Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability

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Abstract

Background. Phosphate binders are required to control serum phosphorus in dialysis patients. A phosphate binder combining calcium and magnesium offers an interesting therapeutic option.

Methods. This controlled randomized, investigator-masked, multicentre trial investigated the effect of calcium acetate/magnesium carbonate (CaMg) on serum phosphorus levels compared with sevelamer hydrochloride (HCl). The study aim was to show non-inferiority of CaMg in lowering serum phosphorus levels into Kidney Disease Outcome Quality Initiative (K/DOQI) target level range after 24 weeks. Three hundred and twenty-six patients from five European countries were included. After a phosphate binder washout period, 255 patients were randomized in a 1:1 fashion. Two hundred and four patients completed the study per protocol (CaMg, $N = 105$; dropouts $N = 18$; sevelamer-HCl, $N = 99$; dropouts $N = 34$). Patient baseline characteristics were similar in both groups.

Results. Serum phosphorus levels had decreased significantly with both drugs at week 25, and the study hypothesis of CaMg not being inferior to sevelamer-HCl was confirmed. The area under the curve for serum phosphorus ($P = 0.0042$) and the number of visits above K/DOQI (≤ 1.78 mmol/L, $P = 0.0198$) and Kidney disease: Improving global outcomes (KDIGO) targets (≤ 1.45 mmol/L, $P = 0.0067$) were significantly lower with CaMg. Ionized serum calcium did not differ between groups; total serum calcium increased in the CaMg group (treatment difference 0.0477 mmol/L; $P = 0.0032$) but was not associated with a higher risk of hypercalcaemia. An asymptomatic increase in serum magnesium occurred in CaMg-treated patients (treatment difference 0.2597 mmol/L, $P < 0.0001$). There was no difference in the number of patients with adverse events.

Conclusion. CaMg was non-inferior to the comparator at controlling serum phosphorus levels at Week 25. There was no change in ionized calcium; there was minimal increase in total serum calcium and a small increase in serum magnesium. It had a good tolerability profile and thus may represent an effective treatment of hyperphosphataemia.

Keywords: calcium acetate; haemodialysis; magnesium carbonate; phosphate binder; safety parameters

Introduction

In patients with chronic kidney disease stage 5 (CKD 5), increasing evidence links inadequate serum phosphorus control to higher morbidity and mortality [1–6]. As a consequence, serum phosphorus lowering appears to be a key therapeutic goal. In addition to optimal dialysis treatment and dietary restrictions, oral phosphate binders are the treatment of choice in patients with hyperphosphataemia [7].

Calcium acetate/magnesium carbonate (CaMg) is a combination phosphate binder. Both components separately or magnesium carbonate together with calcium carbonate are already well-established phosphate-lowering agents [8–18]. As high doses of phosphate binders are often required to achieve sufficient phosphate reduction, the risk of hypercalcaemia must be considered when using a pure calcium salt as a phosphate binder. Calcium–magnesium combined preparations are effective alternatives because the proportion of calcium is reduced compared with drugs containing calcium salts only, limiting the risk of hypercalcaemia and of a continuously positive calcium balance [19].

A possible further advantage of a calcium–magnesium combined preparation is that increased serum magnesium levels have been associated in dialysis patients with beneficial effects such as reduced vascular calcification and improved survival [20–25]. However, only one prospective study, in which intima media thickness was investigated in a small number of patients, provides indirect supporting evidence for reduced vascular calcification [26] with magnesium supplementation.

A phosphate binder combining a reduced calcium exposure and the possible beneficial effect of controlled magnesium administration, potentially offering the double advantage of favourable gastrointestinal tolerance and positive cardiovascular effects, seemed worthwhile to investigate for its phosphorus-lowering capacity in comparison with a well-established drug in a large-scale controlled randomized study for the first time.

Materials and methods

Study population

Patients aged 18–85 years, stable, without serious illness, on 4–6 h haemodialysis (HD) or online haemodiafiltration (HDF) 3× per week for at least 3 months were enrolled in this study. The main eligibility criteria were not taking any magnesium- or calcium-containing supplement, serum phosphorus ≥ 1.78 mmol/L (≥ 5.5 mg/dL), serum calcium ≤ 2.6 mmol/L (≤ 10.4 mg/dL) and serum magnesium ≤ 1.5 mmol/L (≤ 3.65 mg/dL) after washout of phosphate binders (detailed inclusion and exclusion criteria are provided in Supplementary Table 1). Thirty-six dialysis centres in five countries (Germany, Poland, Portugal, Romania and Spain) participated in this study. The study was conducted in conformity with International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. The protocol and informed consent form were approved by the responsible Ethics Committees. The study was registered at the European clinical trial database: EudraCT No.: 2006-002589-20.

Study procedure and study design

This prospective, controlled, randomized, multicentre, investigator-masked, parallel-group study compared tolerability and efficacy of two different oral phosphate binder treatments (CaMg and sevelamer-HCl) for 24 weeks in HD or online HDF patients. The primary endpoint of this trial was the exploration of the efficacy of CaMg compared with sevelamer-HCl as an active control. The primary target variable was serum phosphorus at Week 25. After a washout/run-in phase of 2 to 3 weeks, during which all phosphate binders had to be discontinued and all patients were switched to the study dialysis fluid composition (dialysate calcium of 1.5 or 1.25 mmol/L, dependent on prior prescription, and dialysate magnesium of 0.5 mmol/L) for at least 2 weeks, patients were randomized in a 1:1 ratio (Figure 1A). Randomization was central via Fax and stratified according to the dialysis mode (HD vs online HDF). The dialysate calcium composition was constant throughout the study at either 1.25 or 1.5 mmol/L. Only those patients being treated with a dialysate of 1.25 mmol/L during the study could be switched to a dialysate of 1.5 mmol/L in the event of hypocalcaemia.

Study medication

Patients received one of the two study medications: calcium acetate 435 mg containing 110 mg elemental calcium combined with magnesium carbonate 235 mg containing 60 mg elemental magnesium (OsvaRen®) or sevelamer-HCl 800 mg (Renagel®) for 24 weeks. Blinding of the study medication was virtually impossible, so that an 'investigator-masked' approach was chosen: the trial medication was packed in opaque blister strips and only administered by the study nurse whereby the investigator and other site staff was masked to trial medication. Furthermore, the primary efficacy parameter (serum phosphorus) was determined in a central laboratory blinded to treatment allocation as were all other persons involved in the trial.

Patient compliance with the treatment was checked weekly from patients' diary entries, by counting of used and unused tablets and by the on-site study monitor dispensing cards. Starting dose of study drugs was at least four tablets per day. Thereafter, following each laboratory result and depending on individual dietary intake, the dose was increased by one to three tablets per day (i.e. one to two tablets per meal) in order to reduce serum phosphorus levels below 1.78 mmol/L (5.5 mg/dL) in the absence of hypercalcaemia or hypermagnesaemia. The number of tablets was prescribed on an individual basis according to the estimated phosphate content of each meal. Regular dietary advice took place prior to the start of and throughout the study.

Study parameters

The primary efficacy parameter was serum phosphorus at Week 25. Secondary efficacy parameters were serum calcium and magnesium at Week 25; further efficacy parameters were number of visits with serum phosphorus ≤ 1.78 mmol/L (≤ 5.5 mg/dL) and ≤ 1.45 mmol/L (≤ 4.49 mg/dL), serum calcium level within the Kidney Disease Outcome Quality Initiative (K/DOQI) recommendation of 2.10 to 2.37 mmol/L (8.41–9.50 mg/dL) and number of visits with a serum calcium and magnesium above [upper limit of normal (ULN)] and below [lower limit of normal (LLN)] the normal range, as well as their respective area under the curve (AUC). Other parameters measured included intact parathormone (iPTH), actual bicarbonate, base excess, low-density lipoprotein (LDL)-cholesterol and potassium. Study medication intake (number of ingested tablets per day) was recorded. Ten visits took place at weekly (until Week 5), fortnightly (Weeks 5–9) and four-weekly intervals (Weeks 9–25).

Tolerability was assessed by means of adverse event profile [adverse event (AE); serious adverse event (SAE)], safety laboratory parameters, electrocardiogram (ECG) and vital signs. Blood gas analyser measurements were taken at the bedside; screening values of serum P, Ca, Mg and iPTH were assessed at the local laboratories of the trial centres. All other laboratory parameter measurements were performed at the central laboratory. A Gastrointestinal Quality of Life Index (GIQLI) validated for gastrointestinal disease [27] was evaluated five times during the study.

Statistical analysis

The following non-inferiority hypothesis was tested: H_0: serum phosphorus level under CaMg is more than 0.15 mmol/L (0.46 mg/dL) higher than serum phosphorus level under sevelamer-HCl vs H_1: serum phosphorus level under CaMg is up to 0.15 mmol/L higher, equal or lower than serum phosphorus level under sevelamer-HCl (a Δ of 0.15 mmol/L assumes no clinical difference [28]).

This hypothesis was tested using the principle of 'confidence interval inclusion'. The one-sided 97.5% confidence interval was calculated using an analysis of covariance model including factors for study treatment, centre (pooled), baseline values, dialysate calcium concentration and use of vitamin D and of cinacalcet as covariates as these factors may have a significant influence on the final results.

As the sample size in each treatment group was 100 (a total sample size of 200), a two-group one-sided t-test at a 2.5% significance level had 80% power to reject the null hypothesis that the difference in means of serum phosphorus between CaMg and sevelamer-HCl at Week 25 is >0.15 mmol/L. This was based on the assumptions that the expected difference in means is −0.05 mmol/L and the common standard deviation is 0.5 mmol/L, as in previous research reports. To allow for a dropout rate of about 20% for the per-protocol analysis, a total sample size of 248 patients was suggested.

Response rates were tested using a logistic regression model. The number of visits was tested using Wilcoxon rank-sum tests. All other secondary and further efficacy endpoints were tested using the same analysis of covariance (ANCOVA) model as for the primary endpoint. Baseline characteristics were tested using t-tests or chi-square tests depending on the distribution of the data. These tests were carried out at a two-sided significance level α of 5%.

The main population for the confirmative analysis of the primary efficacy variable was the per-protocol set (PPS), i.e. all patients who were randomized and completed the study per protocol. All analyses of secondary
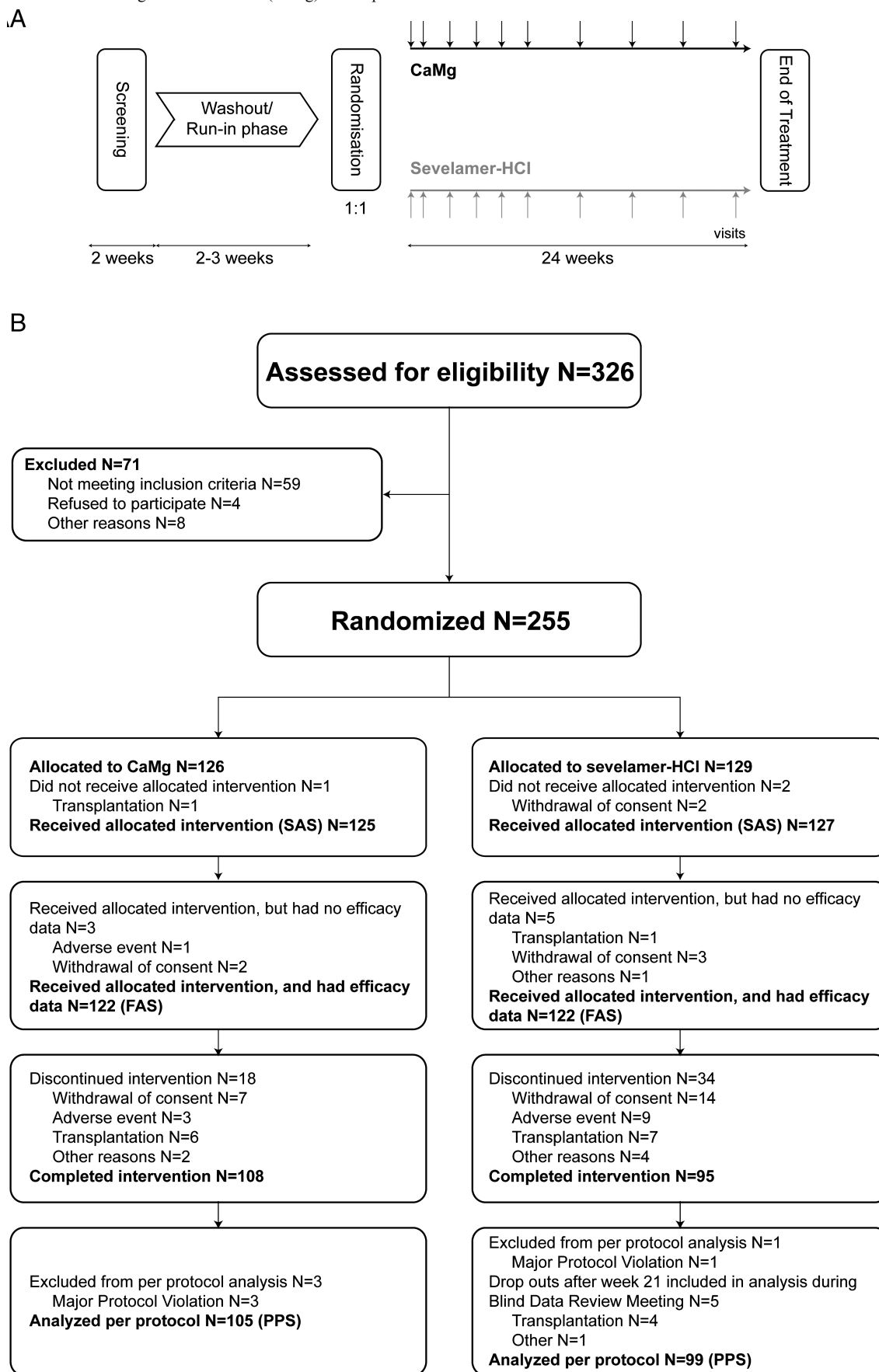
Fig. 1. (**A**) Study design and procedure. (**B**) CONSORT diagram demonstrating patient flow including analysis sets.

Table 1. Patients' demographics, baseline characteristics (PPS, $N = 204$), screening laboratory values and covariate disposition at baseline (data given as mean ± SD, N or %)

Parameter	CaMg	Sevelamer-HCl	P-value
	$(N = 105)$	$(N = 99)$	
Age (years)	59.2 ± 13.72	55.9 ± 11.75	0.0641
Gender N (%)			
Female	49 (46.7)	48 (48.5)	0.6554
Male	56 (53.3)	51 (51.5)	
Weight (kg)	73.8 ± 13.7	74.9 ± 12.4	0.5419
Height (cm)	165.4 ± 8.1	166.9 ± 8.8	0.1980
BMI (kg/m^2)	27.0 ± 4.6	27.0 ± 3.8	0.8857
Dialysis vintage (years)	4.9 ± 3.9	5.1 ± 4.2	0.6777
Primary diagnosis N (%)[a]			
Primary chronic glomerulonephritis N (%)	21 (20.0)	24 (24.2)	0.4652
Pyelonephritis/interstitial nephritis N (%)	20 (19.0)	15 (15.2)	0.4607
Hypertensive nephropathy/vascular disease N (%)	12 (11.4)	11 (11.1)	0.9429
Secondary glomerulonephritis/systemic diseases, including diabetes N (%)	16 (15.2)	19 (19.2)	0.4541
Familiar/hereditary renal diseases N (%)	11 (10.5)	16 (16.2)	0.2311
Aetiology unknown N (%)	20 (19.0)	11 (11.1)	0.1145
Other N (%)	6 (5.7)	7 (7.1)	0.6918
Screening laboratory parameters			
Serum phosphorus N (mmol/L)	2.10 ± 0.54	2.10 ± 0.59	0.9246
Total serum calcium N (mmol/L)	2.14 ± 0.25	2.18 ± 0.21	0.3226
Serum magnesium N (mmol/L)	1.20 ± 0.29	1.23 ± 0.28	0.5236
Serum iPTH N (pg/mL)	382.90 ± 199.07	338.18 ± 180.09	0.0946
Kt/V	1.5 ± 0.24	1.5 ± 0.22	0.4871
Disposition of covariates at baseline N (%)			
Vitamin D$_3$ (any form)	40 (38.1)	29 (29.3)	0.1841
Calcimimetics	9 (8.6)	9 (9.1)	0.8960
Dialysis type			
Haemodialysis	97 (92.4)	85 (85.6)	
Online HDF	8 (7.6)	14 (14.4)	0.1334
Dialysis fluid type (Calcium)			
other	2 (1.9)	1 (1.01)	
1.25 mmol/L	41 (39.1)	30 (30.3)	
1.50 mmol/L	62 (59.1)	68 (68.7)	0.3430

[a]More than one answer could be given.

and further efficacy endpoints were based on the full analysis set (FAS) using the Last Observation Carried Forward (LOCF) method. The FAS consisted of all patients who were randomized, took study medication and had at least one subsequent efficacy evaluation. The safety parameter evaluation was performed on the safety population (SAS), which consisted of all randomized patients who took study medication. Data are presented as means ± SD, figures are presented as means ± SEMs. For differences between groups, the least square means, i.e. the differences within-group means, appropriately adjusted for the other factors in the model, are given. As for all evaluations, the factors pooled centre and baseline value were significant, only the ones in addition to these are mentioned in the Results section.

Results

Patients and baseline characteristics

The first patient entered the study on 26 November 2007, and the last patient completed the study on 25 March 2009. Three hundred and twenty-six haemodialysis patients were enrolled in order to reach the number of patients described above. Seventy-one patients were failures during washout/run-in, the majority due to unexpectedly low serum phosphorus levels measured between screening and the third week of washout ($N = 45$). Finally, 255 patients were randomized, and 204 patients completed the study per protocol (CaMg, $N = 105$; sevelamer-HCl, $N = 99$, see Figure 1B, CONSORT diagram [29]).

The most frequent reasons for dropout after randomization were withdrawal of informed consent (CaMg: $N = 9$, sevelamer-HCl: $N = 19$) and adverse events (CaMg: $N = 4$, sevelamer-HCl: $N = 9$) (Figure 1B).

Baseline demographics, screening laboratory parameters and baseline covariates of the study patients are shown in Table 1. There were no statistically significant differences in any of the parameters between the two groups. There were also no differences between groups with regards to co-morbidities, including diabetes mellitus (24.8% in the CaMg group vs 20.2% in the sevelamer-HCl group, P = 0.4360) and the use of prior and concomitant medications including vitamin D and calcimimetics. The percentage of patients receiving any form of vitamin D was higher at baseline in the CaMg group (CaMg: 38.1%; sevelamer-HCl: 29.3%) and did not change significantly in either group. Also, the use of calcimimetics did not change over time.

The mean percentage compliance with study medication intake was close to 100% in both groups. Average daily study medication intake was slightly but signifi-
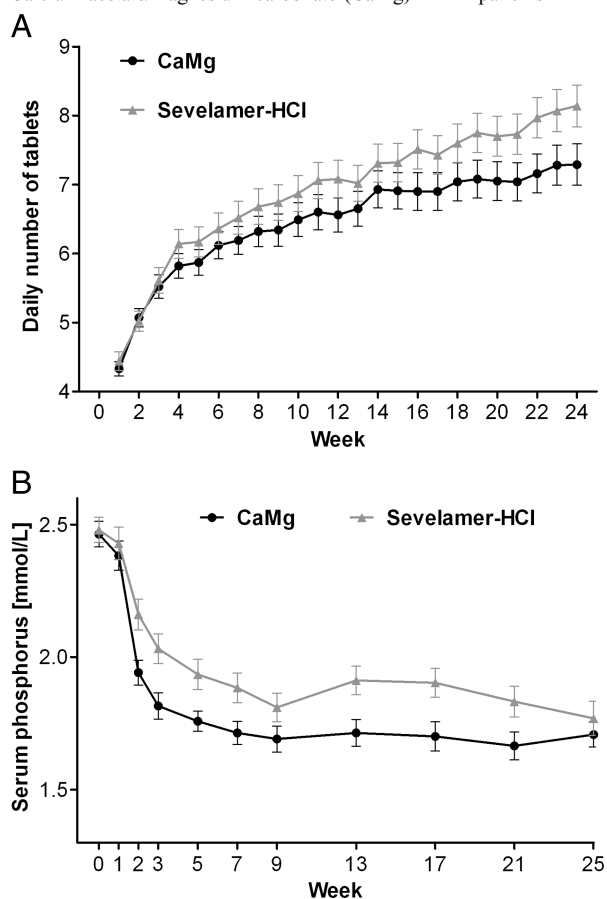
Fig. 2. (**A**) Study medication intake per day and group over time in the CaMg group (*n* = 101) and the Sevelamer-HCl group (*n* = 90) (PPS); P = 0.0420 (ANOVA). (**B**) Time course of serum phosphorus over 24 weeks for the CaMg group (*n* = 105); and the sevelamer-HCl group (*n* = 99) (PPS).

cantly higher in the sevelamer-HCl group at Week 25 (CaMg: 7.3 ± 3.03; sevelamer-HCl: 8.1 ± 2.87 tablets/day; P = 0.0420) (Figure 2A).

Primary efficacy endpoint serum phosphorus

With both study treatments, significant reductions in serum phosphorus were achieved. The mean reduction at Week 25 was not different between the CaMg group (−0.761 ± 0.5805 mmol/L; −2.356 ± 1.7972 mg/dL) and the sevelamer-HCl group (−0.711 ± 0.5850 mmol/L; −2.201 ± 0.8111 mg/dL). Serum phosphorus level achieved after 25 weeks was 1.704 ± 0.4806 mmol/L (5.276 ± 1.4879 mg/dL) in the CaMg group in comparison with 1.769 ± 0.6066 mmol/L (5.477 ± 1.8780 mg/dL) in the sevelamer-HCl group (Figure 2B; Table 2) with a treatment difference of −0.0693 mmol/L (−0.2146 mg/dL). The corresponding one-sided 97.5% confidence interval was [−∞, 0.0692 mmol/L; 0.2142 mg/dL]. As the non-inferiority margin of 0.15 mmol/L was not part of this confidence interval, the non-inferiority of CaMg against sevelamer-HCl was statistically proven (Table 2).

Further phosphorus-related efficacy parameters

The AUC of serum phosphorus was significantly lower in the CaMg group compared with the sevelamer-HCl group with a difference of −24.5264 mmol/L × days (−75.9331 mg/dL × days), (P = 0.0042). Furthermore, the number of visits when target serum phosphorus levels (≤1.78 mmol/L; 5.51 mg/dL and ≤1.45 mmol/L; 4.49 mg/dL) were reached and the time to reach these targets were significantly higher and shorter in the CaMg group in comparison with the sevelamer-HCl group (Table 2).

Calcium-related efficacy parameters

No significant differences for ionized serum calcium were seen between the groups (Table 3; Figure 3A). During the course of the study, total serum calcium increased significantly in the CaMg group, while no changes were observed in the sevelamer-HCl group (Table 3; Figure 3B). The treatment difference was 0.0477 mmol/L (0.1913 mg/dL) (P = 0.0032).

Table 2. Serum phosphorus: values at baseline and at week 25, changes from baseline, area under the curve (AUC) until Week 25, number of visits where target serum phosphorus (sP) was reached and time to reach target values

Parameter	CaMg		Sevelamer-HCl		
	N	(Mean ± SD)	N	(Mean ± SD)	P-value
Serum phosphorus (mmol/L)[a]					
Baseline	105	2.464 ± 0.4930	99	2.480 ± 0.4704	na[c]
Week 25	105	1.704 ± 0.4806		1.769 ± 0.6066	na[c]
Change at Week 25	105	−0.761 ± 0.5805	99	−0.711 ± 0.5850	na[c]
Treatment difference (LS-means) [confidence interval]		−0.0693 [-∞, 0.0692]			
AUC of serum phosphorus (mmol/L × days)[b]	122	298.935 ± 72.0315	122	323.914 ± 81.2415	
Treatment difference (LS-means) [confidence interval]		−24.5264 [−41.1978, −7.8550]			0.0042
No. of visits (N) target sP (≤ 1.78 mmol/L) reached[b]	122	4.91 ± 3.275	122	3.96 ± 3.363	0.0198
No. of visits (N) target sP (≤ 1.45 mmol/L) reached[b]	122	2.65 ± 2.784	122	1.81 ± 2.420	0.0067
Time (days) to target sP (≤ 1.78 mmol/L)[b]	122	16	122	30	0.0018
Time (days) to target sP (≤ 1.45 mmol/L)[b]	122	57	122	140	0.0052

[a](PPS, N = 204).
[b](FAS, N = 244).
[c]Not applicable.

Table 3. Serum calcium and magnesium baseline values, changes from baseline values at Week 25 and number of visits > ULN and <LLN, as well as above and below K/DOQI range (for Ca) (FAS, *N* = 244)

Parameter	CaMg		Sevelamer-HCl		P-value
	N	(Mean ± SD)	*N*	(Mean ± SD)	
Ionized calcium (mmol/L)					
Baseline	113	1.071 ± 0.1608	112	1.076 ± 0.1306	
Week 25	120	1.104 ± 0.1210	119	1.113 ± 0.1063	
Change at Week 25	112	0.036 ± 0.1702	110	0.036 ± 0.1369	
Treatment difference (LS-means) [confidence interval]		−0.0015 [−0.0294, 0.0264]			0.9173
Total serum calcium (mmol/L)					
Baseline	122	2.148 ± 0.2288	122	2.185 ± 0.1820	
Week 25	122	2.219 ± 0.1565	122	2.189 ± 0.1574	
Change at Week 25	122	0.071 ± 0.1790	122	0.004 ± 0.1522	
Treatment difference (LS-means) [confidence interval]		0.0477 [0.0162, 0.0793]			0.0032
No. of visits Ca > ULN (2.6 mmol/L)	122	0.11 ± 0.460	122	0.07 ± 0.563	0.2374
No. of visits Ca < LLN (2.2 mmol/L)	122	4.31 ± 3.695	122	4.55 ± 3.827	0.6839
No. of visits Ca > K/DOQI range (2.37 mmol/L)	122	1.81 ± 2.881	122	1.25 ± 2.412	0.1005
No. of visits Ca < K/DOQI range (2.10 mmol/L)	122	2.23 ± 2.911	122	2.38 ± 3.178	0.4809
Serum magnesium (mmol/L)					
Baseline	122	0.993 ± 0.1544	122	0.996 ± 0.1613	
Week 25	122	1.297 ± 0.2547	122	1.039 ± 0.1851	
Change at Week 25	122	0.304 ± 0.2285	122	0.043 ± 0.1453	
Treatment difference (LS-means) [confidence interval]		0.2597 [0.2137, 0.3056]			<0.0001
No. of visits Mg > ULN (1.05 mmol/L)	122	7.86 ± 2.514	122	4.10 ± 3.797	<0.0001
No. of visits Mg < LLN (0.65 mmol/L)	122	0.04 ± 0.237	122	0.04 ± 0.237	1.0000

Response rates at Week 25 (K/DOQI range: serum calcium between 2.10 and 2.37 mmol/L; 8.41 and 9.50 mg/dL) [30] were also not different between CaMg and Sevelamer-HCl, i.e. 65.6% vs 60.7%, respectively (P = 0.3158). The number of visits of serum Ca > ULN (>2.6 mmol/L; >10.42 mg/dL) and serum Ca < LLN (<2.2 mmol/L; <8.82 mg/dL), as well as above and below the K/DOQI ranges, which are summarized in Table 3, also did not differ. All total serum calcium-related evaluations have been repeated with albumin corrected total serum calcium, confirming the above-mentioned results (data not shown).

Magnesium-related efficacy parameters

Serum magnesium values at baseline and changes from baseline, number of episodes of Mg > ULN (>1.05 mmol/L; 2.55 mg/dL) and of Mg < LLN (<0.65 mmol/L; 1.58 mg/dL) after 24 weeks of treatment are summarized in Table 3. During the course of the study, serum magnesium increased significantly in the CaMg group, while only a slight increase in the sevelamer-HCl group was observed (Figure 4). The treatment difference was 0.2597 mmol/L (0.6313 mg/dL) (P < 0.0001). The number of episodes of Mg > ULN were higher in the CaMg group compared with the sevelamer-HCl group. In both treatment groups, nearly no episodes of Mg < LLN (0.04 ± 0.237 for both groups) occurred during the course of the study.

iPTH and alkaline phosphatase

iPTH decreased during the course of the study in both groups until Week 9 and then increased significantly in the sevelamer-HCl group but without any further significant change in the CaMg group (Table 4, Figure 5). At Week 25, the treatment difference was −64.4773 pg/mL which was statistically significant (P = 0.0085). The AUC of iPTH was also significantly lower in the CaMg group (data not shown). Alkaline phosphatase (AP) increased significantly in both groups until Week 9 (P < 0.0001 for both groups). Thereafter, AP increased like iPTH in the sevelamer-HCl group but not in the CaMg group. At Week 25, the treatment difference was statistically significantly different (P < 0.0001) with the respective mean difference of −24.0067 U/L (Table 4).

Other biochemical parameters

Values of other biochemical parameters are summarized in Table 5. After 25 weeks, a significant difference in actual bicarbonate and base excess was noted between groups. In addition, LDL-cholesterol decreased significantly in the sevelamer-HCl group. No change was observed in the CaMg group. Neither high-density lipoprotein-cholesterol nor triglycerides showed any significant change within groups or difference between groups (data not shown). Serum potassium increased in the CaMg group and stayed almost the same in the sevelamer-HCl group.

Gastrointestinal quality of life index

The GIQLI did not change over time and was not different between groups.

Safety parameters

Adverse events. The number of patients with AEs and SAEs were comparable in both treatment groups. There was no difference regarding occurrence of any AEs between groups. In the CaMg group, fewer patients experi-
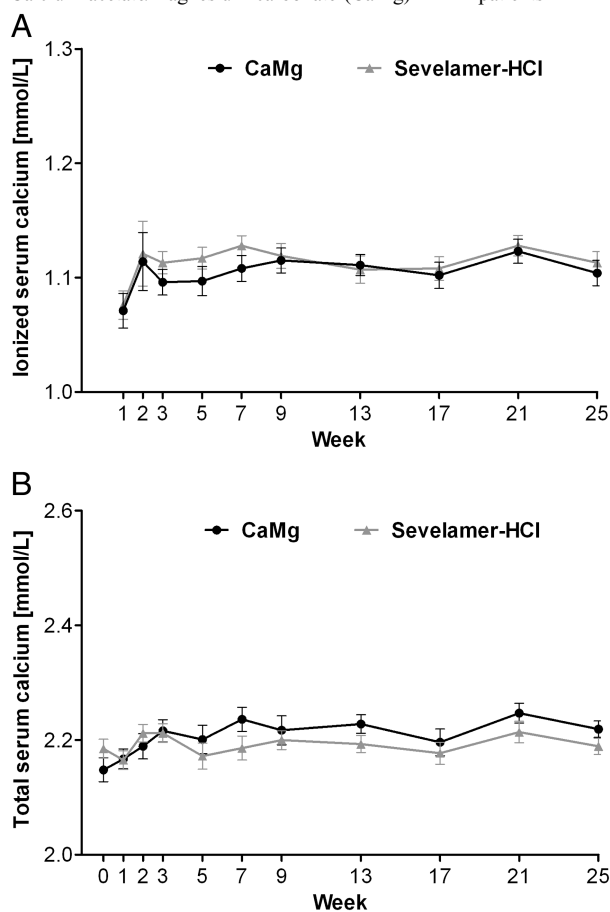
A

B

Fig. 3. (**A**) Time course of ionized serum calcium of the CaMg group ($n = 120$) and of the sevelamer-HCl group ($n = 119$) (FAS); P = 0.9173 (ANCOVA). (**B**) Time course of total serum calcium of the CaMg group ($n = 122$) and of the sevelamer-HCl group ($n = 122$) (FAS); P = 0.0032 (ANCOVA).

Fig. 4. Time course of serum magnesium of the CaMg group ($n = 122$) and of the sevelamer-HCl group ($n = 122$) (FAS); P <0.0001 (ANCOVA).

Discussion

The main purpose of this study was to determine whether treatment of hyperphosphataemia could be achieved efficiently with a phosphate binder combining calcium and magnesium salts in comparison with a well-established non-calcium-containing phosphate binder. Confirming the study hypothesis, serum phosphorus levels at Week 25 were at least as efficiently lowered with the use of CaMg as with sevelamer-HCl. Furthermore, when serum phosphorus control over time was evaluated, it was significantly lower in the group assigned to the CaMg phosphate binder (P = 0.0042). In addition, both predefined target ranges of serum phosphorus (≤1.78 mmol/L; 5.51 mg/dL and ≤1.45 mmol/L; 4.49 mg/dL) were significantly more often reached with CaMg (P = 0.0198 and P = 0.0067, respectively). Furthermore, the time to target was shorter with CaMg; as an example, the time needed for 50% of patients to achieve a target of serum phosphorus ≤1.45 mmol/L was reduced by 84 days. Taken together, these results suggest that the control of serum phosphorus levels could be attained more easily with CaMg. The number of tablets needed to achieve these results was slightly lower in the CaMg group and overall comparable or lower than in other studies using calcium salts [9,10,12]. Also, the described phosphate-lowering effect in this study is comparable with [10,31] or superior to [9,10,32] other studies, in which pure calcium salts were investigated in comparison with sevelamer-HCl. This is in line with recent systematic reviews [33,34]. However, in general it is a challenge to control serum phosphorus adequately [5].

Sevelamer was chosen as a comparator because one of the discussed advantages of sevelamer use is its lack of producing a positive calcium burden, an observation that was repeatedly linked to a decreased rate of calcification [31,35–38]. In this study with a calcium and magnesium-containing phosphate binder, we did not find any difference in ionized serum calcium levels, a small, albeit statistically significant difference in total serum calcium of 0.0477 mmol/L (0.1908 mg/dL) and very few, less than one, hypercalcaemic episodes with no difference between groups. In contrast, in studies where pure calcium salts were administered, a serum

enced AEs leading to study withdrawal (Figure 1B). The intensity of about 80% of AEs was classified as mild. A total of 16.1% AEs in the CaMg group and 19.7% in sevelamer-HCl-treated patients were classified as moderate; 4.0% and 2.5% of AEs, respectively, were judged to be severe. None of the SAEs was judged to be related; their number was slightly lower in the CaMg group. Related gastrointestinal AEs were more frequently noted in the sevelamer-HCl group (23.6% of subjects vs 13.6% in the CaMg group). Related 'metabolism disorders', such as electrolyte disturbances, were more frequent in the CaMg group, most of them were episodes of asymptomatic hypermagnesaemia reported as related AE by the treating physician (8.8% vs 2.4% in the sevelamer-HCl group). In none of the other AEs was there any difference between groups, particularly in relation to cardiac dysrhythmia, muscle spasm or cramps.

Other haematology, biochemistry parameters, vital signs. Mean ± SD values of haematology, bedside laboratory, Kt/V and serum chemistry parameters fluctuated within expected normal variation in both treatment groups. The same applied to vital signs and ECG.
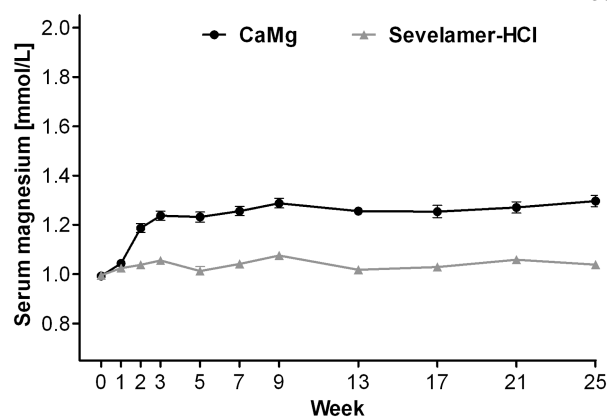
Table 4. Serum iPTH and alkaline phosphatase: values at baseline, week 9 and 25 and changes from baseline (FAS, $N = 244$)

Parameter	CaMg		Sevelamer-HCl		P-value
	N	(Mean ± SD)	N	(Mean ± SD)	
Serum iPTH (pg/mL)					
Baseline	119	450.84 ± 273.494	118	438.97 ± 238.112	
Week 9	118	361.25 ± 278.526	112	357.71 ± 201.909	
Change at Week 9	115	−85.28 ± 195.308	108	−72.69 ± 154.429	0.6059
Week 25	118	337.20 ± 266.357	112	384.67 ± 226.349	
Change at Week 25	115	−109.24 ± 229.903	108	−43.98 ± 171.438	
Treatment difference (LS-means) [confidence interval]		−64.4773 [−112.3087, −16.6459]			0.0085
Significant covariate factor					
Intake of calcimimetics					0.0211
Serum alkaline phosphatase (U/L)					
Baseline	122	100.39 ± 49.689	122	93.00 ± 38.384	
Week 9	116	108.44 ± 52.237	104	120.42 ± 52.675	
Change at Week 9	116	8.85 ± 23.523	104	25.32 ± 27.006	<0.0001
Week 25	116	106.84 ± 53.803	105	125.93 ± 53.479	
Change at Week 25	116	7.26 ± 32.438	105	30.90 ± 34.101	
Treatment difference (LS-means) [confidence interval]		−24.0067 [−32.8963, −15.1175]			<0.0001

calcium increase of up to 0.15 mmol/L (0.6 mg/dL) was observed [9,10,31,32]. The number of hypercalcaemic episodes was also much more pronounced in other studies [10,31,35,37,39]. These results may indicate a clinically meaningful reduction in calcium burden, as the daily elemental calcium applied in this study was only between 25% and 50% of other studies with pure calcium salts [10,12,15,40]. Nevertheless, it was beyond the scope of this study to assess calcium balance, and specific trials would be needed to address this question.

Magnesium-based phosphate binders have been used in the past with excellent results [14–16,24]. However, there always has been some apprehension related to the potential negative consequences of a rise in serum magnesium. The observed increase in serum magnesium in the CaMg group was expected based on past experience [19] and comparable with other studies [15,41–44]. In our study, a plateau was reached at around 7–9 weeks, which was not associated with any clinical side effects, especially not with an apparent increased frequency of diarrhoea. An elevation of serum magnesium levels is common in patients on haemodialysis [21,25,45,46], even when not treated with a magnesium-containing phosphate binder. Serum magnesium levels are largely dependent on dialysis fluid concentration as the only possibility to eliminate magnesium is via dialysis once residual renal function has disappeared [46–48]. In our study population, mean serum magnesium level was already elevated at screening (Table 1). More than 40% of patients had been treated with a dialysis fluid magnesium concentration of 1.00 mmol/L (2.43 mg/dL); their mean serum magnesium concentration was 1.34 mmol/L, which was considerably higher than the mean Mg concentrations at Week 25 in the CaMg group. Therefore, the general recommendation to use a dialysis fluid with a Mg concentration of 0.5 mmol/L or lower, independent of the phosphate binder used, might be considered. However, the optimal dialysate Mg concentration can only be established by specifically designed studies. Magnesium has been described as having a much wider therapeutic range than calcium, and as such hypermagnesaemia at levels up to 1.5 mmol/L (3.65 mg/dL) is not associated with clinical effects [14,43]. Neuromuscular side effects may only become apparent at levels of 2 to 3 mmol/L (4.86 to 7.29 mg/dL) [23].

There is concern that increased serum magnesium levels may have an effect on bone in dialysis patients dependent on its PTH-lowering effect as well as independently of it (discussed in [23]). It was not the aim of this study to investigate bone histology, but identifying the role of magnesium in the development of bone mineral disorders remains an important open question.

On the other hand, it is also important to emphasize the other 'face of the coin': magnesium is a potent inhibitor of the calcification process, as has been shown in vitro [49] and in experimental animal studies which demonstrated that experimental magnesium deficiency is related to the development of dystrophic calcifications [50]. In addition, also in CKD 5 and the general population, mildly elevated magnesium levels have been associ-
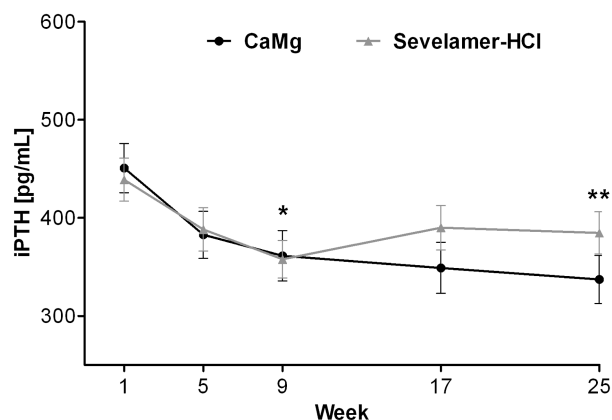

Fig. 5. Time course of iPTH of the CaMg group ($n = 118$) and of the sevelamer-HCl group ($n = 112$) (FAS), P = 0.0085 (ANCOVA); within-group changes CaMg: *Week 9 vs baseline: P < 0.0001, **Week 25 vs Week 9: P = 0.0768; within-group changes sevelamer-HCL: * Week 9 vs baseline: P = 0.0090, ** Week 25 vs Week 9: P = 0.0242.

Table 5. Actual bicarbonate, base excess, LDL-cholesterol and potassium at baseline, changes from baseline and at Week 25 (FAS, $N = 244$)

Parameter	CaMg		Sevelamer-HCl		P-value
	N	(Mean ± SD)	N	(Mean ± SD)	
Actual bicarbonate (mmol/L)					
Baseline	106	21.086 ± 2.6587	102	21.588 ± 3.4209	
Week 25	117	22.496 ± 3.3095	114	21.086 ± 4.0833	
Change at Week 25	106	1.500 ± 3.1117	101	−0.823 ± 4.3323	<0.0001
Treatment difference (LS-means) [confidence interval]		1.8435 [0.9462, 2.7408]			<0.0001
Base excess					
Baseline	110	−3.729 ± 2.9518	107	−3.133 ± 3.6341	
Week 25	121	−2.340 ± 3.4567	118	−3.702 ± 4.2831	
Change at Week 25	110	1.594 ± 3.2531	106	−0.853 ± 4.3851	<0.0001
Treatment difference (LS-means) [confidence interval]		1.9466 [1.0171, 2.8761]			<0.0001
LDL-cholesterol (mg/dL)					
Baseline	122	112.71 ± 31.717	122	115.03 ± 30.346	
Week 25	116	110.19 ± 30.060	105	87.17 ± 27.870	
Change at Week 25	116	−2.85 ± 21.458	105	−28.09 ± 25.746	
Treatment difference (LS-means) [confidence interval]		23.5287 [17.9405, 29.1169]			<0.0001
Potassium (mmol/L)					
Baseline	122	5.50 ± 0.967	122	5.36 ± 0.732	
Week 25	118	5.79 ± 0.793	112	5.39 ± 0.807	
Change at Week 25	118	0.27 ± 0.968	112	0.03 ± 0.776	
Treatment difference (LS-means) [confidence interval]		0.3192 [0.1250, 0.5134]			0.0014

ated with benefits, such as reduced cardiovascular calcifications, reduced hypertension and reduced mortality [23,24]. Generally, CaMg was well tolerated with an AE profile consistent with the co-morbidities of a dialysis patient. AEs definitively related to the study drug were significantly more frequent in the sevelamer-HCl group and were gastrointestinal disorders; otherwise, except for episodes of hypermagnaesemia, no difference was noted between groups in particular regarding hyper- and hypocalcaemia, indicating an overall favourable tolerability profile of CaMg.

Reflecting the KDIGO CKD-MBD guideline [7], CaMg offers an alternative phosphate binder option as switching from pure calcium salts to CaMg may be a possibility restricting the dose of calcium.

In conclusion, CaMg was non-inferior compared with a well-established non-calcium-containing phosphate binder at lowering serum phophorus in this controlled, randomized, investigator-masked study in 255 patients. There was a small increase in total serum calcium and no change in ionized calcium. CaMg led to an asymptomatic increase in serum magnesium and had a good tolerability profile.

Supplementary data

Supplementary data is available online at http://ndt.oxford-journals.org.

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Variations in C-reactive protein during a single haemodialysis session do not associate with mortality

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Abstract

Background. An increase in C-reactive protein (CRP) levels during a single haemodialysis (HD) session has been associated with mortality. These associations, however, are difficult to understand from the current understanding of CRP metabolism.

Methods. In 190 Swedish haemodialysis (HD) patients from the Mapping of Inflammatory Markers in Chronic Kidney Disease (MIMICK) cohort, CRP was measured before and after a HD session. During follow-up, events of death and censoring were recorded, and hazard ratios were calculated and analysed as a function of CRP variation. Results were replicated in 94 Dutch HD patients from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). In this cohort, also correlation and kappa statistics were calculated to assess concordance in CRP changes amid multiple dialysis sessions from the same individuals.

Results. In both cohorts, mean CRP values did not increase during a single HD session. In the MIMICK, median (interquartile range) dialysis vintage was 29.0 (14.8–57.0) months. In both crude [hazard ratio (95% confidence interval): 1.008 (0.971–1.047)] and multivariate Cox models [0.996 (0.949–1.046)], no association was observed with mortality. In the NECOSAD, individuals endured 6.0 (6.0–12.0) months on dialysis. No association was found with mortality neither in a crude [0.961 (0.908–1.018)] nor in an adjusted analysis [0.978 (0.923–1.037)]. Finally, the concordance between changes in different sessions was poor.

Conclusions. CRP changes during a single HD session do not associate with mortality, thereby adding to the biological uncertainty concerning the ability of CRP to rise in such a short period.

Keywords: chronic kidney disease; C-reactive protein; hemodialysis; inflammatory response; mortality

Introduction

Patients with chronic kidney disease (CKD), and especially those with end-stage renal disease (ESRD), are at considerable increased risk of premature death [1]. Since the surplus in CKD mortality is strongly associated with a state of persistent inflammation and chronic activation of the acute phase response, the identification of factors involved in the pathogenesis of the inflammatory response is of considerable therapeutic interest [2–5].

In addition to CKD-related factors, such as decreasing renal function, co-morbidities, infections or the uraemic environment per se [6], the haemodialysis (HD) procedure has been suggested to play a pivotal role in the development of inflammation. Indeed, several studies have shown that intradialytic activation is associated with increased fractional synthesis rates of albumin and fibrinogen as well as of pro-inflammatory cytokines, leading to a state of increased