International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

SAFE USE OF A DAILY 20-MG DOSE OF OMEPRAZOLE IN ORDER TO AVOID HYPOMAGNESEMIA

Cecilia Maldonado; Nicolás de Mello; Pietro Fagiolino; Marta Vázquez*

Pharmaceutical Sciences Department, Faculty of Chemistry, Universidad de la República, Avenida General Flores 2124, P.O. Box 1157, 11800 Montevideo, Uruguay

***Corresponding author e-mail:** mvazquez@fq.edu.uy

ABSTRACT

The objective of the current study was to examine the safe use of a daily standard dose of omeprazole (20 mg) regarding magnesium levels in blood in hospitalized patients. A total of 51 patients (15 women, 36 men) with different characteristics (pathologies, comedications, age, habits, etc) and taking a standard dose of omeprazole for more than three months were included. 17.6 % of the patients showed mild hypomagnesemia but we concluded that the observed low levels of this electrolyte could be attributed to comedications, age and different pathologies rather than the 20-mg dose of omeprazole. So, hypomagnesemia does not eliminate proton-pump inhibitors as a reasonable option; it just requires clinicians to be aware of this problem and use them safely at conventional doses.

Keywords: Omeprazole, 20-mg dose, hypomagnesemia

INTRODUCTION

Proton-pump inhibitors (PPIs) such as omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole are substituted benzimidazoles that covalently bind to the hydrogen-potassium adenosine triphosphatase (H+/K+-ATPase) inhibiting, in this way, the final step in gastric acid secretion.[1,2] All of them are prodrugs that become protonated and converted to the active moiety in the secretory canaliculus of the parietal cell, where an acidic pH is encountered. [3]

PPIs have become the preferred agents for many acid-related disorders[4] not only because they are more potent inhibitors of acid secretion than the histamine receptor antagonists (H_2RA)[1,5] but also because their use does not generate tolerance.[6] These facts resulted in increasing prescriptions of these drugs over the years and in long-term treatments often without appropriate indications.

Concern is focusing nowadays on the problem of overuse, and possible adverse effects.[7,8] Hypomagnesemia has recently been recognized as a side effect of PPIs.[9,10,11,12,13,14] The Food and Drug Administration issued a Drug Safety Communication in 2011[15] related to long term use of PPIs and low levels of magnesium. Body stores of magnesium are primarily the bones (60%); about 20% is in skeletal muscle, 19% in other soft tissues and less than 1% in the extracellular fluid. [16]

Magnesium homeostasis is maintained primarily by two processes, gastrointestinal absorption and renal excretion. Gastrointestinal magnesium absorption occurs through both passive paracellular movement, and active transport through the combined action of TRPM6/7 channels, present in the apical membrane of enterocytes. Considering renal excretion, almost 95% of filtered magnesium is re-absorbed under normal physiological conditions. The majority of its re-absorption (60–70%) is via passive paracellular transport in the thick ascending limb of the loop of Henle. The distal tubule accounts for only 5–10% of magnesium re-absorption via active transport involving TRPM6.[17] Intestinal segments contribute in a different way to magnesium absorption: the duodenum absorbs 11%, jejunum 22%, ileum 56% and the large intestine 11%.

Luminal pH along the gastrointestinal tract is important in magnesium absorption as TRPM transporters and paracellular pores are pH sensitive. Previous studies have found that by changing intestinal pH, PPIs may alter the TRPM6/7 channel's affinity for magnesium.[18]

Under normal conditions, there is an increasing pH along the duodenum, jejunum and ileon (5.6, 6.7 and 6.9, respectively).[19] Although most of the studies suggested increased pH in the duodenum and in the small bowel associated with PPIs use [13,20] , some authors found that PPIs use caused a fall in pH along all the small intestine.[21]

Ion magnesium must be solubilized in order to be absorbed. PPI-induced hypochlorhydria decreases ingested magnesium salt solubility, thus there is potentially less ionized electrolyte in the proximal intestinal and duodenal lumen available for active transport or passive diffusion. According to the literature [18,22], the primary cause of PPI-induced hypomagnesemia could be impaired intestinal absorption rather than favored renal loss.

Hypomagnesia must be considered more deeply as low magnesium levels may cause potentially serious effects, such as tetany, seizures and arrhythmias as well as concurrent metabolic disorders (mainly hypocalcemia and hypokalemia).[23,24] Despite the many reports on long term use of PPIs associated with low levels of magnesium, the true incidence of hypomagnesaemia in patients under long therapy with PPIs is not clear. A review of the literature suggests that long term therapy with PPIs produced hypomagnesemia but in most of the studies conducted with omeprazole, the dose was not cited or a high dose of the drug was used and/or the underlying conditions or comedications in the population made impossible to conclude on the real implication of PPIs on this issue. [12,14,25,26] In a recent meta-analysis conducted [27], the authors exposed several limitations that make impossible to reach a definitive conclusion. Moreover, the impact of hypomagnesemia is underestimated, largely because clinicians fail to measure this electrolyte as part of the routine screening blood tests.

Patients that are prone to this electrolyte disorder may be the ones with certain comedications (loop or thiazide diuretics; aminoglycosides, amphotericin, cisplatin, cyclosporine among others) [28,29] ; or pathological conditions such as type 2 diabetes mellitus (DMT2), liver diseases or with habits such as alcohol consumption[30,31,32]. Age must also be taken into consideration as the elderly may absorb this electrolyte less effectively due to the aclorhidria found in this population. Structural intestinal malabsorption syndromes, such as coeliac disease or chronic pancreatitis can also lead to low levels of magnesium.[33,34]

Given the widespread use of PPIs, it is important to know whether PPIs are a risk factor for hypomagnesemia in routine clinical practice so the objective of the present work was to study the implication of the use of standard doses of omeprazole (20 mg daily) in blood magnesium levels in hospitalized patients.

MATERIALS AND METHODS

A prospective study was carried out in the University Hospital of Uruguay, a tertiary referral center with 320 beds, during 2014. Patients of two General Medicine Services under 20 mg-omeprazole (the PPI used in our Hospital) therapy for at least 3 months prior hospitalization were studied. Data was obtained from clinical charts and a form was designed for patient data collection which included age, reason for hospitalization, medical history, medication, and relevant laboratory results. Magnesium levels were asked during hospitalization as this electrolyte is not routinely monitored.

A blood sample was collected for serum magnesium determination by a calorimetric method using Cobas 6000 Roche, Laboratories. Magnesium levels were informed to physicians and in some cases when hypomagnesemia was found, magnesium supplements were administered until normal levels were restored. In our laboratory, normal magnesium concentration is 1.6 to 2.6 mg/dL Hypomagnesemia is, therefore, defined as a serum magnesium level of less than 1.6 mg/dL.

RESULTS AND DISCUSSION

A total of 51 patients (15 women, 36 men) taking omeprazole were hospitalized in the two services mentioned above. The mean age (range) of the patients was 60 (23-89) years old. Table I summarizes the main characteristics of the patients: sex, age, magnesium level in plasma, diagnosis, time from the date of admittance to hospital, use of diuretics.

All the patients remained hospitalized during the study except for P1. Of the 51 patients involved in the study, nine (P1, P7, P19, P20, P23, P33, P40, P41 and P47, 17.6 %) had hypomagnesemia (see table 1). Omeprazole therapy was not withdrawn in none of

the patients. In 38 out of 51 patients, the cause of omeprazole use was not documented in the clinical chart. In all the cases the initial dose of omeprazole was 20 mg given orally in the morning (8:00 a.m.) thirty minutes before breakfast. P19 was with 20 mg of omeprazole given orally for 31 days when magnesium level was determined (1.6 mg/dL) for the first time. Omeprazole was increased for 6 days (40 mg of omeprazole intravenously every 8 hours) and then a second magnesium level was determined (1.4 mg/dL).

Two patients with hypomagnesemia (P7 and P47) had mild hypokalemia, 3.4 meq/L (normal range 3.5-5.4 meq/L). P1 had a normal magnesium level in the first opportunity and was discharged from hospital. Five months later, the patient was readmitted due to deterioration of her pathology. Cyclosporine was prescribed (250 mg/day) and the magnesium levels in the second and third determination (1.5 mg/dL and 1.4 mg/dL respectively) were below the normal range. P7 was also taking cyclosporine.

Hypomagnesemia in P1 and P7 might be attributed to cyclosporine rather than omeprazole intake. When cyclosporine was introduced in the therapy, magnesium levels fell in P1.This drug produces an increase in magnesium excretion. P2, P10, P13, P19, P21 and P24 were on diuretics during hospitalization but only one patient (P19) was identified with hypomagnesemia during the second determination although the diuretic dose was not modified. P20 was a coeliac patient and suffered from multiple ulcers along the gastrointestinal tract. She was also under platinum derivates therapy. After her magnesium level determination (1.4 mg/dL), she started with parenteral nutrition (1600 mL daily) with the following formulation: sodium (90.0 mEq), potassium (108.0 mEq), magnesium (12.0 mEq), calcium (4.50 mEq) and macronutrients (protein, glucose, lipids, nitrogen, and fat soluble vitamins) were also included. Magnesium levels rose after parenteral nutrition with this electrolyte. In this case both impaired magnesium absorption (coeliac patient) and excretion loss (platinum therapy) might be the cause of her hypomagnesemia.

P23, P33, P40, P41, and P47 showed low magnesium values (1.1,1.4, 1.5, 1.4 and 1.5 mg / dL respectively) and they were not co medicated with any other drugs, apart from omeprazole, that may cause decreased levels of magnesium in plasma , but pathology itself and age may contribute to the values found. After the first magnesium level determination (1.1 mg/dL), P23 received 6 g of intravenous magnesium sulphate in 1000 mL saline solution for four days and the level of magnesium in plasma was located at the upper limit of the range (2.6 mg/ dL). Sixteen days after magnesium supplement discontinuation, the level of magnesium dropped again to 1.5 mg/dL. The cause of the hypomagnesemia could be his pancreatitis.

Hypomagnesemia has been reported to occur at an increased frequency among patients with DMT2 (13.5 to 47.7%). [30] Insulin deficiency or resistance could lead to urinary magnesium excretion. In addition, hyperglycemia and glycosuria may reduce the tubular reabsorption of the electrolyte provoking osmotic diuresis.[35] Although magnesium excretion was not measured in the present study, an increased urinary magnesium loss could be invoked to explain the low concentration of serum magnesium observed in P33 and P40 with DMT2.

In P41 and P47, hypomagnesemia could be potentiated by the age of the patients as in the elderly there is an impaired magnesium homeostasis. Multiple reasons for this fact exist: magnesium intake tends to be low, intestinal absorption is frequently diminished due to aclorhidria, and urinary output is often enhanced. [36]

Patients with acute or chronic use of alcohol have magnesium depletion as it reduces the body's sensitivity to insulin leading to urinary excretion of this ion. Moreover, liver pathologies can produce disorders in the secretion of bile acids.[31,32] This could result in malabsorption of lipids in these patients. Increased amounts of fatty acids in the intestinal lumen form insoluble soaps with magnesium leading to the loss of magnesium from dietary sources. P19 was alcoholic and the level of magnesium was in the lower limit in the first determination. On the second opportunity omeprazole dose was increased and the magnesium level dropped slightly. Even though the cause of hypomagnesemia in this patient seems to be multifactorial, (alcoholism, use of diuretics), only after omeprazole dose was increased, magnesium level fell. The decrease in magnesium level was not important maybe due to the introduction of spironolactone in the therapy as this drug maintained magnesium homeostasis. [37]

Consequences of hypomagnesemia could potentiate the pathologies found in these patients. Low circulating magnesium levels have been related to several cardiac complications: hypertension, dyslipidemia, impaired clotting, increased inflammatory burden, oxidative stress, carotid wall thickness and coronary heart disease Vasoconstricton and subsequent high blood pressure is observed in

patients with low magnesium levels (mainly intracellular levels). This is mediated through an increased concentration of intracellular calcium which activates the fibrin-miosin complex and thus the contraction of arterioles.[38] In addition, hypomagnesemia has been implicated in adversely affecting diabetic complications. [30]

Since magnesium is involved in muscle tone, a decrease in magnesium level in COPD patients or with respiratory failure represents a factor which is detrimental to respiratory function. Low magnesium level induces muscle fatigue. [39] Hypomagnesemia is associated in many cases to hypokalemia. The model proposed by some authors [40] shows that lowering intracellular magnesium increases ROMK-mediated K^+ secretion in the distal tubules. This constitutes the possible mechanism of increased urinary excretion of potassium in the presence of low levels of magnesium.

None of these patients with hypomagnesemia and hypokalemia (P7 and P47) were under diuretics therapy but P7 was also taking prednisone, a medication that also induces potassium loss. PPIs affect not only gastric proton pumps, but also extragastric sites. In this way, PPIs may reduce intestinal luminal pH (opposite to the effect in the gastric lumen) due to inhibition of H+/K+-ATPase in the pancreatic duct plasma membrane. Pancreatic duct proton pumps are necessary for active excretion of pancreatic bicarbonate so a lower intestinal pH is seen as stated in the introduction section [21] and thus an altered TRPM6/7channel affinity for magnesium. [41]

Our patients were medicated with omeprazole for more than three months so it was not a short term therapy and the mild hypomagnesemia observed could be attributed to comedications, age and different pathologies rather than the use of a standard dose of omeprazole. Only in one patient (P19), after an important increase in omeprazole dose, a slight decrease in magnesium level was detected.

There is evidence that omeprazole use, at least in the short term, does not inhibit magnesium absorption.[42] Therefore, it is unlikely that moderate hypochlorhydria resulting from short-term and low dose omeprazole treatment increases the risk for developing magnesium deficiency due to mineral malabsorption. According to some authors [28], there is usually a long delay in the development of severe hypomagnesaemia with PPIs use (approximately 5-10 years). This is a long period of time which was not evaluated in our study. For patients expected to be on prolonged treatment or with high doses of omeprazole or who take PPIs with medications such as cyclosporine or drugs that may cause hypomagnesemia (e.g., diuretics, platinum derivates), or patients with DMT2 or alcoholic patients or in the elderly, health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically. Given the extent of their use, it is clear that PPIs alone do not cause hypomagnesemia in most patients. Underlying patient characteristics and comorbidities, dose and comedications all can contribute to the hypomagnesemia reported in the literature. Mild impairment of magnesium absorption could be compensated by up-regulation of renal TRPM6. [18] But when an intense malabsorption of this electrolyte is present, compensatory renal mechanism becomes insufficient. This could be the case if higher doses of omeprazole were used.

Poor solubilization of magnesium at higher gastric pHs seems to be the limitation step for magnesium absorption impairment. Up-regulation of the intestinal TRPM6/7 channels also occurs when luminal concentrations of magnesium are low playing these channels an important role in maintaining this electrolyte absorption.[18] On PPIs therapy, intestinal concentrations of magnesium are low due to the poor solubilization of this ion in the gastric lumen and as pH in the small bowel is decreased by the inhibition of pancreatic pumps, TRPM6/7 affinity for magnesium is disrupted. The significant heterogeneity among the patients of the study was an obvious limitation. Another limitation of the study was that magnesium levels were not determined in urine. And finally the conventional dose in the study does not allow us to reach definitive conclusions. Well-designed comparative studies with different omeprazole doses and in long periods of time are needed to clarify the risk of PPI-induced hypomagnesemia associated with dose or treatment duration.

CONCLUSIONS

Omeprazole itself given at a dose of 20 mg daily has low risk of generating hypomagnesemia even for a long period of time. Other factors such as patient characteristics (age, habits) and/or underlying conditions that impair renal uptake of this electrolyte disregulate the homeostasis resulting in low levels of magnesium. So all things considered, this potential complication, hypomagnesemia, does not eliminate PPIs as a reasonable option; it just requires clinicians to be aware of it and use them safely at conventional doses**.**

Table 1. Main characteristics of the patients.

Patient	Sex	Age	Mg level (mg/dL)	Diagnosis	Time from the date of admittance to hospital (days)	Diuretics
P1*	F	46	1.9	Psoriasis	15	No
P1	F	46	1.5	Psoriasis	187	No
P1	F	46	1.4	Psoriasis	194	No
P2	M	64	1.9	ADHF	22	F
P3	F	55	2.1	Dermatomyositis	47	No
P4	M	52	1.7	HIV +	37	No
P5	M	57	1.7	Spondylodiscitis	59	No
P6	F	71	1.9	Endocarditis	27	No
P7	F	71	1.4	Pemphigus	48	No
P8	F	64	1.9	Renal neoplasm	16	No
P8	F	64	2.0	Renal neoplasm	23	No
P9	F	46	1.7	Pemphigus	17	No
P10	F	72	1.9	ADHF	14	F
P11	M	62	1.8	Psoriasis	2	No
P12	M	63	2.0	Dyspnea, cardiomyopathy with reduced LVEF	10	No
P13	M	59	2.0	ADHF	15	F
P14	M	80	1.8	ECT	11	No
P15	M	55	1.8	Hansen´s disease, vasculitis	18	No
P16	M	53	1.7	ADHF	19	F
P17	M	70	2.0	CAP	34	No
P18	M	55	2.0	Pulmonary neoplasm	23	No
P19	M	36	1.6	Cirrhosis and chronic liver failure	31	F
P19	M	36	1.4	Cirrhosis and chronic liver failure	37	F,S
P20	F	52	1.4	NHL, coeliac	49	No
P20	F	52	1.7	NHL, coeliac	55	No
P21	M	62	2.1	ADFH	21	F
P22	F	23	1.6	Pyoderma gangrenosum	10	No
P23	M	70	1.1	Vesical neoplasm, HTA, pancreatitis	30	No
P23	M	70	2.6	Vesical neoplasm, HTA, pancreatitis	34	No
P23	M	70	1.5	Vesical neoplasm, HTA, pancreatitis	51	No
P24	M	79	2.1	ADHF	18	F
P25	M	62	1.7	Urinary infection	21	No
P26	M	62	2.1	COPD, HF	5	No
P27	M	75	2.1	PBC	21	No
P28	F	58	1.8	COPD, HTA, ADHF	18	No
P28	F	58	2.3	COPD, HTA,ADHF	24	No
P29	M	78	1.7	HTA, DMT2	8	No
P30	M	59	2.1	HTA, HF, AF	7	F
P30	M	59	1.7	ADHF	76	F
P31	M	77	2.2	Pulmonary and cutaneous nodules	17	No
P32	M	47	2.4	Pulmonary abscess	19	No

P33	M	73	1.4	Aortic stenosis, DMT2, neoplastic resection of rectal sigmoid joint	41	No
P34	M	53	2.1	HTA, DMT2, autoimmune pulmonary disease	6	No
P35	M	65	1.9	Metabolic disorder, edema of upper limbs, DMT2	24	No
P36	M	76	1.9	Prostate cancer	39	No
P37	M	32	2.0	Hyperthyroidism, ictericia	41	No
P38	F	24	1.9	Tuberculosis	6	No
P39	F	76	1.7	HTA, DMT2, obstructive uropathy	9	No
P40	F	80	1.5	Hip fracture, DMT2, HTA	54	No
P41	M	89	1.4	HTA, COPD , ischemic cardiomyopathy	24	No
P42	M	66	2.4	NLH	39	No
P43	M	64	1.6	HTA, degenerative encephalopathy, lower respiratory infection	24	No
P44	M	51	1.8	Alcoholic hepatopathy, ascitis, SBP	6	No
P45	F	68	1.8	ADHF, DMT2, HTA, chronic AF	44	F
P46	F	75	1.6	HTA, confusional syndrome, paraparesis of lower limbs, PTE with stroke	5	No
P47	M	72	1.5	Type 1 respiratory failure	58	No
P48	M	68	1.9	Neck and axillary adenopathy	2	No
P49	M	56	2.2	DMT2,diabetic foot, metabolic disorders	11	No
P50	M	58	1.9	NHL	35	No
P51	M	40	2.2	HIV/AIDS	34	No

*P, patient; F, furosemide; S, spironolactone ;NHL, non-Hodgkin lymphoma; HTA, essential arterial hypertension; ADHF, acute decompensated heart failure; COPD, **chronic obstructive pulmonary disease**; DMT2, type 2 diabetes mellitus; AF, atrial fibrillation; HF, heart failure; PBC, primary biliary cirrhosis; ECT, encephalo-cranial trauma; CAP, community acquired pneumonia**; LVEF, left** ventricular ejection fraction; SBP, **sp**ontaneous bacterial peritonitis; PTE, **pu**lmonary thromboembolism; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome. * P1 was discharged from hospital and re admitted due to deterioration of her clinical condition.*

REFERENCES

1. Richardson P, Hawkey CJ, Stack WA. Drugs, 1998; 56: 307-335.
2. Welage LS, Berardi RR. J Am Pharm Assoc, 2000; 40:52-62.
3. Lorentzon P, Jackson R, Wallmark B, Sachs G. Biochim Biophys Acta, 1987; 897:41-51.
4. Florent C. Clin Ther, 1993; 15: 14-21.
5. Huang JQ, Hunt RH. Best Pract Res Cl Ga, 2001; 15: 355-370.
6. Devlin JW, Welage LS, Olsen KM. Ann Pharmacother, 2005; 39: 1667-1677.
7. Roulet L, Vernaz N, Giostra E, Gasche Y, Desmeules J. Rev Med Interne, 2012; 33:439-45.
8. Reimer C, Bytzer P. Ugeskr Laeger, 2012; 174:2289-2293.
9. Broeren MA, Geerdink EA, Vader HL, van den Wall Bake AW. Ann Intern Med, 2009; 151:755-756.

10. Cundy T, Dissanayake A. Clin Endocrinol, 2008; 69: 338-341.
11. Epstein M, McGrath S, Law F. NEJM, 2006; 355: 1834-1836.
12. Hoorn EJ, van der Hoek J, de Man RA, Kuipers EJ, Bolwerk C, Zietse R. Am J Kidney Dis, 2010; 56: 112-116.
13. Kuipers MT, Thang HD, Arntzenius AB. Neth J Med, 2009; 67:169-172.
14. Mackay JD, Bladon PT. QJM, 2010; 103:387-395.
15. FDA Drug Safety Communication: Available at: http://www.fda.gov/Drugs/DrugSafety/ucm245011. Accessed March, 2014.
16. Swaminathan R. Clin Biochem Rev, 2003; 24: 47-66.
17. Rondón LJ, Groenestege WM, Rayssiguier Y, Mazur A. Am J Physiol Regul Integr Comp Physiol, 2008; 294:R2001-7.
18. Perazella MA. Kidney Int, 2013; 83: 553-556.
19. Lalezari D. Ann Gastroenterol, 2012; 25:333-337.
20. Coudray C, Rambeau M, Feillet-Coudray C, Gueux E, Tressol JC, Mazur A, Rayssiguier Y. Magnes Res, 2005; 18: 215-223.
21. Michalek W, Semler JR, Kuo B. Dig Dis Sci, 2011;56:1735-1742.
22. Florentin M, Elisaf MS. World J Nephrol, 2012; 1: 151-154.
23. Noronha JL, Matuschak GM. Intensive Care Med, 2002; 28:667-679.
24. al-Ghamdi SM, Cameron EC, Sutton RA. Am J Kidney Dis, 1994; 24:737–752.
25. Shabajee N, Lamb E, Sturgess I, Sumathipala R. BMJ, 2008; 337: 173-175.
26. Druce MR, Thomas JDJ, Gorrigan RJ, Kelly PA, Coppack SW, Akker SA. Endocrine Abstracts, 2009; 19: P50.
27. Park CH, Kim EH, Roh YH, Kim HY, Lee SK. PLoS ONE, 2014; 9: e112558. doi:10.1371/journal.pone.0112558.
28. Hess MW, Hoenderop JG, Bindels RJ, Drenth JP. Aliment Pharmacol Ther, 2012; 36: 405-413.
29. Saif W.M. J Support Oncol, 2008; 6: 243-248.
30. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Clin J Am Soc Nephrol, 2007; 2: 366-373.
31. Turecky L, Kupcova V, Szantova M, Uhlikova E, Viktorinova A, Czirfusz A. Bratisl Lek Listy, 2006; 107: 58-61.
32. Long RG, Varghese Z, Wills MR, Sherlock S. Clin Chim Acta, 1978; 84: 239-245.
33. Goldman AS, Van Fossan DD, Baird EE. Pediatrics, 1962; 29:948-952.
34. Liamis G, Gianoutsos C, Elisaf M. Pancreatology, 2001; 1:74-76.
35. McNair P, Christensen MS, Christiansen C, Madsbad S, Transbol I. Eur J Clin Invest, 1982; 12: 81-85.
36. Seelig MS, Preuss HG. Geriatr Nephrol Urol, 1994; 4: 101-111.
37. Gao X, Peng L, Adhikari CM, Lin J, Zuo Z. J Card Fail, 2007; 13:170-177.
38. Efstratiadiss G, Sarigianni M, Gougourelas F. Hippokratia, 2006; 10: 147-152.
39. Singh JP, Kohli S, Devi A, Mahajan S. JK Scienc, 2012; 14: 185-189.
40. Huang CL, Kuo E. Am Soc Nephrol, 2007; 18: 2649-2652.
41. Toh Tatt JW, Ong E, Wilson R. Gastroenterol Rep, first published online August 19, 2014. doi:10.1093/gastro/gou054.
42. Serfaty-Lacrosniere C, Wood RJ, Voytko D, Saltzman JR, Pedrosa M, Sepe TE, Russell RR. J Am Coll Nutr, 1995; 14:364-368.

.