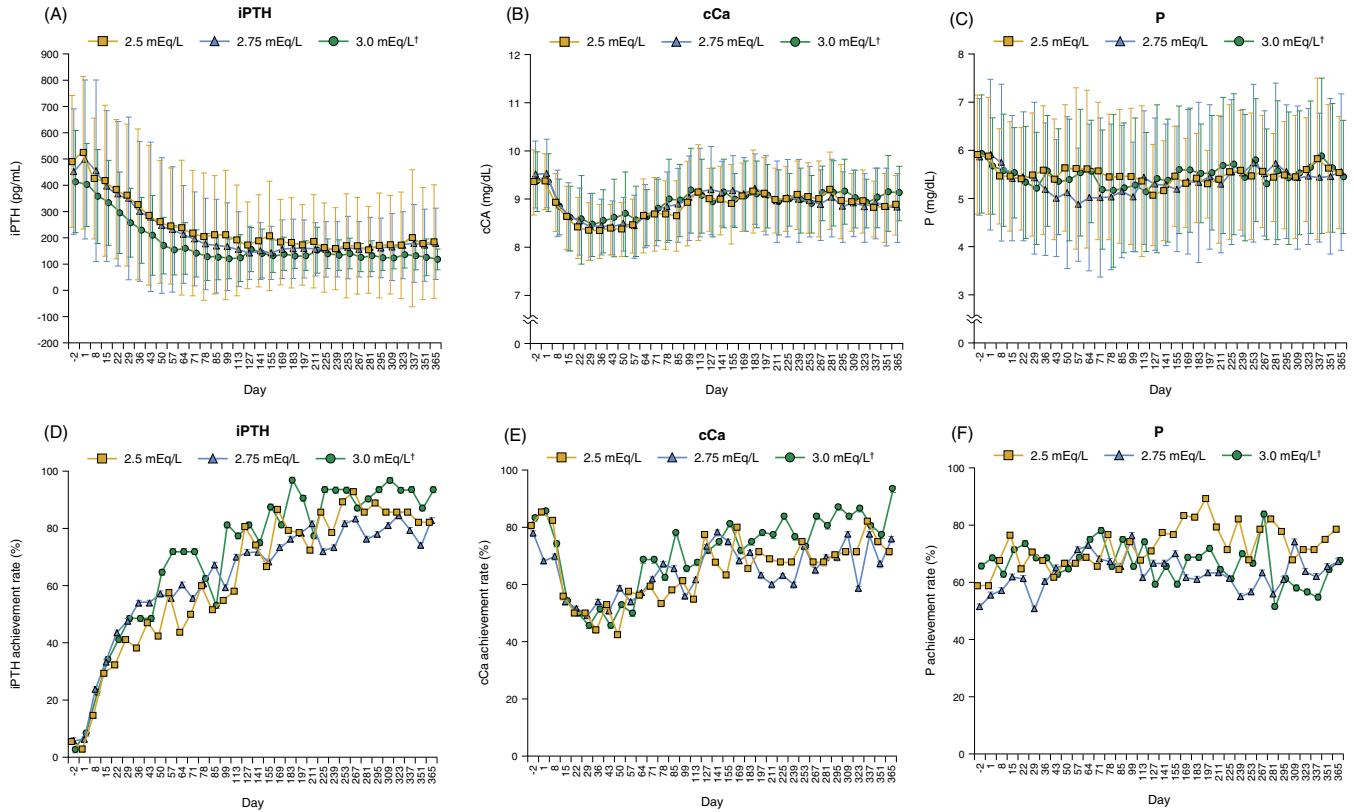
FIGURE 1 A-C, Changes in intact parathyroid hormone (iPTH; A), corrected calcium (cCa; B) and phosphate levels (P; C) according to the dialysate calcium concentration. Values are shown as the mean ± SD. D-F, Percentages of patients with iPTH (D), cCa (E) and P (F) levels within the control targets of 60-240 pg/mL, 8.4-10.0 mg/dL and 3.5-6.0 mg/dL, respectively. †Excludes acetate-free citrate dialysate

TABLE 2 Percentages of patients with serum Ca concentration <8.4 or <7.4 mg/mL

Serum Ca concentration	Dialysate Ca concentration		
	2.5 mEq/L (n = 34)	2.75 mEq/L (n = 64)	3.0 mEq/L[a] (n = 35)
<8.4 mg/mL	29 (85.3)	53 (84.1)	30 (85.7)
<7.4 mg/mL	6 (17.6)	19 (30.2)	7 (20.0)

Note: Results are expressed as number (%) of patients.
Abbreviation: Ca, calcium; cCa, corrected calcium.
[a]Excludes acetate-free citrate dialysate.

rapid decrease in each group (Figure 2B). Overall, these findings are indicative of an improvement in abnormal bone hypermetabolism. Although TRACP-5b and BAP levels tended to track lower in the 3.0 mEq/L group than in the other two groups due to lower baseline levels, there were no significant differences among the three groups at any time during the study.

2.4 | Changes in therapeutic regimens

2.4.1 | Etelcalcetide dosing

We also determined the changes in etelcalcetide doses over time (Figure 3A-C) and the distribution of etelcalcetide doses (Figure 3D-F)

according to the dialysate Ca concentration. Although the etelcalcetide dose tended to be lower in the 3.0 mEq/L group than in the other two groups, there were no statistically significant differences in etelcalcetide doses among the three groups (Figure 3A-C). There were no clear patterns in the distribution of etelcalcetide doses among the three groups (Figure 3D-F), although dosing varied throughout the study in consideration of target iPTH levels and the dose discontinuation and interruption criteria.

2.4.2 | Doses of concomitant drugs

Figure 4 shows the changes in doses of vitamin D preparations (maxacalcitol and calcitriol [injectable only]) and Figure 5 shows the changes in doses of P binders (calcium carbonate, lanthanum carbonate and sevelamer hydrochloride). The maxacalcitol and calcitriol doses tended to increase from baseline over the first approximately 85 days and then declined thereafter in each of the groups. The dose of maxacalcitol tended to be higher in the 2.5 mEq/L group than in the other groups, although this was not statistically significant (Figure 4A-C). Likewise, there were transient increases in the calcitriol doses in each group. However, the number of patients treated with calcitriol was small and there were no clear differences in calcitriol doses among the three groups (Figure 4D-F).
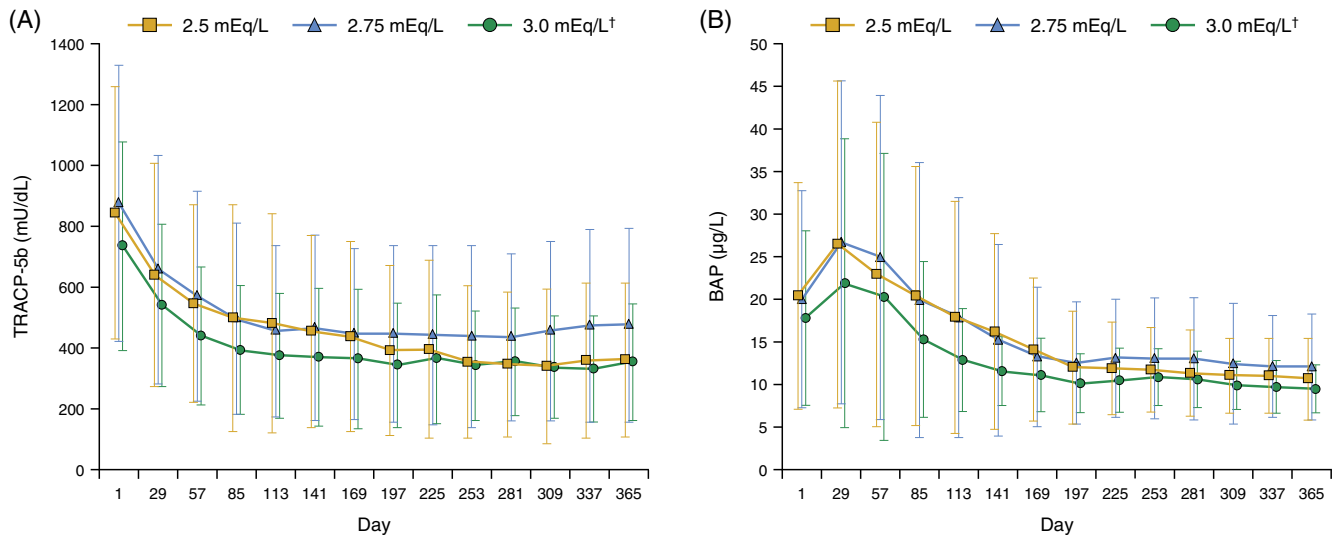
FIGURE 2 Changes in tartrate-resistant acid phosphatase 5b (TRACP-5b; A) and bone alkaline phosphatase (BAP; B) according to the dialysate calcium concentration. Values are shown as the mean ± SD. †Excludes acetate-free citrate dialysate
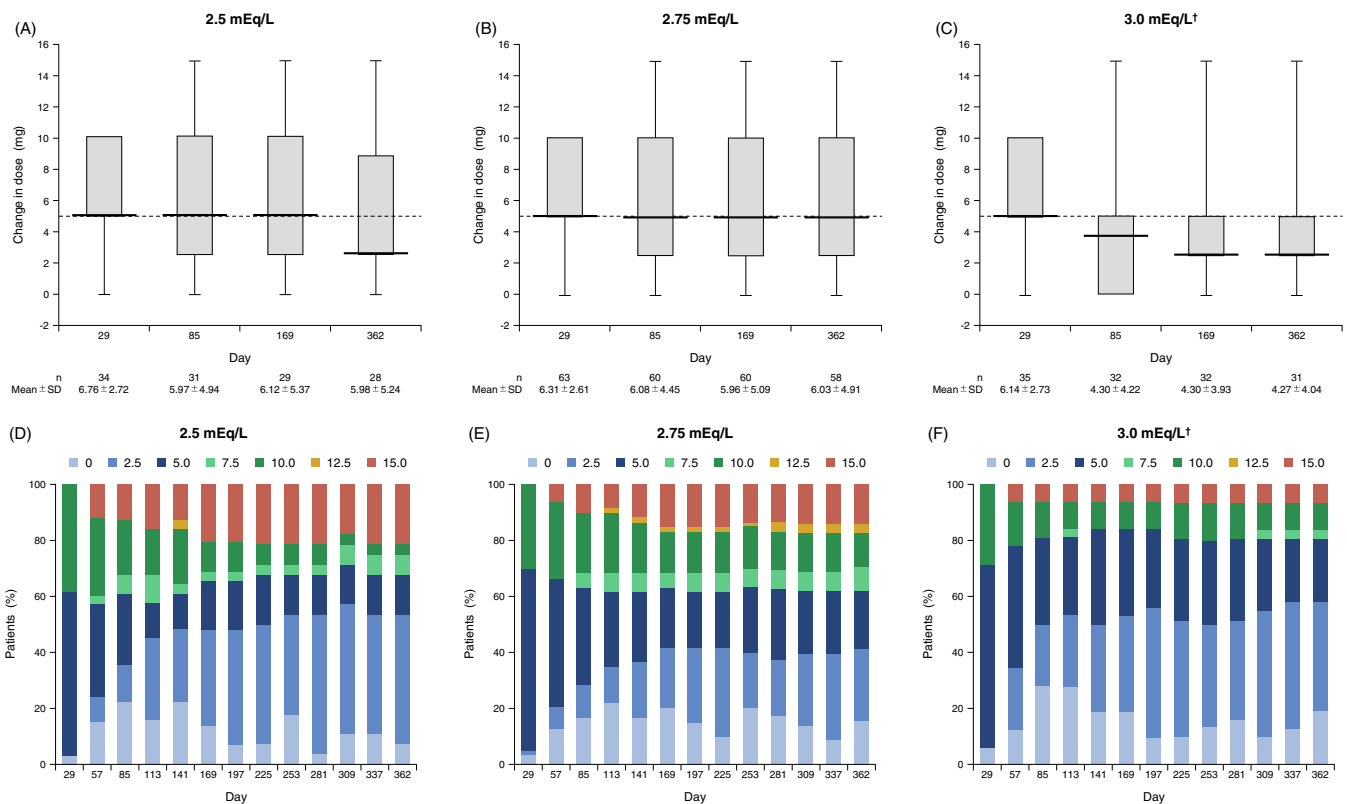

FIGURE 3 Changes in etelcalcetide doses according to dialysate calcium concentration. A-C, Boxplots showing changes in etelcalcetide doses. Boxes represent the first and third quartiles, thick horizontal lines represent the median and the thin vertical lines represent the minimum and maximum values. D-F, Distribution of etelcalcetide doses according to dialysate calcium concentration. A and D, 2.5 mEq/L; B and E, 2.75 mEq/L; C and F, 3.0 mEq/L. †Excludes acetate-free citrate dialysate

As shown in Figure 5A-C, there were no significant differences in the doses of calcium carbonate, a Ca-containing P binder, among the three groups, except at baseline, when the dose was higher in the 2.5 mEq/L group (Figure 5A). For lanthanum carbonate, a non-Ca-containing P binder, no significant differences were found among the three groups, although the dose tended to be greater in
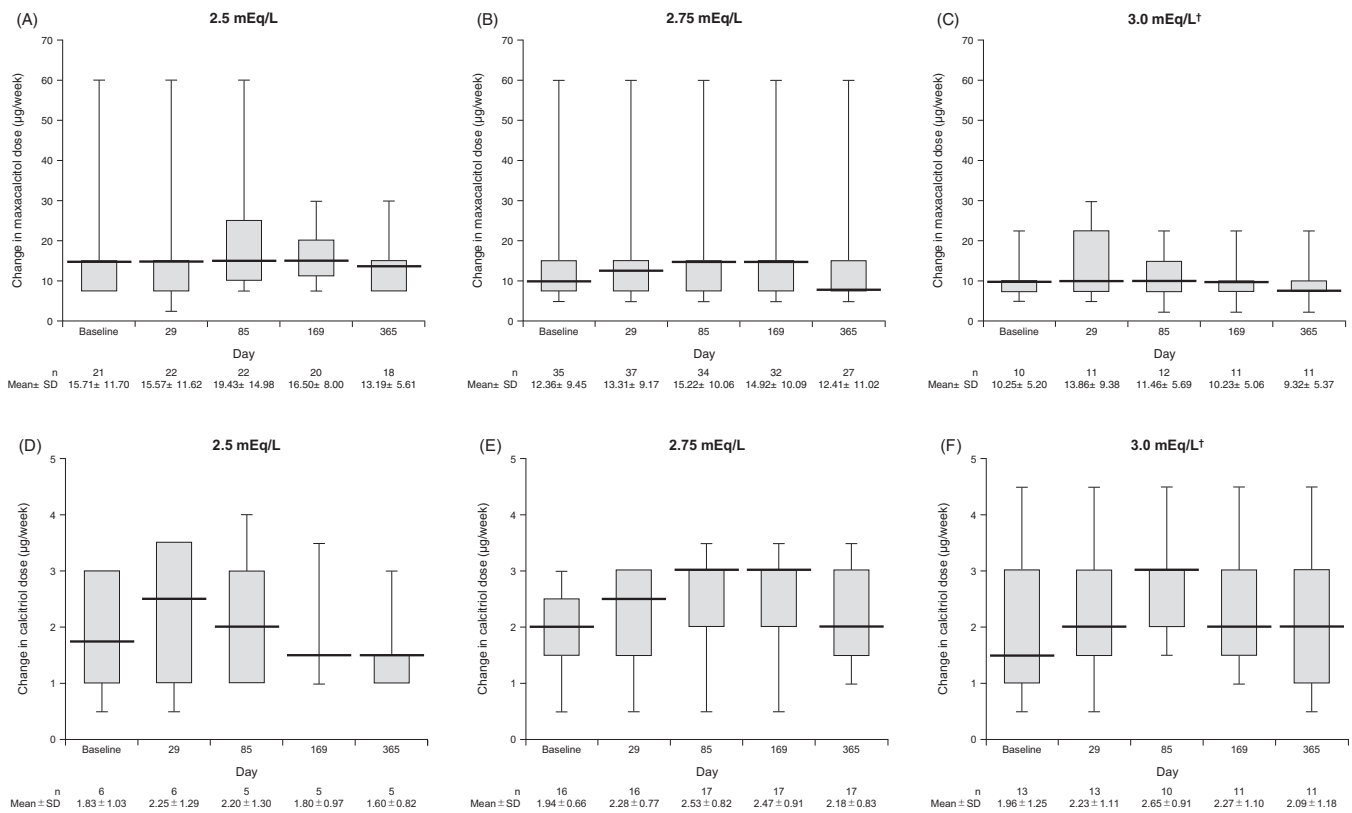
FIGURE 4 Boxplots showing the changes in doses of the vitamin D preparations maxacalcitol (A–C) and calcitriol (D–E) according to the dialysate calcium concentration. A and D, 2.5 mEq/L; B and E, 2.75 mEq/L; C and F, 3.0 mEq/L. Boxes represent the first and third quartiles, thick horizontal lines represent the median and the thin vertical lines represent the minimum and maximum values. [†]Excludes acetate-free citrate dialysate

the 2.5 mEq/L group than in the other groups at baseline and day 29 (Figure 5D-F).

Regarding non-Ca-containing P binders, we found no significant differences in sevelamer carbonate doses among the three groups, although its dose tended to be higher in the 2.5 mEq/L group than in the other groups at baseline (Figure 5G-I). Ferric citrate was used by a small number of patients and no clear differences in doses could be seen among the three groups (Figure 5J-L).

The doses of other vitamin D agents and P binders were not assessed owing to the small numbers of patients using these drugs.

3 | DISCUSSION

Calcimimetics are increasingly being used to regulate PTH levels in patients with SHPT. It is well established that the dialysate Ca concentration may influence PTH levels,[11] such that low Ca concentrations may increase the risk of hypocalcaemia while high Ca concentrations may exacerbate vascular pathologies as a consequence of inappropriate PTH levels.[12,13] Therefore, it is important to assess whether calcimimetics may exacerbate these effects of the dialysate Ca concentration on PTH levels and other clinically relevant endpoints in patients with SHPT. Reassuringly, the present analyses revealed no

clinically meaningful differences in iPTH, cCa or P levels among the three groups of Japanese CKD patients who received dialysates containing different Ca concentrations (2.5, 2.75 or 3.0 mEq/L) over a period of 52 weeks. Serum iPTH levels were only slightly lower in patients who received dialysates with higher Ca concentrations (ie, 3.0 mEq/L) than in the lower Ca concentration group (2.5 and 2.75 mEq/L) and were accompanied by slightly lower etelcalcetide doses in the 3.0 mEq/L group. This was due to lower baseline iPTH levels in 3.0 mEq/L group. Nevertheless, these were not statistically significant, suggesting the dialysate Ca concentration has a negligible influence on the efficacy of etelcalcetide. It is also notable that the frequency of hypocalcaemia, defined as serum Ca <7.4 or <8.4 mg/mL, was comparable among the three dialysate Ca concentrations, suggesting that the risk of hypocalcaemia was not related to the dialysate Ca concentration in these patients treated with etelcalcetide. The doses of concomitant vitamin D and P-binders tended to be higher in the 2.5 mEq/L group than in the other groups. Considering that their doses were already high at baseline in this group and the patterns of changes in their doses after baseline were similar in each group, the trends towards higher doses of these drugs in the 2.5 mEq/L group are unlikely to have been due to etelcalcetide. Given that the mean serum cCa and P levels changed similarly over time and their levels were within the target ranges at Week 52 in all three groups, it may
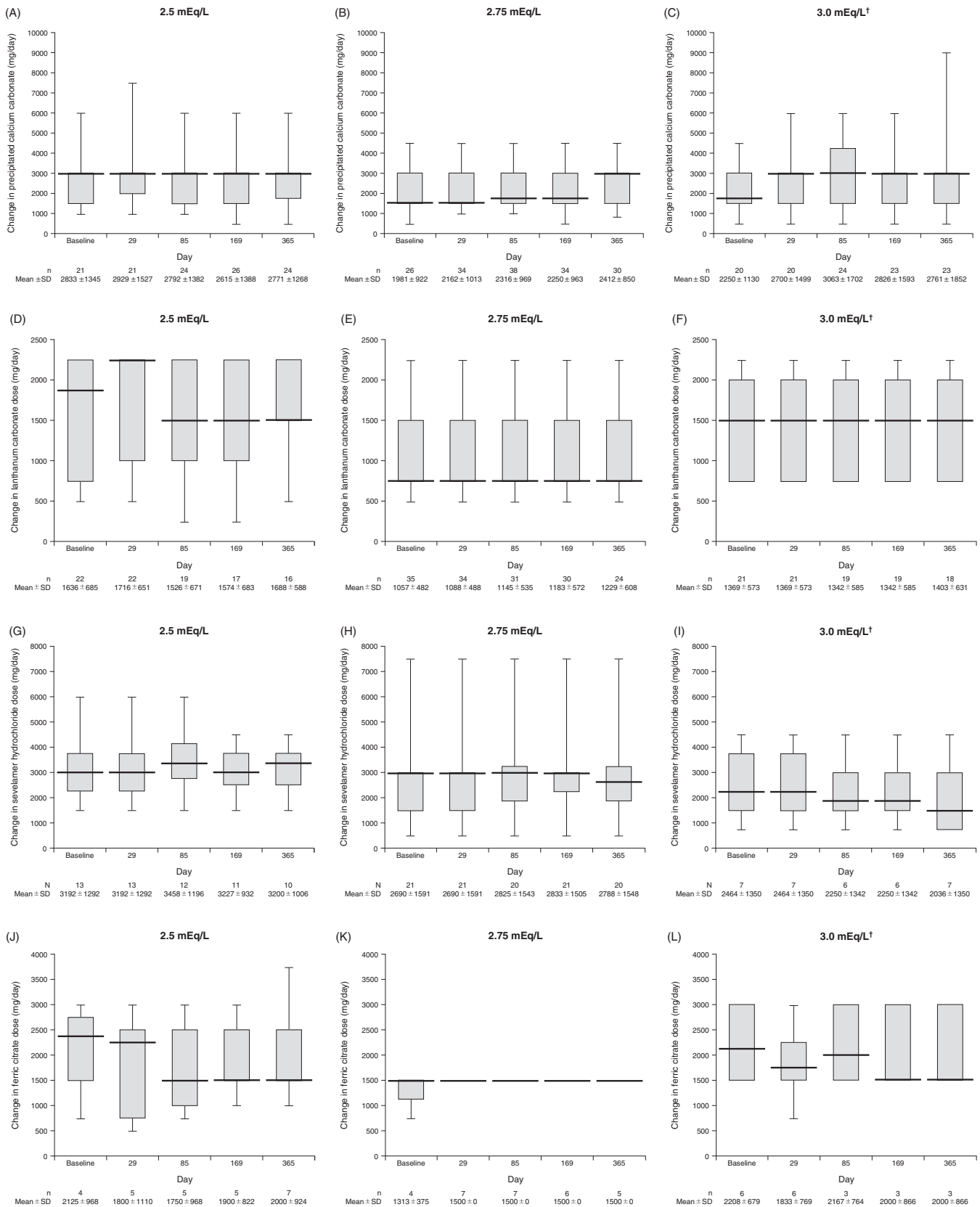
FIGURE 5 Boxplots showing the changes in doses of the phosphate binders precipitated calcium carbonate (A–C), lanthanum carbonate hydrate (D–F), sevelamer hydrochloride (G–I) and ferric citrate (J–L) according to the dialysate calcium concentration. A, D, G, J 2.5 mEq/L; B, E, H, K 2.75 mEq/L; C, F, I, L 3.0 mEq/L. Boxes represent the first and third quartiles, thick horizontal lines represent the median, and the thin vertical lines represent the minimum and maximum values. [†]Excludes acetate-free citrate dialysate

have been necessary to use higher doses of these drugs in the 2.5 mEq/L group than in other groups in order to control cCa and P levels. In the event that iPTH, cCa or P levels move out of the target range, it is possible to adjust the doses of etelcalcetide and/or concomitant drugs, as necessary. Indeed, changes in doses were done and helped maintained serum iPTH, cCa and P levels within their appropriate ranges. Taken together, these results suggest that the dialysate Ca concentration has a negligible impact on the clinical efficacy of etelcalcetide with concomitant drugs, but slight adjustments of the doses of etelcalcetide and/or concomitant drugs might be required to maintain efficacy markers within appropriate ranges.

This is the first study to examine the impact of the dialysate Ca concentration on the efficacy of comprehensive therapy comprising etelcalcetide with concomitant drugs in patients with SHPT. In terms of other calcimimetics, the evaluation of cinacalcet hydrochloride therapy to lower cardiovascular events (EVOLVE) trial revealed that the baseline dialysate Ca concentration and the serum-dialysate Ca gradient did not significantly modify the effects of cinacalcet on the primary composite endpoint (death or first nonfatal myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular event), cardiovascular death or sudden death over 244 weeks of treatment.[16] However, the dialysate Ca concentration was up-titrated for relative hypocalcaemia in the cinacalcet group but not in the placebo group; this was possible because SPDDS were mainly used in EVOLVE trial and allowed the investigator to change the type of dialysate and Ca concentration in individual patients. Therefore, that study did not imply that cinacalcet was effective regardless of the dialysate Ca concentration. In the present study, no changes in the dialysate Ca concentration were made, which reflects haemodialysis practices in Japan. This allowed us to compare the impact of dialysates containing different Ca concentrations on the therapeutic effects of etelcalcetide with concomitant drugs.

Another key finding is that we observed some improvements in biomarkers of abnormal bone hypermetabolism, in terms of reductions in both TRACP-5b as a marker of bone resorption[17] and BAP as a marker of bone formation[18] over the course of the 52-week study. Bone metabolism is mainly regulated by PTH. In this study, there were no differences in serum iPTH levels among the three dialysate Ca concentration groups. Consequently, the changes in biomarkers of bone metabolism were similar regardless of the dialysate Ca concentration. As we reported previously,[15] we believe these effects of etelcalcetide will contribute to improved bone metabolism and could potentially lead to improved quality of life and prognosis. Of course, this would need to be confirmed in prospective studies.

Some limitations warrant mention, including the post hoc design of the present analyses, which means the analyses may not have been adequately powered to test for differences in the endpoints among the three groups. There may also be some confounding bias because patients were not randomised to each dialysate Ca concentration. Nevertheless, the baseline characteristics of the three groups were generally similar.

In conclusion, the results of these post hoc analyses of the 52-week study indicate that there were no clinically meaningful differences in the therapeutic effects of comprehensive treatment comprising etelcalcetide with concomitant drugs among the three dialysate Ca concentrations (2.5, 2.75 or 3.0 mEq/L), and that the dialysate Ca concentration did not influence the doses of etelcalcetide and concomitant drugs or the proportion of patients with low Ca concentrations. In patients with slight fluctuations in efficacy markers, such as iPTH or P, their levels can be maintained within appropriate ranges by adjusting the doses of etelcalcetide and/or concomitant drugs in the three dialysate Ca concentration groups. Furthermore, the patients showed improvements in biomarkers of bone resorption and formation, with similar trends in the three dialysate Ca concentration groups, which may lead to favourable effects on quality of life and patient morbidity through improved bone metabolism.

AUTHOR CONTRIBUTIONS

T.S., M.F., K.Y., T.A. and T.A. played advisory roles in this study. A.F. organized the study. All authors contributed to conception and design of the study and interpretation of data. A.S. contributed to analysis of data and interpretation of data. All authors contributed to manuscript writing/critical revision, and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.