

MgCaCO₃ VERSUS CaCO₃ IN PERITONEAL DIALYSIS PATIENTS – A CROSS-OVER PILOT TRIAL

Baigalmaa Evsanaa,¹ Irene Liu,² Babak Aliazardeh,² Sara Mahdavi,² Gursarn Bajwa,² Jerry Gula,² Michelle Tam,² Elena Sze,² Janet M. Roscoe,² Paul Y. Tam,² and Tabo Sikaneta²

Health Sciences University of Mongolia,¹ Ulaanbaatar, Mongolia; and The Scarborough General Hospital,² Scarborough, Ontario, Canada

◆ **Background:** Despite adverse effects such as constipation, vascular calcification, and hypercalcemia, calcium-based salts are relatively affordable and effective phosphate binders that remain in widespread use in the dialysis population. We conducted a pilot study examining whether the use of a combined magnesium/calcium-based binder was as effective as calcium carbonate at lowering serum phosphate levels in peritoneal dialysis (PD) patients.

◆ **Methods:** This was a cross-over, investigator-masked pilot study in which prevalent PD patients received calcium carbonate alone (200 mg calcium per tablet) or calcium magnesium carbonate (100 mg calcium, 85 mg magnesium per tablet). Primary outcome was serum phosphate level at 3 months. Analysis was as per protocol.

◆ **Results:** Twenty patients were recruited, 17 completed the study. Mean starting dose was 11.35 ± 7.04 pills per day of MgCaCO₃ and 9.00 ± 4.97 pills per day of CaCO₃. Mean phosphate levels fell from 2.13 mmol/L to 2.01 mmol/L (95% confidence interval (CI): 1.76 – 2.30, $p = 0.361$) in the MgCaCO₃ group, and 1.81 mmol/L (95% CI: 1.56 – 2.0, $p = 0.026$) in the CaCO₃ alone group. Six (35%) patients taking MgCaCO₃ and 9 (54%) taking CaCO₃ alone achieved Kidney Disease Outcomes Quality Initiative (KDOQI) serum phosphate targets at 3 months. Diarrhea developed in 9 patients taking MgCaCO₃ and 3 taking CaCO₃. Serum magnesium exceeded 1.4 mmol/L in 5 patients taking MgCaCO₃ while serum calcium exceeded 2.65 mmol/L in 3 patients receiving CaCO₃. When compared to the initial dose, the prescribed dose at 3 months was reduced by 44% (to 6.41 tablets/day) in the MgCaCO₃ group and by 8% (to 8.24 pills per day) in the CaCO₃ alone group.

◆ **Conclusion:** Compared with CaCO₃ alone, the preparation and dose of MgCaCO₃ used in this pilot study was no better at lowering serum phosphate levels in PD patients, and was associated with more dose-limiting side effects.

KEY WORDS: Phosphate-binders; magnesium calcium carbonate; compliance rates; adverse effects.

Current phosphate-lowering strategies include the use of calcium-based dietary phosphate binders. Calcium salt ingestion can lead to constipation, hypercalcemia, and increased vascular calcification rates (1). Sevalemer hydrochloride and lanthanum carbonate, two widely available non-calcium-based binders, are often prohibitively expensive (1,2). Patient compliance with prescribed phosphate-binder regimens is therefore poor, and serum phosphate levels often remain above treatment targets (2). Magnesium salts also bind dietary phosphate, are relatively affordable, and have been shown to be similarly efficacious to calcium-based binders in hemodialysis (HD) patients (3,4). We are aware of only one report examining their use in peritoneal dialysis (PD) patients (5). In 1993, Parsons *et al.* randomized 50 PD patients to receive one of a combination of MgCO₃ and CaCO₃ (starting dose 2.2 g each per day, 32 patients), CaCO₃ alone (starting dose 2.2 g per day, 10 patients), or an aluminum-based binder (dose not reported, 8 patients). No differences after one year were seen in serum phosphate levels (5). No information on compliance rates, eventual prescribed doses, or side effects was provided.

We wished to conduct a pilot study comparing the effectiveness and patient compliance rates of MgCaCO₃ versus CaCO₃ in treating hyperphosphatemia in PD patients. Our expectations were that, compared with a calcium only-based binder, a calcium/magnesium-based phosphate binder would be better tolerated, have higher compliance rates, and be more effective at controlling serum phosphate.

METHODS

A single-blind, randomized, cross-over study design was used (Figure 1). Written approval to conduct this study

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Correspondence to: Dr. T. Sikaneta, 78 Corporate Drive, Unit 10, Scarborough, ON, Canada.

tabosikaneta@yahoo.ca

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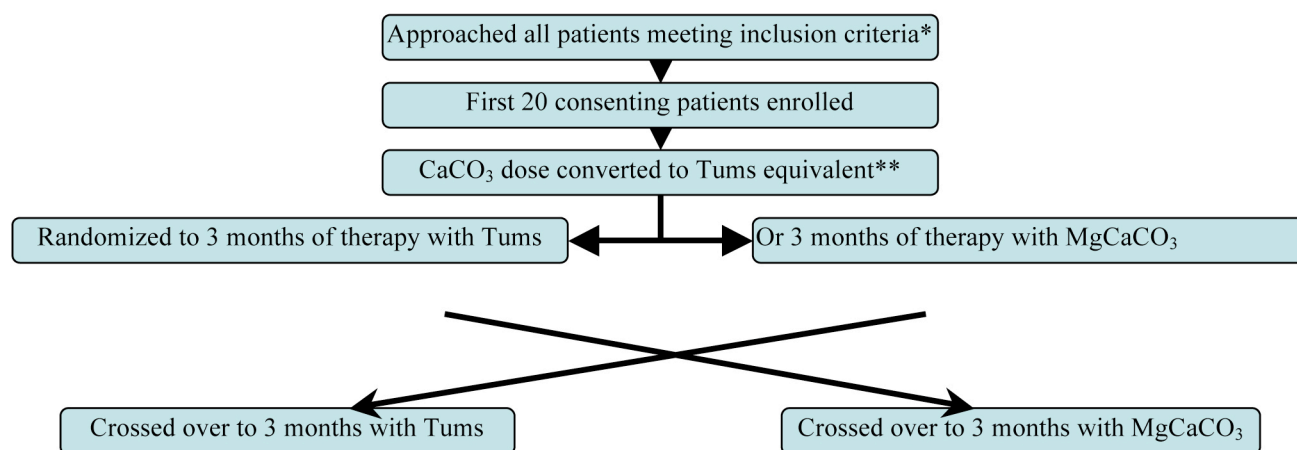


Figure 1 — Study Schema. * Inclusion criteria: prevalent peritoneal dialysis (PD) patients, age >18 years, $PO_4 > 1.80$ mmol/L on 2 occasions, $CaCO_3$ was the only PO_4 binder. ** At enrollment all patients were taking a $CaCO_3$ preparation containing 500 mg elemental calcium per tablet. This was converted to a Tums (GlaxoSmithKline Inc., Mississauga, ON, Canada) equivalent (either Tums with 200 mg elemental calcium per tablet or Magnebind 300 (Nephro-Tech, Inc., Shawnee, KS, USA) with 85 mg elemental magnesium and 100 mg elemental calcium per tablet).

was obtained from our institution's Ethics Review Board, and signed consent obtained from all study participants. Study drugs were $MgCaCO_3$ (Magnebind 300, Nephro-Tech Inc., Shawnee, KS, USA, 85 mg elemental magnesium, 100 mg elemental calcium per tablet) and $CaCO_3$ (Tums, GlaxoSmithKline, Mississauga, ON, Canada, 200 mg elemental calcium per tablet). As a pilot study, and given the lack of literature concerning expected effect size, a sample size calculation was not performed. To minimize pill burden effect, one tablet of $MgCaCO_3$ was considered equivalent to one tablet of $CaCO_3$. Patients were continued on the same dose of $CaCO_3$ as before study enrollment, (or started on an equivalent number of $MgCaCO_3$ pills). Serum phosphate, calcium, and magnesium levels, and pill counts were checked every 6 weeks. The dose of phosphate binder was halved if serum calcium levels exceeded 2.65 mmol/L, if serum magnesium levels exceeded 1.40 mmol/L, or if diarrhea or constipation developed and was deemed drug-related. The treating clinic physician, who was blinded to treatment arm, prescribed calcium carbonate targeting a serum phosphate of less than 1.80 mmol/L. There was no wash-out period before treatment allocation, and no changes were made in PD prescription (standard PD solutions were used, magnesium concentration 0.34 mmol/L, calcium concentration 1.3 mmol/L). All laxatives were discontinued at study enrollment.

STATISTICAL METHODS

Data was coded and prepared in Microsoft Access database and analyzed using SPSS statistical package version 20 (SPSS Inc, Chicago, IL, USA). Mixed model analysis was used to compare treatment effects after taking into

account the correlation between repeated measurements. Primary outcome was serum phosphate after 12 weeks of phosphate binding therapy. Secondary outcomes included serum phosphate at 6 weeks, the numbers of patients achieving Kidney Disease Outcomes Quality Initiative (KDOQI) guideline targets for serum phosphate after 12 weeks of therapy, pill counts, and adverse effects severe enough to warrant dose reduction.

RESULTS

The first twenty consenting patients were randomized. Seventeen patients completed the study after one received a renal transplant (7 weeks after enrollment in the $MgCaCO_3$ arm), another dropped out in the first week because she did not like the TUMS tablets, and a third died following 2 peritonitis episodes (first episode 8 weeks after enrollment in $CaCO_3$ arm, the second (culminating in the patient's death) 7 weeks after crossover into the $MgCaCO_3$ arm).

The mean baseline prescribed $CaCO_3$ was 2.28 grams per day (Table 1). Figure 2 highlights the serum phosphate, calcium, and magnesium concentrations after 6 and 12 weeks of therapy. Mixed model analysis revealed $MgCaCO_3$ to be less effective in reducing serum phosphate level ($p = 0.043$), that $CaCO_3$ associated with higher levels of serum calcium ($p = 0.001$) and lower levels of magnesium ($p = 0.002$), and that there was no significant difference in mean parathyroid hormone levels between treatment groups ($p = 0.196$) (data not shown). KDOQI serum phosphate targets (less than 1.80 mmol/L) were achieved after 12 weeks of therapy in 6 (35%) patients in the $MgCaCO_3$ arm, and 9 (53%) patients in the $CaCO_3$

TABLE 1
Baseline Features (Mean (SD))

Age (years)	51 (22)
Male (number)	7
Dialysis vintage (days)	753 (515)
CaCO ₃ dose (mg/day)	2,282 (1,368)
Laxative use (number patients)	
≤2/week	14
>4/week	3
Active vitamin D, (mcg/week)	1.00 (1.14)

SD = standard deviation.

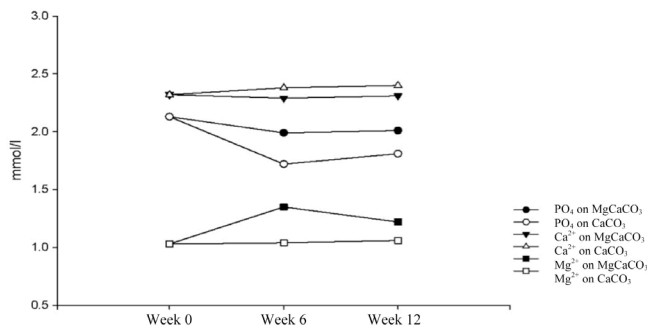


Figure 2 — Mean serum phosphate, calcium, and magnesium concentrations at 0, 6 and 12 weeks. Tums (GlaxoSmithKline, Mississauga, ON, Canada).

arm. Table 2 highlights the frequency of adverse events. There were more dose reductions in the MgCaCO₃ group because of the development of diarrhea (7 dose reductions in 6 patients) or magnesium levels greater than 1.4 mmol/L (6 dose reductions in 4 patients). By week 12, patients were prescribed 56% of the originally prescribed MgCaCO₃ amount ($p=0.004$), and 91.6% of the originally prescribed CaCO₃ amount ($p=0.149$). Pill counts at week 12 were similar between groups (patients ingested 77% of prescribed MgCaCO₃ and 76% of prescribed CaCO₃).

DISCUSSION

Serum phosphate levels were significantly lower after 12 weeks of therapy with CaCO₃ but not with MgCaCO₃ in 17 PD patients with uncontrolled hyperphosphatemia. MgCaCO₃ (mean starting dose 965 mg elemental magnesium, 1,135 mg elemental calcium per day) was not as well tolerated as CaCO₃ alone (mean starting dose 1,800 mg elemental calcium per day). It required more dose reductions primarily because of the development of diarrhea. Previous studies have reported the development of diarrhea in up to 15% of HD patients receiving magnesium-based phosphate binders (3,4). Given that

TABLE 2
Frequency of Adverse Events

Adverse event	Treatment group proportion of patients (95% CI)	
	MgCaCO ₃	CaCO ₃
Diarrhea	0.35 (0.17–0.59)	0.12 (0.04–0.35)
Constipation	0	0
Mg ²⁺ >1.40 mmol/L	0.23 (0.10–0.48)	0
Ca ²⁺ >2.65 mmol/L	0	0.12 (0.04–0.35)
Total	0.59 (0.36–0.78)	0.23 (0.10–0.48)

CI = confidence interval.

constipation rates are reported to be three times higher in HD than PD patients (6), it is perhaps not surprising that we observed higher rates of diarrhea after administration of a magnesium-based phosphate binder in this study.

LIMITATIONS

This was a single-center pilot study enrolling only 20 patients, of whom only 17 completed the study. There was no wash-out period before treatment assignment, and this might have introduced carry-over bias. We started at a large dose based on a pre-study enrollment CaCO₃ dose, rather than starting at a lower dose and titrating up to a target phosphate level. Because high levels of magnesium can lead to significant toxicity and even death, we used a conservative upper limit of serum magnesium (7). At our threshold of 1.40 mmol/L, MgCaCO₃ doses were reduced six times in four patients. This could have biased against the potential benefits of higher MgCaCO₃ doses in patients who might have tolerated higher serum magnesium levels.

CONCLUSIONS

Compared with CaCO₃, MgCaCO₃ was less effective at lowering elevated serum phosphate levels, and required more dose reductions because of the development of diarrhea or elevated magnesium levels in this pilot study of 17 peritoneal dialysis patients.

DISCLOSURES

None of the authors have any financial conflicts of interest to declare.

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