Comparison of Three Formulations of Calcium Acetate Tablets to Evaluate Tolerance and Control of Hyperphosphatemia in Patients with Chronic Renal Failure

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Dear Sir,

In recent publications in this journal, it has been shown that calcium acetate (CaAc) is an effective phosphate binder in patients with hyperphosphatemia due to chronic renal failure [1-3]. However in our patient population using CaAc one of the major complaints is gastrointestinal discomfort, which is supported by data from the literature [1-4]. This often results in discontinuation of the drug.

In an attempt to reduce gastrointestinal discomfort, an enteric coated form of CaAc (CaAcEC) was developed in cooperation with our hospital pharmacy. The enteric coated tablets developed are resistant to a pH < 5.5 and will only disintegrate after passage of the stomach. Thus mixing of CaAc with phosphate in food will take place in the small intestine. Since mixing of CaAc with phosphate from the food in the stomach is an important determinant in phosphate binding [5], mixing in the small intestine could mean a decreased phosphate binding.

In order to evaluate the gastrointestinal tolerance and phosphate binding capacity we started a pilot study to compare a commercially available noncoated form of CaAc (Phos-ex®, Formulation Technology USA, 250 mg elemental calcium) with CaAcEC (Eudragit-L, 125 mg elemental calcium) and a neutral coated (Eudragit-E, 125 mg elemental calcium) form of CaAc (CaAcNC), developed in our hospital pharmacy in a randomized double-blind crossover study. Eight patients (5 female, 3 male with a mean age of 60 years, range 45-77) with moderate to severe renal failure (mean serum creatinine: 597 µmol/l, range 395-1,334; 6.8 mg/dl, range 4.5-15.1) were included, after obtaining informed consent. 5 patients already were on CaAc (Phos-ex) therapy, 3 patients were on CaCO₃ therapy. Week 0 was used to switch these 3 patients from CaCO₃ to Phos-ex, based on an equivalent dose of elemental Ca. At week 1, after randomization, all patients stopped Phos-ex and started double-blind with either CaAcEC or CaAcNC in an equivalent dose with a crossover after 4 weeks. The tablets were taken with meals. We developed a questionnaire to evaluate gastrointestinal complaints.

Table 1 summarizes the means $\pm$ standard deviation of calcium and phosphate before, at the start and during the two periods (of 4 weeks) of CaAc therapy. Body weight and

Mean $\pm$ 1SD. Figures in parentheses represent mg/dl. * = $p > 0.25$, vs. PCa and PP04 levels before CaAc therapy. • 4 weeks' CaAcEC followed by 4 weeks' CaAcNC. b 4 weeks' CaAcNC followed by 4 weeks' CaAcEC.

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serum creatinine were comparable during the whole study. Plasma calcium and phosphate levels were not significantly different ($p > 0.25$; Student t test). Hypercalcemia (PCa > 2.75 mmol/l; 11 mg/dl) was observed in 2 patients, both after 2 weeks' therapy with CaAcEC.

Hyperphosphatemia (PP04 > 2 mmol/l; 6.2 mg/dl) was observed in 1 patient after 2 weeks therapy with CaAcEC.

After evaluating the questionnaires, gastrointestinal tolerance proved to be better in 6 patients using CaAc made by our hospital pharmacy in comparison to Phos-ex. In 4 of them there was no preference for CaAcEC or CaAcNC, 1 patient preferred CaAcNC and 1 patient preferred CaAcEC. Remarkable was the fact that 4 patients preferred the hospital formulations of CaAc because of the smaller size of the tablets, even though they had to take the double amount of tablets compared to Phos-ex.

// conclusion, it seems possible to control hyperphosphatemia with CaAcEC in patients with moderate to severe renal failure. We demonstrated a better gastrointestinal tolerance with the Eudragit (EC or NC)-

coated formulations of CaAc. Here it is not clear whether this is due to the coating of the tablets or the smaller size. A long-term comparative study with more participating patients will be necessary (and is in progress) for further evaluation of tolerance and phosphate binding capacity of CaAcEC and CaAcNC in hemodialysis patients.

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