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Effect of a magnesium-based phosphate binder on medial calcification in a rat model of uremia

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Calcium-based phosphate binders are used to control hyperphosphatemia; however, they promote hypercalcemia and may accelerate aortic calcification. Here we compared the effect of a phosphate binder containing calcium acetate and magnesium carbonate (CaMg) to that of sevelamer carbonate on the development of medial calcification in rats with chronic renal failure induced by an adenine diet for 4 weeks. After 1 week, rats with chronic renal failure were treated with vehicle, 375 or 750 mg/kg CaMg, or 750 mg/kg sevelamer by daily gavage for 5 weeks. Renal function was significantly impaired in all groups. Vehicle-treated rats with chronic renal failure developed severe hyperphosphatemia, but this was controlled in treated groups, particularly by CaMg. Neither CaMg nor sevelamer increased serum calcium ion levels. Induction of chronic renal failure significantly increased serum PTH, dose-dependently prevented by CaMg but not sevelamer. The aortic calcium content was significantly reduced by CaMg but not by sevelamer. The percent calcified area of the aorta was significantly lower than vehicle-treated animals for all three groups. The presence of aortic calcification was associated with increased *sox9*, *bmp-2*, and *matrix gla protein* expression, but this did not differ in the treatment groups. Calcium content in the carotid artery was lower with sevelamer than with CaMg but that in the femoral artery did not differ between groups. Thus, treatment with either CaMg or sevelamer effectively controlled serum phosphate levels in CRF rats and reduced aortic calcification.

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Increased serum phosphate concentrations play a role in transdifferentiation of vascular smooth muscle cells toward osteochondrogenic cells that lead to mineralization of the tunica media of large blood vessels in patients with chronic kidney disease.[1] This biological and bone-resembling process is now well recognized as an important mechanism of medial calcification in chronic renal failure (CRF), a pathological process that ultimately leads to reduced elasticity of the blood vessel wall,[2] increased systolic blood pressure, and left ventricle hypertrophy. Approximately 50% of the mortality in hemodialysis patients is a direct consequence of cardiovascular disease, of which medial calcification is a major risk factor.[3] Phosphate binders are administered to control serum phosphorus levels in end-stage renal disease patients, particularly when treated by dialysis. Phosphate binders based on calcium are rather inexpensive and thus frequently used. In addition, it was shown in an animal model that they—probably because of their phosphate-binding capacity—also slow the progression of vascular calcification as compared with untreated CRF animals.[4] However, compared with non-calcium-based phosphate binders such as lanthanum carbonate (Fosrenol), sevelamer carbonate (Renvela), and sevelamer hydrochloride (Renagel), treatment with calcium-based agents may lead to an increased number of hypercalcemic episodes, which may promote development of vascular calcification.[5] Hence, both hyperphosphatemia[6] and hypercalcemia[7] may contribute to vascular calcification. Another alternative phosphate-binding agent is the calcium acetate/magnesium carbonate–containing phosphate binder (OsvaRen, hereafter named CaMg). The safety and efficacy of this and other magnesium-based phosphate binders has already been demonstrated in clinical studies,[8–11] but their potential to prevent the development and/or progression rate of vascular calcification has not yet been investigated, although *in vitro* studies have already shown a beneficial effect of magnesium on the deposition of calcium and an inhibiting effect on the osteogenic differentiation of cultured vascular smooth muscle cells.[12,13]

In addition, data from clinical studies in dialysis patients demonstrated that low serum magnesium concentrations are associated with progression of vascular calcification[14] and

increased mortality.[15] Higher serum magnesium levels have been reported to protect against the development and progression of vascular calcification,[16] although the mechanisms underlying this effect are rather unknown.

In this study, the effect of the magnesium-based phosphate binder CaMg on the development of vascular calcification in experimental CRF was investigated and compared with that of sevelamer carbonate with equal amounts of active salt (for details see 'Materials and Methods').

RESULTS

Rats were fed a 0.75% adenine/2.5% protein diet to induce renal failure. After 1 week, treatment with phosphate binders or vehicle was started until the time of killing at week 6 (Figure 1). There was limited mortality: one animal from each treatment group died 1 day before the planned day of killing. No statistically significant differences between groups were seen for body weight and water and food consumption (data not shown).

Biochemical analyses

Results of the biochemical analyses of serum and urine samples are listed in Table 1 and Figure 2. A pronounced renal failure was induced in all groups. Renal function decreased significantly after 4 weeks of adenine/low protein treatment as indicated by the increase in serum creatinine concentrations, which were comparable between all groups during the whole study period (Table 1). Hyperphosphatemia developed in vehicle-treated rats and reached levels of up to 20 mg/dl after 4 weeks of CRF (Table 1 and Figure 2a). At this time point, treatment with 750 mg/kg CaMg already significantly reduced serum phosphorus levels, whereas this reduction occurred only at week 6 for the sevelamer-treated group. Urinary phosphate levels decreased in both CaMg-treated groups from week 4 onwards, whereas sevelamer lowered phosphate concentrations in the urine only at the end of the study (Table 1 and Figure 2b). After 4 and 6 weeks of CRF, serum intact fibroblast growth factor 23 (iFGF-23) levels were dramatically increased in all groups; however, phosphate binder treatment could not reduce iFGF-23 concentration in the circulation (Table 1). Total serum calcium levels significantly increased in all phosphate binder–treated groups compared with week 0 as well as in CaMg-treated groups at the end of the study compared with vehicle-treated animals (Table 1). However, ionized calcium levels significantly decreased throughout the study in all groups and no significant difference could be found between groups at any time point (Table 1 and Figure 2c). Urinary excretion of calcium was significantly increased in all groups as compared with baseline values (Table 1). As could be expected, serum magnesium concentrations dose-dependently increased during the study in CRF groups treated with CaMg (Table 1). Induction of CRF went along with a significant increase in serum parathyroid hormone (PTH) concentrations. Treatment with CaMg dose-dependently suppressed this increase whereas sevelamer did not (Table 1).

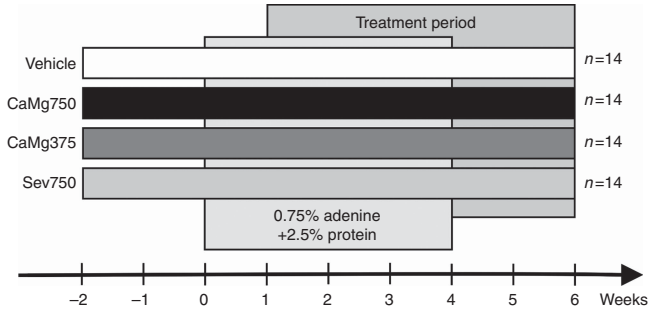

Figure 1 | Study setup. CaMg, calcium acetate/magnesium carbonate; CaMg375, CaMg 375 mg/kg; CaMg750, CaMg 750 mg/kg; Sev750, 750 mg/kg sevelamer.

Vascular calcification

After 6 weeks of CRF, vehicle-treated CRF animals developed severe calcification in the aorta, femoral and carotid arteries (aortic calcium content of rats with normal renal function 0.35 ± 0.40 mg per g wet tissue),[17] as shown in Figure 3a representing the aortic calcium content. Treatment with both 750 mg/kg CaMg (CaMg750) and 375 mg/kg CaMg (CaMg375) significantly reduced the aortic calcium content as compared with vehicle-treated CRF animals, whereas no significant effect could be observed for sevelamer. Histological analysis of von Kossa–stained sections of the aorta showed a significantly reduced percent area of calcification in the CaMg-treated animals as well as in the sevelamer-treated group (Figure 3b). Treatment with sevelamer carbonate, but not with CaMg, was associated with significant lower tissue calcium content in the carotid artery. There was no significant difference at all between CRF groups regarding calcium content of the femoral artery.

Although no significant difference in the magnesium content of the aorta could be found between groups, magnesium content differed in the CaMg750 group for carotid artery (increased) and in Sev750 for femoral artery (decreased) compared with vehicle (Table 2). The Mg/Ca ratio increased in all phosphate binder–treated groups, but this should be interpreted in light of the reduced calcium deposition in the vessels of these animals.

Synchrotron-based X-ray diffraction analysis of the aortic calcifications in CaMg-, sevelamer- and vehicle-treated animals indicated mineral precipitates of the various groups to exclusively consist of calcium hydroxyapatite (Figure 4). None of the samples contained whitlockite or any other type of calcium phosphate mineral.

Gene expression analyses

Figure 5 illustrates the expression of osteochondrogenic genes in the aorta. The expression of *bmp-2* (bone morphogenetic protein 2), the chondrocyte-specific transcription factor *sox9* (sex determining region Y-box 9), and the calcification inhibitor *mgp* (matrix gla protein) was significantly increased in CRF rats compared with rats with normal renal function. Interestingly, in CRF animals the expression of *bmp-2*, *sox9*, and *mgp* was clearly associated with the presence of vascular

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