

The effect of sevelamer carbonate and lanthanum carbonate on the pharmacokinetics of oral calcitriol

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Abstract

Background. Lanthanum carbonate and sevelamer carbonate are non-calcium-based phosphate binders used to manage hyperphosphataemia in patients with chronic kidney disease (CKD). Patients with CKD may require intravenous or oral active vitamin D. We investigated the effects of lanthanum carbonate and sevelamer carbonate on the bioavailability of oral calcitriol.

Methods. This was a three-period, crossover study in healthy volunteers. Forty-one individuals were randomized to one of six possible sequences, each consisting of three treatment periods separated by washouts. The treatments were calcitriol (1 µg at lunch), calcitriol with lanthanum carbonate (3000 mg/day) and calcitriol with sevelamer carbonate (7200 mg/day). Serum calcitriol levels were assessed at baseline and throughout the study.

Results. Co-administration of lanthanum carbonate with calcitriol had no significant effect on area under the curve over 48 h (AUC_{0–48}) for serum exogenous calcitriol [least-squares (LS) mean, calcitriol with lanthanum carbonate vs calcitriol alone: 429 pg h/mL vs 318 pg h/mL, respectively; $P = 0.171$]. Similarly, there was no significant effect on maximum concentration (C_{max}). In contrast, co-administration with sevelamer was associated with a significant reduction in bioavailability parameters for calcitriol (calcitriol with sevelamer carbonate vs calcitriol alone, LS mean AUC_{0–48}: 137 pg h/mL vs 318 pg h/mL, respectively; $P = 0.024$; LS mean C_{max} : 40.1 pg/mL vs 49.7 pg/mL, respectively; $P < 0.001$).

Conclusions. Sevelamer carbonate significantly reduces serum concentrations of exogenous calcitriol when administered concomitantly with oral calcitriol, whereas lanthanum carbonate has no significant effect. This should be considered when treating CKD patients who require phosphate binders and oral vitamin D.

Keywords: bioavailability; calcitriol; chronic kidney disease; lanthanum carbonate; sevelamer carbonate

Introduction

Vitamin D insufficiency and deficiency are common in patients with chronic kidney disease (CKD), owing to decreased synthesis of 1,25-dihydroxyvitamin D (calcitriol, the active form of vitamin D) in the kidney [1,2]. A decrease in 1,25-dihydroxyvitamin D, along with an increase in parathyroid hormone, is one of the earliest changes seen in mineral metabolism parameters in patients with CKD and this decrease tends to worsen as CKD progresses [3]. Vitamin D insufficiency is strongly associated with hyperparathyroidism [4], as well as an increased risk of cardiovascular events and changes in bone metabolism [5,6]. The Kidney Disease Outcomes Quality Initiative and the Kidney Disease: Improving Global Outcomes guidelines both recommend that vitamin D insufficiency and deficiency are treated appropriately [7,8]. Several preparations of vitamin D and vitamin D analogues are available; some are administered orally and others intravenously. Such agents have been found to be extremely effective in controlling hyperparathyroidism in patients with advanced kidney disease [9] and in reducing mortality in patients on haemodialysis [10]. Thus, it is important for nephrologists to be aware of any drug–drug interactions that may impact on the effectiveness of vitamin D treatments.

Phosphate binders are often used to sequester dietary phosphate in the gastrointestinal tract, thereby reducing phosphate absorption and helping to manage hyperphosphataemia in patients with CKD. Several binders are currently available; among these, non-calcium-based lanthanum carbonate (FOSRENOL[®], Shire Pharmaceuticals, Basingstoke, UK) and sevelamer (Renagel[®] and Renvela[®], Genzyme Corporation, Cambridge, MA, USA) have been shown to be effective in reducing serum phosphorus levels in patients with CKD on dialysis [11,12] and may improve survival, in comparison with calcium-based binders, in patients over 65 years of age [13,14]. These non-calcium-based binders have been developed as an alternative to the older calcium-based agents, which may increase the progression of calcification [15].

The mechanism of action of all phosphate binders involves direct physical binding of phosphate in the contents of the gastrointestinal tract. In addition to binding phosphate, sevelamer has a high affinity for bile salts [16]. Indeed, it has been shown *in vitro* that bile salts displace phosphate from sevelamer, but not from lanthanum [17]. As sevelamer binds bile salts, it may impair the absorption of fat-soluble molecules, such as vitamin D [18]. Sevelamer hydrochloride has been shown to reduce the bioavailability of calcitriol in beagle dogs [19], but no specific calcitriol interaction studies have been reported in humans. Sevelamer carbonate is a new formulation of sevelamer, which may also reduce the absorption of fat-soluble vitamins.

To date, there are no published clinical data in humans regarding the effect of sevelamer carbonate/hydrochloride or lanthanum carbonate on the absorption of the vitamin D supplement, oral calcitriol, which is indicated for patients with CKD who are vitamin D deficient. In this clinical pharmacology study, the effects of lanthanum carbonate and sevelamer carbonate on the pharmacokinetics of oral calcitriol in healthy volunteers were compared.

Materials and methods

Design

This was an open-label, three-period crossover study comparing the bioavailability of calcitriol (ROCALTROL[®], Validus Pharmaceuticals, Inc. Parsippany, NJ, USA) during the following regimens:

- calcitriol alone (1 µg at lunch, given as two 0.5 µg capsules)
- calcitriol (1 µg at lunch) with lanthanum carbonate (one 1000 mg tablet at breakfast, lunch and dinner)
- calcitriol (1 µg at lunch) with sevelamer carbonate (2400 mg at breakfast, lunch and dinner, given as three 800 mg tablets).

The dose per day of lanthanum carbonate (3000 mg) was chosen based on the highest doses usually required in clinical studies; most patients received 1500–3000 mg/day in order to reach targets [12,20,21]. Data on the required dosage of sevelamer carbonate are limited; Ketteler *et al.* reported a final mean dose of 7800 mg/day in a recent treat-to-target study [22]. Data on sevelamer hydrochloride suggest a mean dose requirement of 5400–6900 mg/day [13,23–26] to achieve control of serum phosphate. Thus, we considered a daily dose of sevelamer carbonate of 7200 mg/day to represent a dose within the typical range used in clinical practice.

Eligible healthy volunteers were admitted to a single study centre and randomized to one of six treatment sequences (Figure 1), with each sequence including all three treatment regimens. Treatment periods each lasted 3 days and were separated from each other by a 7-day washout. Study treatment was given only on day 1 of each treatment period. Identical meals were served across the treatment periods and contained 300–400 mg of phosphorus and 200–300 mg of calcium. Treatments were administered orally with 240 mL of de-ionized water half-way through ingestion of the meal. The study was undertaken in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

Participants

Eligible healthy volunteers were aged 19–45 years and had a body mass index of 20.0–29.9 kg/m². Women of childbearing potential and sexually active men were required to use an acceptable method of contraception. Exclusion criteria included current or recurrent disease that could affect

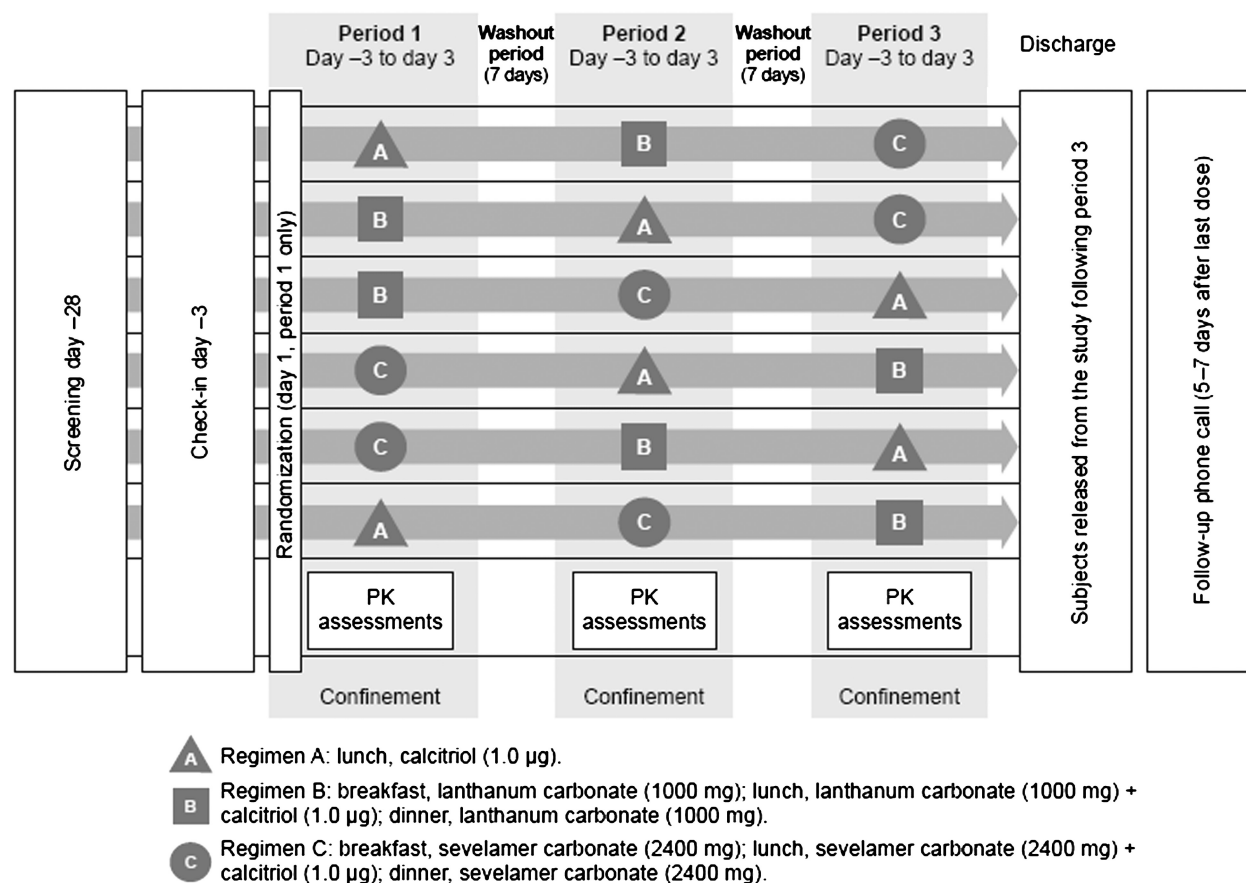


Fig. 1. Study design. Study medications were administered orally with 240 mL of de-ionized water half-way through ingestion of the meal.

the action, absorption or disposition of the investigational products; current or relevant previous history of any medical disorder that might require treatment or make the subject unlikely to be able to complete the study; significant illness within 2 weeks of the first dose of study medication; use of any medication within 2 weeks of the first study dose, with the exception of hormonal replacement therapy or hormonal contraceptives; a positive test for human immunodeficiency virus antibodies, hepatitis B surface antigens or hepatitis C antibodies; pregnancy or lactation; smoking or use of nicotine-containing products; a history of alcohol abuse, or consumption of more than 21 units/week for men or more than 14 units/week for women; routine consumption of more than 2 units of caffeine per day; inability to follow a standardized diet and meal schedule or inability to fast as required during the study; substantial changes in eating habits in the 30 days before first study dose; and use of any other investigational agents in the 30 days before first study dose.

Objectives and assessments

The primary objective was to assess the effects of lanthanum carbonate (1000 mg t.i.d. with meals) and sevelamer carbonate (2400 mg t.i.d. with meals) on the pharmacokinetics of oral calcitriol (1 µg o.d.). The primary endpoint was predefined as the change from baseline in area under the curve over 48 h (AUC_{0-48}) for exogenous calcitriol (i.e. day 1 total calcitriol minus baseline endogenous calcitriol). Secondary pharmacokinetic endpoints included maximum concentration (C_{max}), AUC until last measurable time point (AUC_{0-t}) and time to maximum concentration (t_{max}) for exogenous calcitriol and all the above parameters for total calcitriol.

Blood samples for assessment of serum calcitriol levels were collected from each participant prior to lunch on the 2 days before study dosing in each treatment period (days -2 and -1) and at the following time points after dosing in each treatment period: 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36 and 48 h. Serum concentrations of calcitriol were determined by a validated radioimmunoassay with a working range of 5–210 pg/mL. Samples from the same individual for different treatment regimens were analysed in separate batches; however, an incurred sample reproducibility test confirmed acceptable inter-batch reproducibility. Serum calcitriol levels in quality control samples (12.5, 50.0 and 175 pg/mL) analysed alongside study samples were determined with an accuracy of between -6.5 and 6.9% and a precision (inter-assay coefficient of variation) of between 7.3 and 9.5%. Baseline endogenous serum calcitriol levels were determined from the mean of values for days -2 and -1. Exogenous serum calcitriol values at each sampling time following dosing were calculated from the total serum concentration at that time minus the baseline endogenous serum calcitriol concentration. This method of determining exogenous calcitriol concentration could result in negative calculated values. Serum exogenous calcitriol AUC_{0-48} and AUC_{0-t} were calculated using individual values for exogenous serum calcitriol levels and could also have negative values. AUC_{0-48} , AUC_{0-t} , C_{max} and t_{max} for total calcitriol were also determined for each treatment.

The secondary objective was to evaluate the safety and tolerability of lanthanum carbonate and sevelamer carbonate when co-administered with calcitriol. This was assessed through recording of adverse events and laboratory assessments.

Statistical methods

Based on published data, the mean AUC for exogenous serum calcitriol corresponding to a dose of 1 µg oral calcitriol per day was estimated to be 256 pg h/mL [27]. In this study, an inter-participant coefficient of variation of 22% was reported for total calcitriol levels (endogenous plus exogenous). Based on this degree of variability, it was estimated that a total of 30 participants would allow detection of a 20% reduction in AUC for serum calcitriol between calcitriol alone and calcitriol with lanthanum carbonate or sevelamer carbonate, with a two-sided significance level and 90% power. Assuming that the intra-participant coefficient of variation (which was not available) would be lower than the inter-participant variability, sample size was likely to have been overestimated.

The primary hypothesis tested was that there were no differences in the AUC_{0-48} for exogenous calcitriol when calcitriol was co-administered with either lanthanum carbonate (lanthanum carbonate + calcitriol versus calcitriol alone) or sevelamer carbonate (sevelamer carbonate + calcitriol versus calcitriol alone). The primary analysis was performed on the pharmacokinetic population, which consisted of all participants with no major deviations related to study drug intake for whom the primary pharmaco-

Table 1. Volunteer disposition

Population	n (%)
Screened	86
Enrolled/randomized	41
Safety population	41 (100.0%)
Pharmacokinetic population	41 (100.0%)
Completed	36 (87.8%)
Discontinued	5
Adverse event	0 (0.0%)
Refused further participation	2 (4.9%)
Withdrew consent	3 (7.3%)

kinetic data were considered sufficient and interpretable. AUC_{0-48} , AUC_{0-t} and C_{max} for exogenous calcitriol were analysed using a mixed-effect linear model containing sequence group, period and treatment group as fixed effects and participant-within-sequence as the random effect. Baseline endogenous calcitriol was included as a covariate. AUC_{0-48} , AUC_{0-t} and C_{max} for total calcitriol were analysed using the same model as for exogenous calcitriol with the exceptions that the log-transformation was applied before analyses and baseline serum calcitriol was not included in the model. The t_{max} values for exogenous and total calcitriol were analysed using Wilcoxon signed-rank sum test.

Results

Volunteer disposition and demographics are shown in Tables 1 and 2. All 41 participants who were randomized were included in the safety and pharmacokinetic analyses.

Mean serum concentrations of exogenous and total calcitriol after a single dose, with or without co-administration of lanthanum carbonate or sevelamer carbonate, are shown in Figure 2. For all regimens, mean exogenous calcitriol concentrations rapidly reached a plateau that was maintained for up to ~6 h, with concentrations then decreasing to a calculated level lower than baseline by 48 h after dosing.

There were no significant changes in exogenous calcitriol least-squares (LS) mean AUC_{0-48} or C_{max} values when lanthanum carbonate was co-administered with calcitriol, compared with calcitriol alone (Table 3). This was also the case for total calcitriol. However, median t_{max} for exogenous calcitriol and for total calcitriol was longer when lanthanum carbonate was co-administered with cal-

Table 2. Volunteer demographics (safety population)

Parameter	Total (n= 41)
Sex, n (%)	
Male	22 (53.7%)
Female	19 (46.3%)
Race, n (%)	
White	21 (51.2%)
Black	18 (43.9%)
Asian	2 (4.9%)
Ethnicity, n (%)	
Hispanic or Latino	8 (19.5%)
Not Hispanic or Latino	33 (80.5%)
Age, years (mean ± SD)	30 ± 7.6
Weight, kg (mean ± SD)	72 ± 11.0
Body mass index, kg/m ² (mean ± SD)	24 ± 2.8

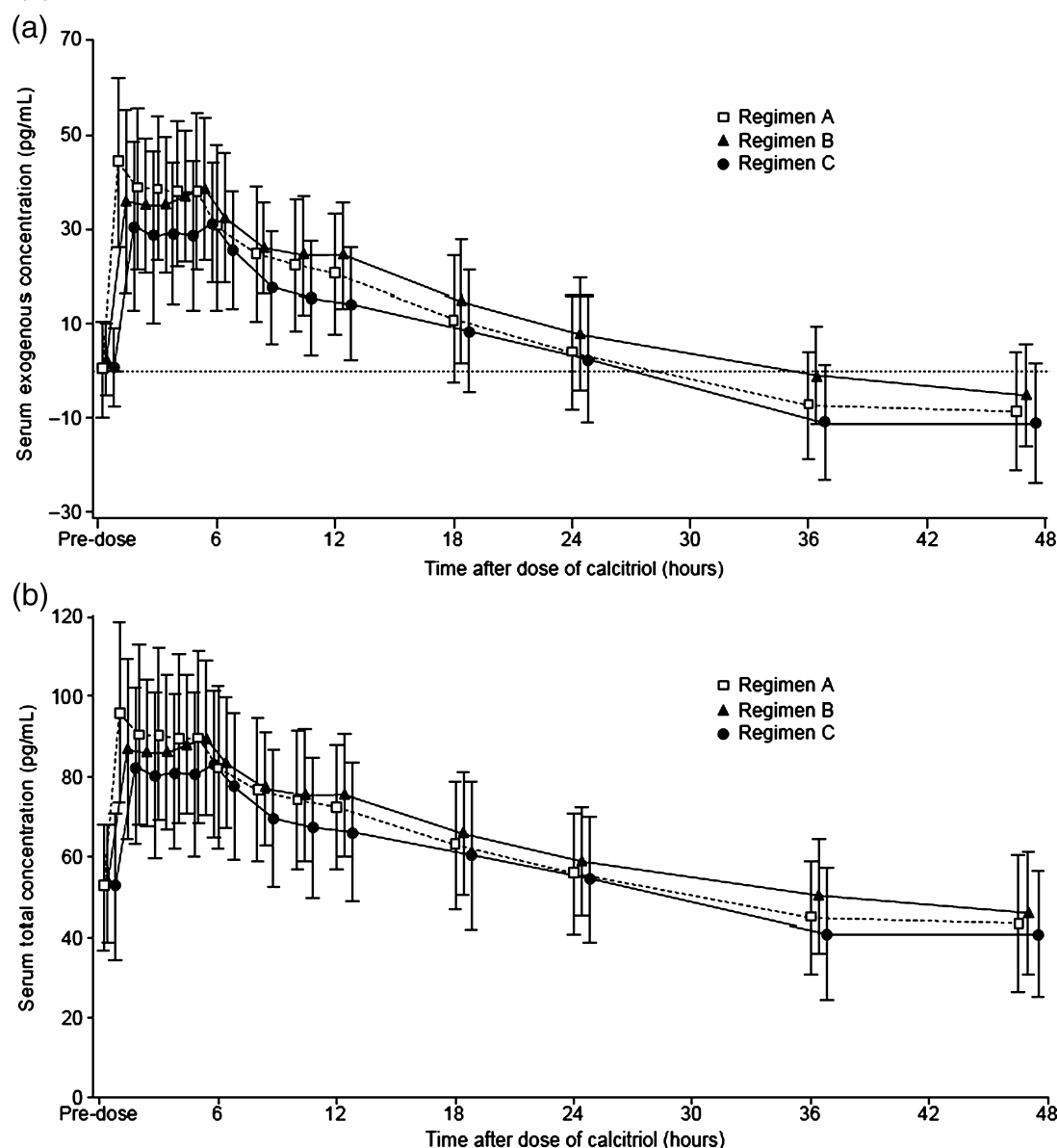


Fig. 2. Mean serum concentrations of (a) exogenous and (b) total calcitriol after a single dose, with or without co-administration of lanthanum carbonate or sevelamer carbonate. Regimen A: calcitriol 1.0 μ g; regimen B: calcitriol 1.0 μ g + lanthanum carbonate (1000 mg t.i.d.); regimen C: calcitriol 1.0 μ g + sevelamer carbonate (2400 mg t.i.d.).

Table 3. Analysis of exogenous and total calcitriol pharmacokinetic parameters: lanthanum carbonate plus calcitriol versus calcitriol alone

Exogenous calcitriol^a				
Parameter	Calcitriol	Calcitriol + lanthanum carbonate	Difference (95% CI)	P-value
AUC ₀₋₄₈ (pg h/mL)	318	429	111 (-49, 270)	0.171
C _{max} (pg/mL)	49.7	47.0	-2.7 (-8.1, 2.6)	0.313
t _{max} (h)	2.0	4.0	1.3 (0.0, 2.5)	0.039
Total calcitriol^b				
Parameter	Calcitriol	Calcitriol + lanthanum carbonate	Geometric mean ratio (95% CI)	P-value
AUC ₀₋₄₈ (pg h/mL)	2748	2889	1.05 (0.99, 1.12)	0.114
C _{max} (pg/mL)	98.6	96.7	0.98 (0.91, 1.05)	0.579
t _{max} (h)	2.0	4.0	1.3 (0.0, 2.5)	0.039

Note: AUC_{0-t} values were identical to AUC₀₋₄₈ values. AUC₀₋₄₈ = area under the serum concentration-time curve from time 0 to 48 h after dosing; AUC_{0-t} = area under the serum concentration-time curve from time 0 to time (t) of the last quantifiable plasma concentration; C_{max}, maximum serum concentration; t_{max}, time of maximum serum concentration.

^aValues for AUC and C_{max} are least-squares mean; median values are given for t_{max}.

^bValues for AUC and C_{max} are geometric least-squares mean; median values and median difference are given for t_{max}.

Table 4. Analysis of exogenous calcitriol pharmacokinetic parameters: sevelamer carbonate plus calcitriol versus calcitriol alone

Exogenous calcitriol^a				
Parameter	Calcitriol	Calcitriol + sevelamer carbonate	Difference (95% CI)	P-value
AUC ₀₋₄₈ (pg h/mL)	318	137	-181 (-338, -24)	0.024
C _{max} (pg/mL)	49.7	40.1	-9.6 (-14.9, -4.3)	<0.001
t _{max} (h)	2.0	2.5	0.5 (-0.5, 1.5)	0.305
Total calcitriol^b				
Parameter	Calcitriol	Calcitriol + sevelamer carbonate	Geometric mean ratio (95% CI)	P-value
AUC ₀₋₄₈ (pg h/mL)	2748	2579	0.94 (0.88, 1.00)	0.047
C _{max} (pg/mL)	98.6	89.7	0.91 (0.85, 0.98)	0.009
t _{max} (h)	2.0	2.5	0.5 (-0.5, 1.5)	0.305

Note: AUC_{0-t} values were identical to AUC₀₋₄₈ values. AUC₀₋₄₈ = area under the serum concentration–time curve from time 0 to 48 h after dosing; AUC_{0-t} = area under the serum concentration–time curve from time 0 to time (*t*) of the last quantifiable plasma concentration; C_{max}, maximum serum concentration; t_{max}, time of maximum serum concentration.

^aValues for AUC and C_{max} are least-squares mean; median values are given for t_{max}.

^bValues for AUC and C_{max} are geometric least-squares mean; median values and median difference are given for t_{max}.

citriol (calcitriol with lanthanum carbonate: 4.0 h; calcitriol alone: 2.0 h; *P* = 0.039 for both exogenous calcitriol and total calcitriol) (Table 3).

Co-administration of sevelamer carbonate with calcitriol resulted in a statistically significant reduction in LS mean AUC₀₋₄₈ for serum exogenous calcitriol levels compared with calcitriol alone {calcitriol with sevelamer carbonate: 137 pg h/mL; calcitriol alone: 318 pg h/mL; difference [95% confidence interval (95% CI)]: -181 pg h/mL (-338, -24.0); *P* = 0.024} (Table 4). Similarly, co-administration with sevelamer carbonate was associated with a reduction in LS mean C_{max} for exogenous calcitriol levels (calcitriol with sevelamer carbonate: 40.1 pg/mL; calcitriol: 49.7 pg/mL; difference [95% CI]: -9.6 [14.9, -4.34]; *P* < 0.001) (Table 4). Significant reductions in LS mean AUC₀₋₄₈ and C_{max} were also observed for total calcitriol when administered with sevelamer carbonate compared with calcitriol alone (Table 4).

No serious adverse events were reported and none of the volunteers withdrew due to an adverse event. In total, 6/38 individuals (15.8%) experienced adverse events during treatment with calcitriol alone (headache, haematoma, hypoaesthesia [two patients], diarrhoea and urinary tract infection). This compares with 10/38 individuals (26.3%) during treatment with calcitriol and lanthanum carbonate and 5/40 individuals (12.5%) during treatment with calcitriol and sevelamer carbonate. The majority of adverse events were mild or moderate in nature and were not related to lanthanum carbonate or sevelamer carbonate; only three events were considered related to treatment, two occurring during treatment with lanthanum carbonate plus calcitriol (anxiety and headache) and one occurring during treatment with sevelamer carbonate and calcitriol (dry mouth). No clinically important changes in laboratory parameters, physical examinations or electrocardiograms were detected during the study in any of the treatment arms.

Discussion

The results of this study demonstrate that, unlike lanthanum carbonate, sevelamer carbonate reduces serum levels of exogenous calcitriol when these agents are co-administered.

Our study showed that sevelamer carbonate reduced the systemic exposure to oral calcitriol (measured as AUC₀₋₄₈) by ~57%, whereas lanthanum carbonate had no statistically significant or clinically relevant effect. Furthermore, C_{max} for calcitriol was significantly (19%) lower when volunteers were co-administered with sevelamer carbonate and calcitriol compared with calcitriol alone. Our results extend to human details contained within the prescribing information for sevelamer carbonate, which highlight reductions in vitamin D levels in rats and dogs when given sevelamer hydrochloride and suggest monitoring for reduced vitamin D [28]. In contrast to the results with sevelamer carbonate, lanthanum carbonate had no significant effect on C_{max}. These findings are in line with previous observations by Finn *et al.* who showed that lanthanum carbonate does not affect concentrations of 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D (the inactive and active forms of vitamin D, respectively) in patients with CKD stages 3 and 4 [29].

A direct impact of sevelamer on calcitriol metabolism is unlikely because absorption of sevelamer is negligible [30]. However, an indirect interaction (by altering the absorption of an agent that affected calcitriol metabolism) cannot be entirely excluded. A more likely explanation for the reduction in AUC₀₋₄₈ is that the non-selective binding properties of sevelamer result in reduced absorption of both phosphate and calcitriol. Sevelamer consists of a cross-linked polyallyl skeleton with protonated primary and secondary amine groups [31]. The hydrocarbon polymer will have affinity for aliphatic polycyclic molecules (e.g. bile acids, vitamin D, vitamin K) through intermolecular van der Waals attraction [31]. Indeed, sevelamer has been proven to bind the fat-soluble vitamin K *in vitro*, fully sequestering a test sample [32].

Co-administration of calcitriol with lanthanum carbonate resulted in a delay in t_{max} compared with calcitriol alone. However, examination of all the concentration–time curves suggests that a plateau is rapidly reached and maintained for at least 5 h. For the calcitriol alone regimen, the concentration at 2 h was transiently higher but declined to a plateau consistent with levels seen with the calcitriol/lanthanum carbonate regimen by the time of the next sampling point. Given this observation, it is possible that the apparent difference in t_{max} (2 h for calci-

triol only; 4 h for calcitriol with lanthanum carbonate) is a chance finding. Even if there is some reduction in the absorption rate of calcitriol when given with lanthanum carbonate, it is unlikely to have any clinical impact because systemic exposure is not significantly altered. Results for total calcitriol were consistent with those for exogenous calcitriol.

In this study, volunteers received a single dose of calcitriol alone (1 µg at lunch), a single dose of calcitriol plus three doses of lanthanum carbonate (1000 mg at breakfast, lunch and dinner) or a single dose of calcitriol plus three doses of sevelamer carbonate (2400 mg at breakfast, lunch and dinner). We acknowledge that the co-administration of oral calcitriol and phosphate-binding agents in this regimen may not be representative of how these treatments are taken by patients in clinical practice. There are no specific guidelines regarding when oral calcitriol should be taken relative to phosphate binders but, for convenience, patients receiving oral vitamin D supplements and phosphate binders may take the agents simultaneously in the absence of guidance concerning any drug–drug interaction.

An interesting observation in this study is the apparent fall of serum calcitriol concentrations below baseline levels for all treatment regimens by 48 h post-dose. The reason for this phenomenon is unclear. There are data to suggest that calcitriol administration can induce production of 24-hydroxylase [33], thus degrading calcitriol and maintaining calcium balance. In theory, this induction could lead to a reduction in overall calcitriol levels compared with baseline. However, in a previous pharmacokinetic study of calcitriol in healthy individuals, calcitriol concentrations did not return to baseline within a 24-h period [34]. Therefore, the results in our study cannot be unequivocally attributed to induction of 24-hydroxylase. On examining the concentration–time curves, it is clear that the standard deviations about the mean calcitriol concentrations for baseline and 48-h values overlap. Hence, there is some uncertainty whether the apparent decline in calcitriol concentrations below baseline is real.

Conclusion

Sevelamer carbonate significantly reduces serum concentrations of exogenous calcitriol when co-administered with oral calcitriol in healthy volunteers, whereas lanthanum carbonate has no clinically relevant effect on exogenous calcitriol. The most likely explanation for the effect of sevelamer is a reduction in bioavailability through sequestering the fat-soluble calcitriol. These findings may represent an important consideration in patients with CKD who often require vitamin D supplementation.

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Conflict of interest statement. All authors, except SH, are employees of Shire Pharmaceuticals. SH received funding for this study. The results have not been published in whole or in part elsewhere with the exception of congress abstracts.

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