Effect of Omeprazole on the Phosphate-Binding Capacity of Calcium Carbonate

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Dear Sir,

Calcium carbonate is the most commonly used phosphate binder in chronic renal failure (CRF). Recently it has been shown that its phosphate-binding capacity is limited at low pH [1]. This study was performed to assess the effect of the proton pump inhibitor omeprazole on the phosphate-binding capacity of calcium carbonate.

Six normal subjects aged 25-44 years were studied. Subjects fasted for 10 h prior to and during each of the 3 phases of the study. Each phase commenced at 09.00 h on 3 separate days within a 2-week period.

Phase 1. After a baseline blood sample (5 ml) an oral phosphate load consisting of 17.4 g of disodium hydrogen phosphate B.R. (1.5 g of elemental phosphate) dissolved in 200 ml of water was administered over a 2-min period [2]. Further 5-ml samples were taken at 30, 60, 90, 120 and 180 min. Samples were centrifuged immediately and the serum stored for later analysis of total calcium and phosphate concentrations.

Phase 2. The protocol was identical to phase 1 except that the administration of the phosphate load was immediately preceded by the oral administration of calcium carbonate (Calcichew, Shire pharmaceuticals Ltd.) in a dose of 1.5 g of elemental calcium.

Phase 3. The protocol was identical to phase 2 except that omeprazole (Losec, Astra pharmaceuticals Ltd.) (20 mg) was administered at 22.00 h on the day preceding the study and again at 08.00 h on the day of the study.

The increments in serum phosphate levels in response to oral phosphate loading were calculated by subtracting the baseline serum phosphate level from values obtained at 30, 60, 90, 120 and 180 min after the oral phosphate load. The results in each phase of the study are shown in the figure. The mean area

under the phosphate increment curve obtained after oral phosphate loading alone (phase 1) was 40.6 ± 16.8 (SD) mmol l⁻¹ min. This was significantly reduced by prior in-gestion of calcium carbonate (phase 2) to 20.5 ± 10.5 mmol l⁻¹ min ($p = 0.008$ by paired t test, 95% confidence interval for the mean difference = 8.01-32). The prior ingestion of both calcium carbonate and omeprazole (phase 3) produced a further significant reduction to 14.0 ± 9.7 mmol l⁻¹ min ($p = 0.035$, 95% confidence interval = 0.69-12.4). The changes in serum calcium level in each phase of the study were calculated in a similar fashion. The mean area under the calcium increment curve (fig. 1) obtained after oral phosphate loading alone (phase 1) was -7.53 ± 5.63 mmol L⁻¹ min. Prior ingestion of calcium carbonate (phase 2) caused a

significant increase to $6.40 \pm 6.12 \text{ mmol l}^{-1} \text{ min}$ ($p = 0.014$, 95% confidence interval = -4.24 to -23.6). Prior ingestion of both omeprazole and calcium carbonate (phase 3) produced a significant fall from the phase 2 level to $-1.48 \pm 3.05 \text{ mmol l}^{-1} \text{ min}$ ($p = 0.015$, 95% confidence interval = 1.14 to 13.7). The mean areas under the calcium increment curve in phases 1 and 3 were not significantly different.

The study demonstrates that prior administration of calcium carbonate significantly reduced the increment in serum phosphate levels after an oral phosphate load, and that the addition of omeprazole significantly augments this effect. Our interpretation is that the phosphate-binding capacity of calcium carbonate is increased by inhibition of gastric acid secretion. Gastric acid has a number of effects on the reaction between phosphate and calcium carbonate. The solubilisation of calcium carbo-

Fig. 1. a Mean increments in serum phosphate levels in response to an oral phosphate load in each of the 3 phases of the study. b Mean change in serum calcium in response to an oral phosphate load in each of the 3 phases of the study. Bars indicate standard error of mean. ■ = Phosphate; □ = phosphate + calcium carbonate; EB = phosphate + calcium carbonate + omeprazole.

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nate is significantly enhanced and hence the availability of calcium ions for phosphate binding is increased. However the phosphate-binding avidity of H^+ is greater than that of Ca^{2+} so that the following reaction is preferred:

The net result is the delivery of large quantities of calcium ion to the small intestine where it is available for both absorption and phosphate binding. The increment in calcium levels in phase 2 of the study may suggest that a considerable quantity of calcium is absorbed.

In the absence of gastric acid the solubilisation of calcium carbonate in the stomach is reduced, but those calcium ions which are generated are available to bind phosphate because of the lack of competing protons:

Many less calcium ions are delivered to the small intestine and the amount of calcium ion absorbed is less. The absence of a rise in serum calcium in phase 3 of the study may support this contention. Improved phosphate binding by calcium carbonate in the stomach in the absence of gastric acid secretion and the reduction in calcium ion absorption which occurs in these circumstances are both factors which may contribute to the significantly reduced increments in serum phosphate noted in phase 3 of the study.

There may be other factors. Phosphate binding occurs either by a reaction between intraluminal phosphate and the cation of the binder to form an insoluble and hence unabsorbable phosphate compound or by adsorption of intraluminal phosphate onto the surface of binder particles [2, 3]. The decreased solubilisation of calcium carbonate in the stomach in the absence of gastric acid would ensure the delivery of increased amounts of insoluble calcium carbonate into the small intestine where it would be available to adsorb phosphate. The relative importance of these potential mechanisms cannot be established by this study.

There are several problems with this interpretation. Factors other than intestinal absorption influence serum levels after an oral phosphate load, including the rate of gastric emptying, intestinal motility and intracellular phosphate shifts. However, the method has been shown to discriminate between phosphate absorption in normal subjects and that in subjects with a variety of causes of phosphate malabsorption [2, 4, 5] and to demonstrate the beneficial effect of vitamin D analogues on phosphate malabsorption in CRF [4]. Changes in serum calcium levels after an oral calcium load are less likely to provide a valid measure of calcium absorption. Hence inferences drawn from differences in increments of serum calcium in the 3 phases of this study must be tentative. Finally, we did not, for logistic reasons, assess the effect of omeprazole on phosphate absorption in the absence of calcium carbonate. However, we think it is unlikely that inhibition of gastric acid secretion has a direct effect on intestinal phosphate absorption. The pH in the small intestine, where the bulk of phosphate absorption occurs, is not significantly changed by such manoeuvres, and any increase in small intestinal pH which did occur would be expected to augment phosphate absorption rather than reduce it [6, 7]. We have demonstrated that omeprazole augments the phosphate binding capacity of calcium carbonate by a factor of about 30%. To be clinically relevant would require the translation of this effect from the fasting state in normal subjects to the fed state in CRF patients. This is debatable since, in achlorhydria, calcium is malabsorbed after administration of calcium carbonate in the fasting state whilst its absorption is normal after administration with food [8].

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