Calcium ketoglutarate *versus* calcium acetate for treatment of hyperphosphataemia in patients on maintenance haemodialysis: a cross-over study

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**Abstract** Since dietary restrictions and phosphorus removal by haemodialysis (HD) are not sufficient to control serum phosphate (s-phosphate) levels in dialysis patients the use of oral phosphate binders is mandatory. Calcium ketoglutarate (CaKE) is an analogue of glutamic acid exerting phosphate binding properties. Therefore we compared this substance to calcium acetate (CaAC) in a 24-weeks open cross-over trial in 28 maintenance HD patients. Medications and HD prescriptions were kept unchanged during the trial. Following 2 weeks of withdrawal of phosphate binders, patients were randomly assigned to one of the calcium salts for 12 weeks; after a second withdrawal of 2 weeks, all patients were shifted to the other treatment for another 12 weeks. All patients received equimolar doses of CaKE and CaAC with respect to the amount of prescribed elemental calcium. Treatment with CaAC and CaKE significantly reduced s-phosphate levels after 4 weeks (CaAC 1.95 ± 0.6 vs 2.4 ± 0.53 mmol/l, *P* = 0.004; CaKE 1.95 ± 0.4 vs 2.47 ± 0.63 mmol/l, *P* = 0.0001) reaching a virtually stable plateau over the remaining observation time without significant differences between the groups. The incidence of hypercalcaemia defined as a serum calcium level ≥2.8 mmol/l was significantly higher in CaAC than in CaKE treated patients (*n* = 8 vs *n* = 1, *P* = 0.03). There were no significant differences in serum intact parathyroid hormone (PTH) bicarbonate, albumin or calcitriol levels between the groups after 12 weeks treatment. We conclude that CaKE is as effective as CaAC for treatment of hyperphosphataemia in chronic HD patients and may be particularly helpful in patients who are prone to develop hypercalcaemia.

**Key words:** hypercalcaemia; phosphate binders; renal insufficiency

**Introduction**

Virtually all patients on chronic haemodialysis (HD) develop hyperphosphataemia with its known detrimental impact on the progression of secondary hyperparathyroidism, renal osteodystrophy and vascular calcifications [1,2]. Since the surplus of phosphorus can not sufficiently be removed by HD or reasonably restricted by dietary means the use of oral phosphate binders is necessary in almost all patients to control s-phosphorus levels [2]. Phosphate binders based on calcium salts like calcium carbonate (CaCA) or calcium acetate (CaAC) have been used successfully in the past to treat hyperphosphataemia widely displacing the previously used more toxic aluminium containing agents [2]. However, the main side effect of these substances, hypercalcaemia, limits their use in patients prone to this complication [2]. Calcium ketoglutarate (CaKE), a semi-synthetic analogue of the amino acid glutamic acid exerts phosphate binding properties apparently without inducing hypercalcaemia [3,4] or other side effects as were shown in uncontrolled studies by Zimmermann *et al.* in chronic HD patients. Furthermore, putatively beneficial effects on the nutrional status of dialysis patients were described by Riedel and colleagues [5]. CaAC is regarded as the most potent calcium based phosphate binder both *in vitro* and *in vivo* [6,7]. So far no study has investigated if CaKE is equally effective when compared to CaAC. Since calcium is the phosphate binding moiety of the above mentioned substances we designed a study to compare CaAC *versus* CaKE given in equimolar amounts of elemental calcium (Ca²⁺) with respect to their phosphate binding potency and the incidence of hypercalcaemia in patients on maintenance HD.

**Methods**

**Subjects**

The participating centres were the Hospital’s Dialysis Unit within the Vth Department of Medicine, University Hospital...
Mannheim and the Dialysis Centre Drs Zimmermann/Wassmer, Mannheim, Germany. All patients had chronic renal failure and were on maintenance HD for at least 12 months. Thirty two stable chronic HD patients were enrolled after giving informed consent. Inclusion criteria were hyperphosphataemia after withdrawal of phosphate binding agents (s-phosphorus > 1.7 mmol/l), known adherence to therapy, prior dialysis time > 12 months and an intact PTH level smaller than the ten-fold upper normal level. Previously, control of s-phosphorus was obtained by CaCA, CaKE or CaKE given in dosages of between 1000 and 2000 mg of Ca²⁺. Of the 32 patients initially enrolled 20 had been treated with CaKE before. Prior, and during the study, all patients received 3–5 h dialysis treatment three times per week using a bicarbonate dialysate with a calcium concentration between 1.25 and 1.75 mmol/l. No patient was taking vitamin D supplements. In both dialysis prescription and drug treatment were kept unchanged except the phosphate binders during the trial. A randomized open cross over design was employed consisting of two treatment periods lasting 12 weeks each. After withdrawal of all phosphate binders for 14 days hyperphosphataemic patients were randomized to start on either CaAC (Renacet, Nephromed Bartz GmbH, Hüttengen, Germany) or CaKE (Calcium-Ketoglutarat, Nephromed Bartz GmbH, Hüttengen, Germany). Following a second withdrawal of 14 days after 12 weeks, all patients crossed over to the other treatment for another 12 weeks. For each drug patients were instructed not to change their dietary habits and to take the phosphate binders with food in the middle of each main meal.

**Materials**

CaAC was prescribed in a 475 mg capsule form corresponding to 120 mg Ca. CaKE was prepared from the manufacturer only for the purpose of this study in a special 2900 mg soluble granulate form containing 860 mg ketoglutarate and 240 mg Ca²⁺ in order to facilitate the prescription of equimolar amounts of Ca²⁺. Prior to use, the granulate was dissolved in 25–50 ml of water. Dosages of both drugs followed an empirical formula [3] depending on s-phosphate levels at the end of the withdrawal period, body weight and the thus calculated ‘phosphate surplus’ (PS): PS units = (change s-phosphate mmol/l exceeding 1.4 mmol/l) × body weight in kg. Each 20 units of PS corresponded to 1 × 2 capsules of CaAC or 1 × 1 soluble granulate of CaKE both containing a total amount of 240 mg Ca²⁺ (example: s-phosphate 2.4, body weight 60 kg; change = 2.4 mmol/l – 1.4 mmol/l = 1 mmol/l, 1 mmol/l × 60 kg = 60 units PS, 60 units/20 = 3 = 3 × 2 capsules CaAC or 3 × 1 granulate CaKE). After the initial prescription, the dosages of both substances were kept constant during each study period. No dose adjustments were made in case normal s-phosphate levels were not achieved. Serum analysis included predialysis determination of baseline values at the end of withdrawal followed by 2-weekly predialysis controls of phosphate, calcium and venous bicarbonate levels. Intact PTH, calcitriol and s-albumine values were obtained at the start and at the end of each treatment period. The study was approved by the Human Studies Research Review Committee located at the University Hospital Mannheim, Faculty of Clinical Medicine of the University of Heidelberg.

**Laboratory methods**

Intact PTH was measured by RIA (Nichols Institute Diagnostika GmbH, Bad Nauheim, Germany). The normal range in our laboratory is 2–6 pmol/l. All other parameters were determined by standard techniques.

**Statistics**

Thirty-two patients were originally enrolled in the trial. Statistical analysis was performed on 28 patients who completed the whole study (10 women, 18 men, mean age 61 years, range 37–87 years). Results are given as mean values ± SD. Comparisons of mean values were made by the Students t-test for paired data; for comparison of the incidence of hypercalcaemia Fisher’s exact test was used. A P value < 0.05 was considered statistically significant.

**Results**

Of the 32 patients initially enrolled, 28 completed both periods of the study. Of the remaining four, one died of myocardial infarction, one was admitted due to a severe intercurrent illness, one received a kidney transplant, and one took an unexpected holiday for three months. After the 14-day washout periods s-phosphate levels were significantly elevated when compared to initial values obtained with previous phosphate-binders (CaAC 2.4 ± 0.53 vs 2.16 ± 0.52 mmol/l, P = 0.0004; CaKE 2.47 ± 0.63 vs 2.12 ± 0.52 mmol/l, P = 0.0005). Treatment with CaAC and CaKE significantly reduced s-phosphate levels after 4 weeks, (CaAC 1.95 ± 0.6 vs 2.4 ± 0.53 mmol/l, P = 0.004; CaKE 1.95 ± 0.4 vs 2.47 ± 0.63 mmol/l, P = 0.0001) reaching a virtually stable plateau over the remaining observation time without significant differences between both groups. From the eighth week on there was a tendency towards lower s-phosphate levels in the CaAC group, however these differences never reached a statistically significant level (Figures 1 and 2). In both groups there was an unsignificant increase in s-calcium concentrations during the study periods (Figure 3). The incidence of hypercalcaemia was not different between the groups when defined as s-calcium levels ≥ 2.6 mmol/l (CaAC: 16 episodes of 168 measurements; CaKE: 14 of 168, P = NS). However, more severe hypercalcaemia defined as s-calcium levels of ≥ 2.8 mmol/l occurred significantly more in CaAC treated patients when compared to CaKE (eight episodes of 168 measurements vs 1 of 168, P < 0.05). The amount of ingested Ca²⁺ per day was not significantly different between the groups (CaAC 851 ± 473 vs CaKE 920 ± 571 mg). Intact PTH, calcitriol, albumin and venous bicarbonate levels were neither significantly different between the groups at study entry or after 12 weeks treatment (Table 1).

**Discussion**

In this open randomized cross over study in 28 chronic haemodialysis patients we demonstrated clearly that CaKE, when given in equimolar amounts of Ca²⁺, exerts the same phosphate binding effect as CaAC.
Despite a stable significant reduction of s-phosphate levels over the whole study time in both groups normal s-phosphate levels were not reached because the initial dosage based on an empirical formula was too small and we did not change the initial dosage since we wanted to compare both substances given in equimolar amounts of Ca\(^{2+}\). This is reflected by the relatively small amount of prescribed Ca\(^{2+}\) (CaAC 851 ± 473 vs CaKE 920 ± 571 mg, n.s."") which was not significantly different between the groups. Generally, more than a two-fold amount of Ca\(^{2+}\) is required both for CaAC and CaKE to decrease s-phosphate levels back in the normal range [2,8]. Thus, despite the significant reduction of serum phosphorus induced by both agents...
phosphate control was surely not adequate during our study.

The incidence of severe hypercalcaemia defined as s-calcium level of > 2.8 mmol/l was significantly higher in CaAC treated patients when compared to CaKE. Recently, it was demonstrated in an unblinded cross-over study of 10 patients, that CaKE had the same phosphate binding capacity but induced significantly lesser increments in s-calcium levels when compared to CaCA [8]. This in vivo finding corresponds to in vitro findings, that CaKE has a similar phosphate-binding effect as CaCA with a smaller amount of Ca\(^{2+}\) available for resorption [9]. Furthermore, Zimmermann et al. in their two reports of successful use of CaKE as an phosphate binding agents reported no occurrence of significant hypercalcaemia [3,4]. Thus CaKE showed the same phosphate binding potency as the two well established phosphate binders CaCA and CaAC. However, the propensity of CaCA to increase s-calcium levels or of CaAC to induce hypercalcaemia seems not to be shared by CaKE making it the ideal agent for patients prone to hypercalcaemia.

Bro et al. [8] reported a high incidence of gastrointestinal complaints in haemodialysis patients receiving CaKE. In their study comparing CaKE to calcium carbonate in an open cross over design 29% patients were withdrawn from CaKE therapy within the first 2 weeks due to gastrointestinal symptoms like vomiting, anorexia and diarrhoea. However, Bro et al. stated also that all of these patients had pre-existing gastrointestinal symptoms. In contrast, none of our patients in the CaKE limb developed these symptoms. In our centres CaKE had been used for about 10 years and it is our general impression that it is a very well tolerated drug with no special gastrointestinal side effects. This is supported by studies from Zimmermann and Riedel who also reported no gastrointestinal complaints using CaKE in a similar dosage of 900–1000 mg elemental calcium per day in haemodialysis patients treated up to 36 months [3–5]. Nevertheless, the dosage of elemental calcium which was used in these studies as well as in our study was rather low and not sufficient to control phosphate levels. Thus, besides the possibility that CaKE is not well tolerated in patients with

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**Fig. 3.** S-calcium levels during 12 weeks treatment with CaAC or CaKE. The values represent means ± SD.

**Table 1.** Values for intact PTH, s-albumin, s-calcitriol and venous bicarbonate at study entry and after 12 weeks treatment with CaAC or CaKE. The values represent means ± SD

<table>
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<tr>
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<th>CaKE Entry/after 12 weeks</th>
<th>CaAC Entry/after 12 weeks</th>
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<tbody>
<tr>
<td>Parathormone (PTH) (pmol/l)</td>
<td>20.6 ± 15.6/18.5 ± 14.1</td>
<td>21.4 ± 13.3/19.4 ± 16.7</td>
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<tr>
<td>Albumin (g/l)</td>
<td>38.2 ± 5.3/39.4 ± 4.8</td>
<td>37.9 ± 4.8/38.3 ± 4.1</td>
</tr>
<tr>
<td>Calcitriol (ng/l)</td>
<td>23.0 ± 11.7/22.8 ± 12.2</td>
<td>20.9 ± 6.4/19.9 ± 8.3</td>
</tr>
<tr>
<td>Venous bicarbonate (mmol/l)</td>
<td>20.4 ± 1.6/22.5 ± 3.5</td>
<td>20.5 ± 2.6/21.2 ± 1.8</td>
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pre-existing gastrointestinal complaints, the apparent paucity of gastrointestinal side effects could be a dose related phenomenon since Bro et al. used more than twice as much CaKE, reflected by a mean intake of elemental calcium of 2.44 g a day after 12 weeks treatment. However, all symptoms appeared in the first 14 days of treatment when the dosage of CaKE was comparable to that we used. Thus, the exact reason for this discrepancy in side effects remains obscure but may be related to the fact that in our centres both patients and nephrologists are used to CaKE and is therefore not considered to be a new drug with potential unknown side effects. Moreover 20 out of the 32 patients initially included had been treated with CaKE before study start, and were therefore familiar with this drug.

The main disadvantage of CaKE is its relatively high price when compared to CaAC or CaCA [8]. Thus, besides its potential usefulness in patients prone to hypercalcemia, its putative anabolic effect thereby improving malnutrition in haemodialysis may justify a more widespread use of this agent. The rationale for this consideration is the fact, that ketoglutarate is a central metabolite of the tricarboxylic acid cycle serving as a precursor for several non-essential amino acids [10]. In this context Riedel et al. have shown recently that in haemodialysis patients after 12 months of treatment with a similar amount of CaKE as in our study not only s-phosphate was reduced but plasma concentrations of l-arginine, proline and histidine were increased as well as was the body weight [5]. Furthermore, Kardasz et al. reported improved acid-base status, increased levels of certain s-amino acids and a slower rise of s-creatinine after 6 months of treatment with CaKE in patients with chronic renal failure [11]. Interestingly, studies by a Swedish workgroup demonstrated that in patients undergoing elective abdominal surgery, ornithine-alpha-ketoglutarate or alpha-ketoglutarate supplementation added to total parenteral nutrition decreased muscle protein catabolism after surgical trauma [12–14]. Taken together these data suggest that CaKE exerts an anabolic and nitrogen sparing effect preventing muscle breakdown in states of distress. In our study, s-albumin as a marker for the nutritional status of dialysis patients [15] was slightly higher in CaKE treated patients when compared to CaAC, however this was not statistically significant. However, the study periods might be too short to reveal differences between the groups and our trial was not designed to investigate nutritional alterations. Since malnutrition is frequent among dialysis patients [16] and has a major impact on their outcome [15] further studies are warranted to investigate the intriguing anabolic property of CaKE.

References

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