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RESEARCH ARTICLE

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RANITIDINE AND OMEPRAZOLE EFFECT ON SERUM PHOSPHORUS IN HEMODIDLYSIS PATIENTS

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ABSTRACT

Hyperphosphatemia induces extraskeletal calcification of soft tissue, a link found between gastric hyperacidity and hyperphosphatemia in dialysis patients. Patientsts categorized into 3 groups viz., Group I (38 Patients) control group, Group II (39 Patients) $CaCo_3$ with Ranitidine 150 mg and Group III (31 subjects) same dose calcium carbonate with Omeprazole 20 mg. Blood samples were collected monthly during hemodialysis sessions.Group II showed increase in serum phosphorus at 6th months with increase in calcium-phosphorus biproduct, decreased serum calcium. Group III showed no significant change in serum calcium, phosphorus, Parathyroid hormone and calcium-phosphorus biproduct value. Co-administration of Ranitidine with calcium carbonate may aggravate hyperphosphatemia increasing the incidence of complications. Co-administration of Omeprazole with calcium carbonate may have a beneficial role in minimizing those complications in those patients.

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KEYWORDS

Hypocalcemia, Hyperphosphatemia, Omeprazole, Ranitidine.

INTRODUCTION

Abnormalities in calcium–phosphate balance develop early in the course of chronic kidney disease. A tight association has been observed between elevated serum phosphate, intact parathyroid hormone, calcium-phosphate product and mortality. It seems likely that the relationship between calcium–phosphate balance and outcome of patients on dialysis can be explained to a large extent by the effect of the observed abnormalities on the cardiovascular system [1]

The consequences of altered phosphorus and calcium metabolism include increased risk of bone disease, and extraskeletal calcification of soft tissues, including blood vessels, kidneys, and joints [2 -3.]

Phosphorus sequestering agents contain calcium or aluminum. The use of the latter is limited by toxicity. Calcium containing agents may increase calcium load and soft tissue calcification. So, metal-free, calcium-free phosphate binders may have an important role in such a condition [3-4.]

Chronic renal failure and particularly end stage renal failure is accompanied by digestive bleeding from gastroduodenal ulcers, erosive gastritis by gastroesophagial reflux are frequent. The use of inhibitors of gastric acid secretion is the base for the treatment of these complications. Long time ago, a link has been reported between gastric hyperacidity and hyperphosphatemia in dialysis patients [4.]

PATIENTS AND METHODS

Prospective, controlled, open labeled study was conducted at National Institute of Urology And Nephrology in Matariya, and Ain Shams University Specialized Hospital Cairo, Egypt.

Methods: This study was approved by the hospital ethical committee. Written consents from all patients enrolled in the study were obtained. From patients history, 108 patients were categorized into three groups; Group I included 38 patients (7) females and (31) males, represent the control group .They received Calcium Carbonate capsules (2-12gm three times daily). Group II included 39 patients (23) females and (16) males, received the same dose of $CaCo_3$ capsules with Ranitidine tablets (150 mg twice daily). Group III included 31 patients (18) females and (13) males, received the same dose of $CaCo_3$ capsules with Omeprazole capsules (20 mg once daily). All patients received their medications for 6 months.

Blood sampling:

Blood sampling was performed during the hemodialysis sessions. Five ml blood was collected from antecubital vein at the start of the study and monthly for six months for assessment of the following:

1-Serum calcium level was measured on Microlab 200 (MERCK Instrument Inc.; Scientific Instrument Division, Germany) by using kits supplied by STANBIO laboratories (USA).Using colorimetric assay according to the method of ***Stern and Lewis., 1957; Sarkar and Chauhan., 1967*** [5-6.]

2-Inorganic serum phosphorus was measured on Microlab 200 (MERCK Instrument Inc.; Scientific Instrument Division, Germany) by using kits supplied by STANBIO laboratories (USA).Using spectrophotometric assay according to the method of ***Fiske and Subbarow., 1925; Goodwin, 1970*** [7-8.]

3-Serum ALP was measured on Microlab 200 (MERCK Instrument Inc.; Scientific Instrument Division, Germany) by using kits supplied by STANBIO laboratories (USA).Using kinetic method according to the method of ***Fujita 1939; Bowers and McCOMBR., 1966*** [9-10].

4-Serum PTH was assayed on VIDAS multiparametric immunoanalyzer (Biomerieux Inc.; Scientific Instrument Division, Marcy l'Etoile, France) by using VIDAS kit supplied by BIOMERIEUX laboratories (France) using double sandwich technique according to the method of ***Armitage1986; Kao et al., 1992*** [11-12].

5-Serum Ca x P**:** this product was regarded as normal or abnormal according to the **National Kidney Foundation Kidney Disease Outcome Quality Initiative** guidelines maintaining serum Ca x P <**55** mg^2/dL^2.

RESULTS

(1) Demographic characteristics showed no significant differences between the three studied groups. Patients in group I (n=38) had a mean age of 51.71± 9.61 years and a mean duration of dialysis 91.89±56.3 months. Patients in group II (n=39) had a mean age of 45.6± 10.08 years and a mean duration of dialysis 92.08±49.24 months, while patients in group III (n=31) had a mean age of 45.19±12.14 years and a mean duration of dialysis 93.19±53.59 months.

Table (1)
Demographic characteristics of the three studied groups

Characteristics		Group I N =38 Mean ± SD	Group II N =39 Mean ± SD	Group III N =31 Mean ± SD	*P*-Value	Significance
Age (year)		51.71± 9.61	46.56± 10.08	45.19±12.14	0.4104	NS
Sex	Male (%)	31 males (81.6%)	16 males (41%)	13 males (41%)	0.8669	NS
	Female (%)	7 females (18.4%)	23 females (59%)	18 females (58%).		
Duration of dialysis (months)		91.89±56.3	92.08±49.24	93.19±53.59	0.9582	NS

-NS= non-significant. -N= Number of patients. -Group I: (control group).
-Group II: (Ranitidine/$CaCo_3$ group). - Group III: (Omeprazole /$CaCo_3$ group).

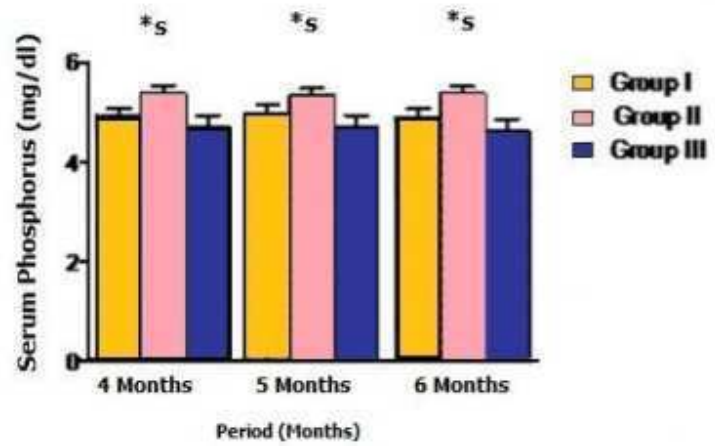

Figure (1)
Serum phosphorus level in 3 studied groups at 4th, 5th and 6th month

Data are presented as Mean ±SEM and analyzed by One Way ANOVA followed by Tukey Kramer post test at (p< 0.05).

(2) Serum phosphorus level in 3 studied groups at 4th, 5th and 6th month show the following: Serum phosphorus levels were higher in group II than group I at 4th month (4.663±0.2244) versus (5.385±0.1564) with *p* =0.0210, 5th month (4.734±0.2293) versus (5.351±0.1462) with *p* =0.0153 and 6th month (4.739±0.2221) versus (5.405±0.1534) with *p*=0.0319 respectively, with no significant change in group III than group I and group II (Figure 1).

(3) Serum calcium level at baseline, 3 and 6 months between the different studied groups. The results showed that hyperphosphatemia in group II augmented by the significant decrease in serum calcium level in group II (8.244±0.0767) more than group I (8.871±0.1630) after 6 months, with no significant difference in group III from group I and II at baseline, 3 and 6 months.

Table (2)
Effect of Ranitidine or Omeprazole co-administration with $CaCo_3$ on serum calcium (mg/dl) level at baseline, 3 and 6 months between different study groups.

Interval	Group I N =38 Mean±SEM	Group II N =39 Mean±SEM	Group III N =31 Mean±SEM	*P* -Value	Significance
Baseline	8.55±0.169	8.84±0.21	9.02±0.13	0.1854	NS
3 months	9.05±0.14	8.75±0.16	8.62±0.18	0.1824	NS
6 months	8.871±0.1630*	8.244±0.0767*	8.571±0.1383	0.0028	S*

Data are presented as Mean ±SEM and analyzed by One Way ANOVA followed by Tukey Kramer post test at (p< 0.05).
-NS: Non-significant.
-S*: Significant.
-N: Number of patients.
-Group I: (control group).
-Group II: (Ranitidine / $CaCo_3$ group).
-Group III: (Omeprazole / $CaCo_3$ group).

(4) Ca x P product in our study it showed significant increase at 6 months in group II than group I (49.49±1.738 versus 42.02±2.112),with no significant change in group III (44.40±2.036) versus group I (42.02±2.112) and group II (49.49±1.738) respectively.

(5) Serum PTH and ALP table(3) showed the effect of Ranitidine or Omeprazole co-administration with $CaCo_3$ on serum PTH and ALP serum level in the three studied groups at the start and end of the study (baseline and 6 months).

Table (3)

Effect of Ranitidine or Omeprazole co- administration with $CaCo_3$ on serum PTH and serum ALP in the three study groups at the start and end of the study (baseline and 6 months).

Group *parameter*	Group I N =38 Mean± SD	Group II N =39 Mean± SD	Group III N =31 Mean±SD	*P*-Value	Significance
PTH (Pg/ml)	375.8±59.71	374.6±51.13	221.1±35.90	0.1789	**NS**
ALP (IU)	507.5±62.06	176.3±11.76	151.2±7.817*	0.0001	**HS***

Data are presented as Mean ±SD and analyzed by Kruskall Wallis followed by Dunn's post test at (p< 0.05).
-Group I: (control group)
-Group II: (Ranitidine / $CaCo_3$ group) -Group III: (Omeprazole / $CaCo_3$ group)
-PTH: parathyroid hormone - ALP: alkaline phosphatase
- HS*: High significant -N: Number of patients -NS: Non significant.

DISCUSSIONS

Derangements of mineral metabolism occur during the early stages of chronic kidney disease (CKD) [13].

Phosphorus serum levels are usually within normal range until the GFR falls below approximately 30 ml/min according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification [14].

In the present study it has been found that the regular use of 150 mg twice daily of Ranitidine with $CaCo_3$ for 6 months worsens the hyperphosphatemia in chronic renal failure patients on hemodialysis. These data agree with ***Tan et al*** who studied the effect of Ranitidine 300 mg or placebo on 15 patients with ESRD. He explained that mean serum phosphate concentrations were higher during the Ranitidine phase than the placebo phase of the study. As Phosphate concentrations increased during the Ranitidine phase compared with the placebo phase in 12 patients and were decreased in three patients [15].

These effects explained by ***Takahashi et al and Jono et al*** they reported that the phosphate binding properties of calcium carbonate depends on gastric acid. Gastric hydrochloric acid increases the solubility of calcium carbonate providing more free calcium ions for binding of phosphate and it is responsible for the partial conversion of calcium carbonate to calcium chloride [16]. Calcium chloride is formed, which is highly water soluble in neutral and even in alkaline milieu. At pH 7 the pKa value of calcium chloride being above pH 7 indicating that the calcium is well ionized and soluble when transferred from the stomach acid to the small intestine as calcium chloride [17].

In the present study Ranitidine aggravated the condition for the patients by augmenting hypocalcaemic state after 6 months. This effect is supported by ***Goss et al ., 2007 and Goss et al.,2008*** who explained that at neutral pH, calcium carbonate is practically insoluble in water but although the solubility of calcium salts may be highly pH dependent, calcium absorption is unaffected by alterations in gastric acid secretion [18-19].

The results of the present study are contradicting with ***Jono et al*** who reported no significant differences in calcium levels during the study. The contradiction may be due to ***Jono et al*** study was for one month and the present study was for six months.

After calculation of Ca x P product in the present study, it became crystal clear that after 6 months of treatment with Ranitidine the product increased significantly showing less control of the hyperphosphatemia of the patients. These findings is in line with ***Slatopolsky et al*** who reported that hyperphosphatemia associated with progressive renal failure can lead to secondary hyperparathyroidism and accompanying elevated phosphorus and calcium-phosphate product (Ca x P) [20].

In this study, it has also been found that co-administration of Ranitidine with calcium carbonate did not show any significant change in serum PTH which contradicted by the study of ***Bricker*** who suggested that original proposal was that phosphate retention as a result of reductions in glomular filtration rate would cause transient decreases in the levels of calcium which would in turn trigger an increase in PTH secretion and a new steady state would be achieved, with restoration of normal calcium and phosphate levels but with the consequence that high levels of PTH now would be required to maintain homeostasis [21].

The present study shows significant decrease in serum ALP level upon administration of Ranitidine in combination with$CaCo_3$; this is in agreement with ***Kinjo et al and Roux et al*** who reported that long-term use of H2-receptor antagonists result in a slight reduction in bone mineral density. The author explained recognition of the functional activity of free alkaline phosphatase toward its natural substrates in serum is reduced over 50% by normal extracellular phosphate concentrations and will increase or decrease significantly in response to variations in inorganic phosphate [22-23].

Regular Omeprazole co-administration with $CaCo_3$ in the present study produced no significant change in the serum phosphorus level. ***Hardy et al*** reported no significant difference in the control of phosphatemia in 16 patients on chronic hemodialysis [24].

Further support of our data is found in the study of ***Osler et al*** who concluded that Omeprazole augmented the phosphate binding capacity of calcium carbonate in six normal subjects the inhibition of phosphatemia would be due to greater intragastric binding of phosphorus by $CaCo_3$ even if its dissociation were less because although generated in smaller amounts all the calcium ions would be captured by Po_4 because fewer protons would be competing with them for phosphate binding [25].

In uremic patients, plasma phosphate levels are dependent not only on the intestinal absorption of phosphate but also on the transmembraneous shift of intracellular phosphate toward the extracellular compartment with acidosis and on the plasmatic physicochemical inverse equilibrium of plasma phosphate and calcium [26].

Our data are contradicting with that of ***Graziani et al*** who found that the stimulating effect of gastric secretion on Po_4 intestinal absorption would be due to better solubilization of dietary phosphate for which passive absorption by the duodenum is facilitated in its acid form the rest of the phosphate absorption in its basic form taking place more distally under the control of calcitriol [27].

By determination of calcium level in group III it showed no change in serum calcium

from control group values. This effect is contradicted by ***Carr and Shangraw*** they reported that daily omeprazole increased the median stomach pH and that the corrected calcemia were significantly lower under Omeprazole [28].

The decrease in calcemia with Omeprazole had already been observed by ***Straub*** who found that the use of (PPIs) decrease basal and maximal outputs of acid, and will therefore diminish the quantity of acid available for dissociation of calcium salts post prandially [29].This may be due to the explanation of ***Yang and Metz.*** They reported that in the stomach, the systemically absorbed PPIs are delivered to the basolateral surface of the parietal cell. They are weak bases diffuse through the cytoplasm of the cell into the secretory canaliculus. This secretory canaliculus is acidic with a pH of less than 4.0 such that the weakly basic drug undergoes protonation and is then trapped in this acidic compartment so calcium can be absorbed in the duodenum even in the absence of gastric dissociation because the duodenal brush border locally produces an acid environment [30].

As for Ca x P product, the present study showed no significant change upon administration of Omeprazole. ***Laine*** demonstrated stable serum phosphorus and calcium levels as upon decrease acid secretion significantly. Long term use of these drugs in high doses may raise the risks of calcium malabsorption [31].

For serum PTH level is stable in our results which coincide with ***Hardy et al*** [24].While the results is contradicted by the findings of ***Mizunashi et al*** who suggested that omeprazole treatment is associated with elevated concentrations of PTH in the circulation but it is not clear whether this resulted directly from gastrin-mediated hyperplasia of parathyroid gland[32].

Data presented in this work showed the significant decrease in serum ALP level upon combining Omeprazole with $CaCo_3$.***Hilliard et al*** demonstrated that endogenous phosphate interferes with the determination of alkaline phosphatase in urine and suggested that the wide variation in serum inorganic phosphate concentrations in diseases such as uremia or renal tubular disease might interfere with alkaline phosphatase measurements in serum [33].

Fox explained that alkaline phosphatase might be inhibited by phosphate under normal intracellular conditions. Indicate that inorganic phosphate is an important physiological regulator of extracellular alkaline phosphatase activity [34].

Although there are few studies showing the effect of co- administration of either Ranitidine with $CaCo_3$ ***Takahashi et al*** or either omeprazole with $CaCo_3$ there is no data compare between both combinations regarding the effect on hyperphosphatemia[16].

CONCLUSIONS

Co-administration of Ranitidine with $CaCo_3$ may aggravate hyperphosphatemia increasing the incidence of complications. Co-administration of Omeprazole with $CaCo_3$ may have a beneficial role in minimizing those complications in those patients.

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