



Risk Assessment of Proton Pump Inhibitors in Ckd and Non-Ckd Patients in a Tertiary Care Hospital

Nomy P Benny*, Rahul Radhakrishnan and Arul Balasubramanian
Department of Pharmacy Practice, Vinayaka Mission's College of Pharmacy,
Vinayaka Mission's Research Foundation (Deemed to be University), Salem, Tamil Nadu.

Received: 19 Mar 2019 / Accepted: 21 Apr 2019 / Published online: 1 Jul 2019

*Corresponding Author Email: nomybenny@gmail.com

Abstract

Background: Proton pump inhibitors are one of the most widely prescribed classes of drugs mainly used for acid suppression therapy for more than 20 years. The approved indication for the use of PPI include gastro esophageal reflux diseases (GERD), peptic ulcer diseases, erosive esophagitis. **Methods:** A Retrospective observational study was conducted for 3 months who are admitted in the hospital. Patients of both genders were included in the study. From the data of 70 CKD & NON CKD cases, 35 cases were chronic kidney diseases patients and the remaining 35 cases were non chronic kidney diseases patients. The study was carried out by patient history interview, case record analysis and from laboratory values. The results are tabulated by simple statistical methods. **Results:** A total of 70 CKD and NON CKD Patients with different co-morbidities were included in the study. The Study reveals that 32(91%) of patients was having increased value of creatinine on the last day of treatment with PPI compared to first day in CKD patients and in non CKD patients, the value of normal level creatinine found higher on the last day on PPI than the first day. Evaluation of Quality of Life among CKD patients indicates that 50% of patients scored having medium quality of life. **Conclusion:** The increase in the value of serum creatinine, blood urea nitrogen and decreased level of sodium (Hyponatremia) were found in CKD patients treated with PPI.

Keywords

Proton Pump inhibitors, Chronic Renal Failure, Renal parameters, Medication adherence.

INTRODUCTION:

Proton pump inhibitors are one of the most widely prescribed classes of drugs mainly used for acid suppression therapy for more than 20 years. The approved indication for the use of PPI include gastro

esophageal reflux diseases (GERD), peptic ulcer diseases, erosive esophagitis¹. It has been estimated that up to two thirds of all people on PPI do not have a verified indication for the drug. The duration of use frequently extends beyond recommended guidelines²,

Oral bioavailability of PPIs ranges from 30 – 90%. All are highly protein bound and maintain a small volume of distribution (0.17 – 0.45 l/kg). Proton pump inhibitors are metabolized via the cytochrome P450 (CYP450) system. CYP450-2C19 and CYP450-3A4 are the primary enzyme systems involved in their metabolism. Lansoprazole is metabolized equally by both enzymes, but metabolism of esomeprazole, pantoprazole and omeprazole is predominately by CYP450-2C19. Rabeprazole is metabolized by the same cytochrome enzymes, but also undergoes non-enzymatic metabolism, circumventing the CYP450 pathways and allowing continued metabolism despite the presence of agents that compete for the CYP450 enzymes. These subtleties have important implications for drug-drug interactions. Medications that are metabolized by these enzyme systems compete and may promote excessive drug levels and their associated toxicity. PPI are prescribed for most of the patients to treat gastrointestinal symptoms³, an overuse of PPI in patients with chronic kidney diseases could produce adverse effect like hospital acquired pneumonia, hyponatremia, hypomagnesaemia and elevated level of serum creatinine and glomerular filtration rate.

A lack of gastric acid in the stomach will reduce indigestion, pain, heartburn and aid in healing of peptic ulcer. However, a related concern is the risk of respiratory tract infection resulting from profound acid inhibition due to the use of PPIs may be associated with increased risk of community acquired pneumonia.

Hyponatremia is a rare complication of PPI therapy. It is defined as a decrease in serum sodium below 136mmol/L, is a common occurrence in both inpatients and outpatients. The pathophysiologic mechanism of hyponatremia is unclear, but seems most likely related to inappropriate antidiuretic hormone (ADH) production. Discontinuation of PPI and fluid restriction corrected underlying hyponatremia. Cessation of PPI reduced the urinary sodium to concentrations appropriate to sodium intake and volume status. Taken together, the association of PPIs and hyponatremia is rare, but should be alert when evaluating the hyponatremic patient who is receiving a PPI

Hypomagnesemia can be a serious side effect to PPI therapy, it may tend to variety of symptoms including potentially life threatening complication such as seizures, cardiac arrhythmias and secondary electrolyte disturbance hypomagnesemia develop due to gastrointestinal and or renal diseases. PPI impairs the intestinal magnesium absorption of

through a molecular effect on magnesium transporters in genetically predisposed individuals. Chronic kidney diseases are rapidly growing public health problem with a population prevalence of 5%-15% in developed countries. CKD is associated with substantially increased risk of co-morbid complications and death, accounting for disproportionately large burden of healthcare and disability cost. Identifying individuals at risk of CKD and understanding the modifiable factors that accelerates the loss of kidney function are vital⁴. There are concern regarding overutilization of proton pump inhibitors often started inappropriately and with treatments prolonged without clear medication⁵.

Exposure to PPI may also associate with an increased risk of incident CKD and CKD progression⁶. Its use has been linked with the incidence of a number of infrequent but serious adverse effect that are community acquired pneumonia, acute interstitial nephritis, hyponatremia and hypomagnesaemia in CKD patients⁷.

METHODS:

A Retrospective observational study was conducted in the Fortis hospital, Bennerghatta road, Bangalore from June to august 2018. A total of 70 patients who met the inclusion criteria of this study were randomly choosed from the Patients having or not having CKD undergone treatment with PPI. Patients of both the genders were included in the study. Out of 70 patients, 35 patients were having chronic kidney diseases and 35 patients is not having chronic kidney diseases. The data were analysed to find out the possible abnormalities in serum creatinine, GFR, Sodium and magnesium level in the serum. The possible risk of hospital acquired pneumonia are assessed by patient history interview, case record analysis and from laboratory values. The results are tabulated by simple statistical methods.

MEASURES:

Elevated level of serum creatinine:

Elevated level of glomerular filtration rate:

Hyponatremia: is a rare complication of PPI therapy. It is defined as a decrease in serum sodium below 136mmol/L, is a common occurrence in both inpatients and outpatients. The pathophysiologic mechanism of hyponatremia is unclear, but seems most likely related to inappropriate antidiuretic hormone (ADH) production.

Community acquired pneumonia: A lack of gastric acid in the stomach will reduce indigestion, pain, heartburn and aid in healing of peptic ulcer,

However, a related concern is the risk of respiratory tract infection resulting from profound acid inhibition due to the use of PPIs may be associated with increased risk of community acquired pneumonia

RESULT AND DISCUSSION:

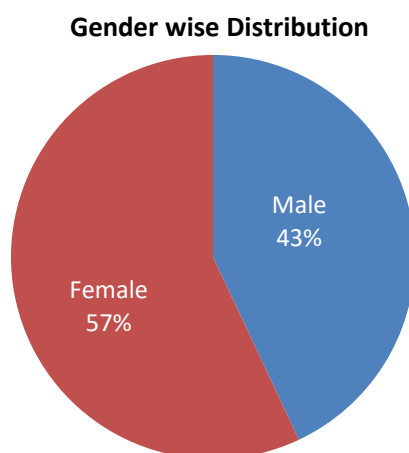


Figure No.1: Gender Wise Distribution of Patients

Table No.1: Age Wise Distribution of Patients:

S.No	Age	No Of Patients (%)	CKD patients with PPI (%)	Non CKD patients with PPI (%)
1	20-30	4 (6%)	1(3%)	3(8%)
2	30-40	6 (8%)	3(8%)	3(8%)
3	40-50	8 (11%)	5(14%)	3(8%)
4	50-60	9 (13%)	5(14%)	4(12%)
5	60-70	25 (36%)	10(29)	15(43%)
6	70-80	14 (20%)	8(24%)	6(18%)
7	80-90	4 (6%)	3(8%)	1(3%)
TOTAL		70	35	35

A total of 70 CKD patients were included in this study, in which 35 patients were having CKD and undergoing treatment with PPI and 35 patients were not having CKD and and undergoing treatment with PPI. Out of 70 patients, 43% of patients were males and 57% of patients were females (Figure no 1) and Age wise classification of patients reveals that 36% of patients were found to be in the age group of 60-70 years, followed 22% in the age group of 70-80years (Table no.1)

On assessing various co-morbidities associated with CKD, founds that most commonly reported co-morbidities were Gastro intestinal diseases (36%), Diabetes mellitus (16%), Hypertension (26%), Hyperlipidemia (22%) and both hypertension and Diabetes Mellitus together (22%).

The CKD patients are classified based on the diagnosis into four categories like patients after surgery (30%), Gastrointestinal diseases with CKD (16%), Fever with CKD (43%) and other diagnosis with CKD (11%).

TABLE NO.3: Different Class of proton pump inhibitors using for CKD and Non-CKD Patients: (N=70)

S. No	Types of PPI used	No of Patients	Percentage of Patients
1	Pan 40	68	97
2	Razo D	2	3
3	TOTAL	70	100

In this study, it founds that Pan 40(Pantoprazole) were given in almost 97% of the patients followed by 3% with Tab. Razo D (Rabeprazole+ Domperidone). (Table No 3)

TABLE NO.4: Creatinine value of CKD and Non-CKD patients: (N=35)

SL NO:	Creatinine value	CKD patients		Non CKD patients	
		1 st day on PPI	Mean 10 th day on PPI	1 st day on PPI	Mean 10 th day on PPI
1	<0.6	0	0	7	5
2	.6-1.2	7	3	22	25
3	>1.2	28	32	6	5
TOTAL		35		35	

The study found that 91% of CKD patients on treatment with PPI were having increased value of serum creatinine on the mean 10th Day of treatment with PPI compared to first day of treatment with PPI and also founds that CKD patients with normal creatinine value were comparatively low (9%) on the

mean 10th day of treatment than the first day of treatment with PPI in the CKD patients (3%). But in case of non CKD patients, high number of patients remains in the normal serum creatinine category on mean 10th day on PPI than the first day. (Table No 4)

TABLE NO.5: Blood urea nitrogen value of CKD and Non CKD patients: (N=35)

S NO:	Blood Urea Nitrogen	CKD Patients		NON CKD Patients	
		1 st day on PPI	Mean 10 th day on PPI	1 st day on PPI	Mean 10 th day on PPI
1	<6	0	0	2	2
2	6-20	6	2	20	21
3	>20	29	33	13	12
4	TOTAL	35		35	

The increased value of BUN was found in CKD patients on PPI (94%) in the mean 10th day of treatment compared to first day on PPI (83%) and also founds that CKD patients with normal BUN value were comparatively less (6%) on the mean 10th day of treatment than the first day (17%). But in non CKD patients, high number of patients remains in normal BUN level category on mean 10th day on PPI (60%) than the first day (57%). (Table No 5)

The decreased value of sodium was found in 30 CKD patients (86%) in the last day of treatment with PPI compared to first day on PPI that is 24 (69%), followed by normal sodium value comparatively less that is 3 (9%) on the mean 10th day of treatment than the first day that is 7 (20%). But in non CKD patients, 21 patients (60%) remains in the normal sodium level category on mean 10th day on PPI than the first day that is 2 patients (6%).

TABLE NO.6: Range of hospital acquired pneumonia in CKD and Non-CKD patients: (N=35)

SL NO	Hospital acquired pneumonia	CKD Patients		NON- CKD Patients	
		No of patients	%	No of patients	%
1	Yes	10	29	1	3
2	No	25	71	34	97
3	TOTAL	35	100	35	100

The range of hospital acquired pneumonia in the CKD patients is 10 (29%) higher than that of non-CKD patients on PPI 9 (3%) in CKD patients. (Table No 6)

CONCLUSION:

The study found that long-term use of proton pump inhibitors was associated with increased risk of development of CKD and death. It can lead to increase in the value of serum creatinine, blood urea nitrogen and tend to decrease sodium (Hyponatremia), thereby worsening the health stage of kidney patients.

CONFLICTS OF INTEREST:

There are no conflicts of interests.

ABBREVIATIONS USED:

CKD –Chronic Kidney Disease
PPI- Proton Pump Inhibitors

ACKNOWLEDGEMENTS:

Author like to express sincere thanks to Chakrapani konduru, HOD of Fortis hospital, and clinical pharmacist Ancy Varghese, Varghese Titus, Aravind. Also like to express sincere thanks to all faculty of Department of pharmacy Practice, Vinayaka Mission's College of Pharmacy.

BIBLIOGRAPHY:

1. Pradeep Arora, Anu Gupta. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. *BMC Nephrology* (2016) 17:112 DOI 10.1186/s12882-016-0325-4
2. Chih-Hung Chen, Hsiu-Chen Lin, Hsiu-Li Lin, Yi-Tsung Lin, Jung-Min Chou. Proton pump inhibitor usage and the associated risk of pneumonia in patients with chronic kidney disease. *Journal of Microbiology, Immunology and Infection* (2015) 48, 390-396
3. Linda Härmak,1 Hans E. van der Wiel, 2 Mark C. H. de Groot. Proton pump inhibitor-induced acute

interstitial Nephritis. *British Journal of Clinical Pharmacology*.

DOI:10.1111/j.1365-2125.2007.02927.

4. Benjamin Lazarus, MBBS1,2, Yuan Chen, MS1, Francis P. Proton Pump Inhibitor Use and Risk of Chronic Kidney Disease *JAMA Intern Med.* 2016 February 1; 176(2): 238–246.
doi:10.1001/jamainternmed.2015.7193.
5. Derk C. F. Klatte, Alessandro Gasparini, Hong Xu, Association Between Proton Pump Inhibitor Use and Risk of Progression of Chronic Kidney Disease. *Gastroenterology* 2017; 153:702–710.
6. Yan Xie, Benjamin Bowe, Tingting Li, Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. *Kidney International* (2017) 91, 1482–1494.
7. Mark A Perazella et al. Proton pump inhibitors and the kidney: Critical review. *Clinical nephrology*. September 2007, DOI: 10.5414/CNP68065