Reviewer's report

Title: The relationship between proton pump inhibitor use and serum magnesium concentration among hemodialysis patients: a cross-sectional study

Version: 2
Date: 31 March 2015
Reviewer: IOANNIS TZANAKIS

Reviewer's report:

REVIEW
General comment
I think that it is a very interesting article that provides very useful information of clinical importance. The idea to examine the hypothesis that PPIs probably increase the intestinal loss of magnesium and subsequently cause hypomagnesaemia by studying patients with no or limited renal magnesium excretion such as the ESRD patients is very good. Probably the prolonged use of PPIs is the cause of an otherwise unexplained low serum magnesium levels in hemodialysis patients. I think it is a worth published article but after elucidating and revising some points.

Specific comments (according to MBC Nephrology Quidlines).
No revisions

The question posed by the authors is well defined.

All data and figures are genuine and not manipulated.

I think that that the authors clearly acknowledge the study (ref. 10) Alhosaini M, Walter JS, Singh S, Dieter RS, Hsieh A, Leehey DJ. Hypomagnesemia in Hemodialysis patients: role of proton pump inhibitors. Am J Nephrol 2014; 39:204-9. To the best of my knowledge this is the only study published in the English literature that evaluates the role of PPIs in ESRD patients concerning the development of hypomagnesemia. The present study confirms the results of the above study and enhances the information on this field.

The statistical analysis is proper and acceptable.

The conclusions are well balanced and adequately supported by the data.

The writing style of the manuscript is quite acceptable for a medical article; English is the author’s mother language so I have not any comment on spelling or on syntax.

Major Compulsory Revisions
A. Patients and Methods

In generally the methods are appropriate and well described, however I think that the authors have to provide some more information concerning patients' data:

a) Adequacy of dialysis (mean K.t/v index)
b) Did (and how many) patients were receiving Mg containing compounds either as phosphate-binders or as laxatives or as alimental supplementations?

c) Were among the examined patients some preserving a residual diuresis i.e. more than 600 ml daily or receiving diuretics?

d) Mean serum Albumin, Calcium, Phosphate, iPTH levels

e) Estimated dietary protein intake (if possible)

All these data must be included in the statistical analysis

B. Results

Tables

1. There is not any table in the manuscript with patient’s laboratories. Table 1 contains only patient’s demographic data as well as data concerning hemodialysis (duration and dialysate Mg concentration). So, the authors must either incorporate the patient’s laboratories, which they have included in to the analysis, in to the Table 1, or to construct a new one table.

2. Furthermore table 1 must be modified as follows:

   a) A column showing the p-values and the statistical significance must be added.

   b) The percentage sign (%) must be seen only in the first column beside the qualitative variables but not in the other columns beside the values.

3. One more table showing the chi-square test analysis for the categorical variables is need.

4. Each table should have a title (above the table) that summarizes the whole table.

5. Figure. I think that the columns that shows the patients’ (both PPIs abusers and not) average serum Mg levels should be appeared side by side in a single schema.

Minor Essential Revisions

A. Abstract

The title of the article describes accurately the examined topic and the abstract is well constructed. However I have a notion: In the first sentence of the abstract “It is known that serum magnesium (Mg) concentration is inversely related to vascular calcification and hyperparathyroidism among patients with end-stage renal disease (ESRD)”, the remark and hyperparathyroidism is according to my opinion “too much” for an opening phrase. The association between low serum magnesium and hyperparathyroidism is confirmed but is weak.

B. Discussion

1. Note clearly in the discussion that the PPIs cause a decrease of the intestinal fluid PH which subsequently inhibits the TRPM 6/7 affinity to the magnesium and impair its absorption. (Bai J, Hausman E, Lionberger R, Zhang X: Modeling and simulation of the effect of proton pump inhibitors on magnesium homeostasis. 1.

2. When studying magnesium we should have in mind that:
   a) Magnesium is a predominately intracellular ion,
   b) Serum albumin levels alter serum magnesium levels,
   c) Ionized magnesium fraction is the biological active form of this element
So I think that the authors should to note and comment these issues in the discussion.

3. The limitations of the work are clearly stated; however I think that the authors have to add that it is a single center study.

4. Use the term PPIs (plural) instead of PPI.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.