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Original Research Article

Association of proton pump inhibitors with renal dysfunction: a cross-sectional study

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ABSTRACT

Background: Proton pump inhibitors are the most frequently prescribed class of medications for prescription and over-the-counter, and the data suggest that comorbidities, polypharmacy, self-medication, no clear indications and duration beyond the recommended guidelines PPIs use are associated with renal dysfunction. Aim was to study the proportion of renal dysfunction among patients using oral PPIs and determine the association between the duration of oral PPIs use and the severity of renal dysfunction.
Methods: The data collection of 250 patients was done at the time of contact, which included demographic profiles, complete medical history, physical examination, and laboratory investigation in this study. For analysis, name of oral PPIs used, duration and dosage of oral PPIs therapy, laboratory values of serum blood urea, serum creatinine, eGFR, and serum electrolytes parameters have been considered.
Results: Amongst 250 patients with PPIs used for a week, 23 patients showed mildly reduced kidney function (p=0.000), PPIs used for >1 to 2 weeks, 29 patients showed grade 2 kidney function (p=0.001), while PPIs used for >2-3 weeks only two patients showed grade 3 kidney function (p=0.44). Patients aged >50 years in all groups showed grade 2 renal function, regardless of the duration of PPIs use. Increasing age, males, rural, smoking, and alcoholics were the risk factors for renal dysfunction. PPIs use significantly impacts eGFR.
Conclusions: Collectively, this study found a significant association between PPIs use and renal dysfunction. PPIs used for >2 weeks in elderly patients have shown a 4−fold increased risk of developing renal dysfunction.

Keywords: Proton pump inhibitors, Renal dysfunction, Serum creatinine, Estimated glomerular filtration rate

INTRODUCTION

PPIs have arisen as a class of drugs for the treatment of acid related diseases and remain the most effective treatment. They act by reducing acid production from the oxyntic cells by blocking the H+/K+ Adenosine Triphosphatase (ATPase) enzyme. PPIs available in the market are omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole, and dexlansoprazole.[1,2] They are the most frequently prescribed class of medications across the world and are available both for prescription and for sale over the counter.[3] The authorized uses of PPIs are gastric ulcer, duodenal ulcer, eradication of Helicobacter pylori infections, severe peptic ulcer bleeding (following endoscopic treatment), dyspepsia, Gastro-Oesophageal

Reflux Disease (GERD), prevention and treatment of NSAIDs-induced ulcer, Zollinger-Ellison syndrome.[1,2]

Table 1: Stages/severity of renal dysfunction determined by the following criteria.

Stages	GFR	Description
1	90+	Normal kidney function
2	60 -89	Mildly reduced kidney function.
3A, 3B	45-59, 30-44	Moderately reduced kidney function
4	15-29	Severely reduced kidney function
5	<15 or on dialysis	Very severe, or end-stage kidney failure

Omeprazole was the first PPI to be marketed, synthesized in 1979, launched in 1988, and became one of the best-selling medications of all time.[4,5] In 2009, PPIs were listed as the third best-selling class of drugs.[6] Lansoprazole, followed by rabeprazole, pantoprazole, and esomeprazole, respectively, was next in the sequence to be launched in the market.[7] Esomeprazole and pantoprazole come under the top 10 drugs by prescription counts.[8]

The most frequent and short-term complications of all PPIs are seen in 2% to 5% of the population, which includes headache, nausea, constipation, flatulence, diarrhoea, skin rash, and dizziness.[1,2,9] These adverse effects are mostly less severe, resolve on their own, and are independent of dose and age. Predominant effects are seen with lansoprazole and pantoprazole, which include central nervous system effects (mainly), cardiovascular and gastro-intestinal tract effects.[1-3,9] Only a short course of PPI therapy (4-8 weeks) is required in GERD, but long-term therapy is commonly seen.[3,10,11] In recent years, PPIs began to be prescribed irrationally to patients without clear-cut indications, for duration beyond the recommended guidelines, and are taken as self-medication.[9,12]

The overuse of PPIs among inpatients and outpatients has increased due to the efficacy, convenience, and easy availability of medications.[10,13,14] Another possible reason for the increased risk of adverse drug events is comorbidities and polypharmacy.[15,16] The number of dispensed prescriptions of PPIs was enhanced by 20% from approximately 74 million prescriptions to 95 million. Many reports have suggested that the over-prescription of PPIs has also increased in primary and secondary healthcare centers worldwide.[17] In the Indian population, few studies have documented the association between PPIs and renal parameters. This study will provide additional information to the literature and decrease substantial disease. Also, none of the studies has shown the proportionality of renal dysfunction in patients using PPIs.

METHODS

Study design

The enrolled patients were provided with a patient information sheet explaining the study procedures, risks, benefits, responsibilities, etc. Their complete information patient was filled in CRF that contained all demographic profiles such as age, sex, address, phone no, OPD C.R. - unit/ward, education, and occupation. Also, a complete history of the patient, including intake of other drugs, patient complaints, past medical history, family history, drug history, personal history, BP, pulse rate, S. creatinine, S. blood urea, S. electrolyte (Na+, K+, Cl−), eGFR, and FBS at the time of contact were also collected.

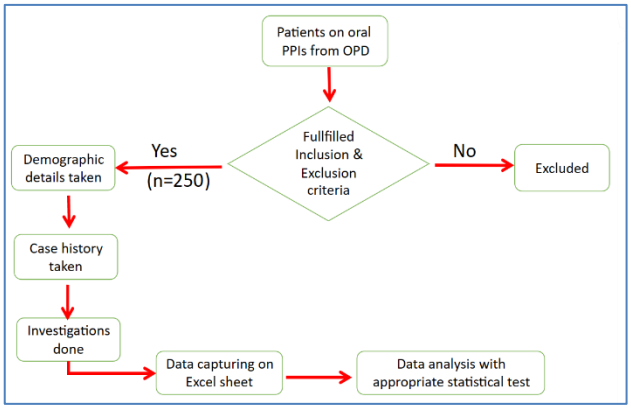

Figure 1: Study work flow.

The gathered data were used for analyzing the following parameters: name of oral PPIs used; duration and dosage of oral PPIs therapy; laboratory values of blood urea, S. creatinine, eGFR, and S. electrolytes. In this study, investigations were done after the beginning of the therapy. The baseline examination includes BP monitoring, pulse rate, and laboratory investigation like S. creatinine, S. blood urea, S. electrolytes (Na+, K+, and Cl−), eGFR, and FBS.

Calculation of eGFR

eGFR calculated by the abbreviated MDRD (modification of diet in renal diseases).[18]

$$eGFR = 186 * (Creatinine/88.4) - 1.154 \times (Age) - 0.203 \times (0.742\ in\ female) \times (1.210\ if\ black)$$

S. creatinine measured in mg/dL and age in years was taken. Data were statistically analyzed using a non-parametric test (Fisher's exact test, Chi-square test, and others) and p values on SPSS version 20.0 software. Here, p value <0.05 was considered significant.

RESULTS

A total of 250 patients were studied during a period of one year. Among 250 patients, the maximum number of patients were in the age group of 41-50 years with 21.2% (53 patients), while the patients with age greater than 70 years were only 2.8% (7 patients). 140 patients (56%) were males, while 110 patients (44%) were females (Table 2). 57.2% of patients were from rural areas and 42.8% were from urban areas. The data reveals that 29.6% of patients consumed alcohol, and 84.8% were non-smokers. The maximum patient FBS level was within the normal range. Only 2% of patients had FBS levels less than or equal to 80 mg/dl (Table 3).

Table 2: Age and gender distribution of subjects.

Age (years)	N	Males	Females	%
18-20	20	7	13	8
21-30	51	31	20	20.4
31-40	46	23	23	18.4
41-50	53	32	21	21.2
51-60	44	21	23	17.6
61-70	29	20	9	11.6
>70	7	6	1	2.8
Total	250	140	110	100

Table 3: FBS, pulse rate, serum creatinine levels and serum blood urea in study subjects.

Tests	Value	N	Age (years)					%
			18- 30	31- 40	41-50	51- 60	>60	
Fasting blood sugar level (mg/dl)	≤80	5	0	2	0	1	2	2
	81-85	50	14	6	19	7	4	20
	86-90	78	20	15	15	12	16	31.2
	91-95	67	20	12	11	14	10	26.8
	96-100	50	17	11	8	10	4	20
Pulse rate (beats/min)	≤60	2	0	0	0	2	0	0.8
	61-70	31	6	4	9	5	7	12.4
	71-80	82	27	12	16	13	14	32.8
	81-90	91	27	17	18	18	11	36.4
	91-100	44	11	13	8	8	4	17.6
Serum creatinine levels (mg/dl)	≤ 0.5	5	1	1	2	0	1	2
	0.6-0.7	80	21	22	21	14	2	32
	0.8-0.9	106	30	14	28	18	16	41.6
	1.0-1.1	49	17	8	2	11	11	19.6
	1.2-1.3	10	3	1	0	1	5	4.8
Serum blood urea (mg/dl)	≤15	2	1	0	0	0	1	0.8
	16-20	45	14	10	6	8	7	18
	21-25	42	11	8	12	6	5	16.8
	26-30	47	12	7	12	5	11	18.8
	31-35	48	15	11	5	12	5	19.2
	36-40	38	10	7	7	9	5	15.2
	41-45	28	8	3	11	4	2	11.2

Table 4: Estimated glomerular filtration rate in study subjects.

Grade	eGFR values (ml/min/1.73m^2)	N	Age (years)					%
			18-30	31-40	41-50	51-60	>60	
G1	≥90	192	64	41	50	28	9	76.8
G2	60-89	56	7	5	3	16	25	22.4
G3	30-59	2	0	0	0	0	2	0.8

Table 5: Association between duration of PPIs use and estimated glomerular filtration rate.

Grade	eGFR (ml/min/1.73 m^2)	Duration of PPIs use				P valve
		1 week	>1-2 weeks	>2 -3 weeks	Total	
G1	≥90	89	95	8	192	0.013
G2	60-89	23	29	4	56	
G3	30-59	0	0	2	2	
Total N (%)		112 (44.8)	124 (49.6)	14 (5.6)	250	

Table 6: Effect of 1-week PPIs use on eGFR.

Grade	eGFR (ml/mi n/1.73 m^2)	1 week, N (%)	Age (years)					P value
			18-30	31-40	41-50	51-60	>60	
G1	≥90	89 (79.5)	33	19	22	13	2	0.000
G2	60-89	23 (20.5)	3	0	1	6	13	
G3	30-59	0	0	0	0	0	0	
Total		112	36	19	23	19	15	

Table 7: Effect of >1-2 weeks PPIs use on eGFR.

Grade	eGFR (ml/mi n/1.73 m^2)	>1-2 weeks, N (%)	Age (years)					P value
			18-30	31-40	41-50	51-60	>60	
G1	≥90	95 (76.6)	28	20	26	14	7	0.001
G2	60-89	29 (23.4)	4	5	1	8	10	
G3	30-59	0	0	0	0	0	0	
Total		114	124	32	25	28	17	

Table 8: Effect of >2-3 weeks PPIs use on eGFR.

Grade	eGFR (ml/mi n/1.73 m^2)	>2-3 weeks, N (%)	Age (years)					P value
			18-30	31-40	41-50	51-60	>60	
G1	≥90	8 (57.1)	3	2	2	1	0	0.44
G2	60-89	4 (28.6)	0	0	0	2	2	
G3	30-59	2 (14.3)	0	0	0	0	2	
Total		14	3	2	2	3	4	

Table 9: Association of type of PPIs use and dosage with eGFR

Grade	eGFR	Panto-prazole	Pantoprazole	Omeprazole	Omeprazole	Rabeprazole	Rabeprazole	Total
	(ml/min /1.73m^2)	40 mg	80 mg	20 mg	40 mg	20 mg	40 mg	
G1	≥90	141	9	24	2	14	2	192
G2	60-89	44	1	5	3	2	1	56
G3	30-59	0	2	0	0	0	0	2
Total		185	12	29	5	16	3	250
Percentage		74	4.8	11.6	2	6.4	1.2	

Total 36.4% patients had a pulse rate between 81-90 beats/min, whereas only 2 patients (0.8%) had a pulse rate of less than or equal to 60 beats/min (Table 3). Serum creatinine levels in 41.6% patients were between 0.8-0.9 mg/dl and 2% patients had less than 0.5 mg/dl. Also, out of 41.6% patients, the maximum patients were in the age group under 30 years who were on PPIs (Table 3). From the S. blood urea test, the maximum number of patients were between 31-35 mg/dl while 0.8% patients had serum blood urea value ≤15 mg/dl (Table 3). In the study, the MDRD equations were used to calculate the eGFR, and found that 76.8% of the patients had an eGFR value in grade 1 (Table 4). Electrolytes such as s. Na+ levels, S. K+ levels and S. Cl- levels were within the normal range in all patients. 124 patients consumed PPIs for more than 1 week but less than or equal to 2 weeks, out of which 29 patients had an eGFR value less than 90 mL/min/1.73m^2 and 95 patients had an eGFR value greater than or equal to 90

mL/min/1.73m^2, respectively (Table 5). It also shows that out of 250 patients, 56 patients who consumed PPIs for 1-3 weeks showed mildly reduced kidney function and 2 patients (grade 3) who consumed PPIs for >2-3 weeks showed moderately reduced kidney function and the remaining 192 patients had normal kidney function. The eGFR value was calculated using the MDRD equation. To further analyze the impact of PPIs, a Fisher's exact test was performed. The SPSS version 20.0 software was used to perform this test. The generated p value was 0.013, which is significant (p value >0.05). Among 112 patients, 79.5 % had normal kidney function, and the rest had mildly abnormal kidney function (Table 6). 76.6 % of patients had normal kidney function and 23.4 % of patients had mildly deranged kidney function (Table 7). Out of 124 patients, 17 were in the age group >60 years. 14.3% patients have an eGFR in the range of 30-59 ml/min/1.73m^2 (Table 8). The table also shows two patients in age >60 years lie in this range was a significant decrease in eGFR. The relationship between eGFR and different types of PPIs, namely, pantoprazole, omeprazole, and rabeprazole, has been studied in this work. The table depicted 74% patients were on pantoprazole (40 mg), out of which 141 patients showed normal kidney function with an eGFR value greater than or equal to 90 ml/min/1.73m^2, and 4.8% were prescribed pantoprazole (20 mg), of whom 10 showed normal kidney function. Patients prescribed omeprazole and rabeprazole were less, and out of whom 11.6% were prescribed 20 mg of omeprazole and 6.4% were prescribed 20 mg of rabeprazole. Study shows that most of the patients who were prescribed either pantoprazole, omeprazole, or rabeprazole with lesser dosage showed normal kidney function rather than higher dosage (Table 9).

DISCUSSION

Recent studies have proven that PPIs are the most effective treatment of acid-related disease as they minimize acid production from the oxyntic cells by blocking H+/K+ ATPase enzymes.[1-3] The previous study has shown that PPIs therapy in GERD is required for 1-2 month. Non-judicious prescription of PPIs to patients without complete information may lead to a rise in mortality, adverse drug events, and death.[1,9,12] The irrational overuse of PPIs and self-medication is a huge concern for mankind. In the present observational study, PPIs considered are omeprazole, pantoprazole, and rabeprazole with different doses for 1-3 weeks. The study contributes to finding the proportion of renal dysfunction among patients using PPIs. Moreover, the study also observes the association between the duration of PPIs use and the severity of renal dysfunction.

A study conducted by Benjamin Lazarus et al. showed that increasing age is one of the risk factors for CKD and AKI.[13-19] Gulipalli Sowjanya et al. also showed that patients within the age group of 56-60 years are at higher risk of renal diseases.[20-27] Arora et al cohort study reported that younger individuals were more likely to develop CKD associated with PPIs use.[28] In this study, the patients were in the age group of 18-75 years with a mean age of 55.5 years. The study shows that age is one of the risk factors for renal dysfunction.

Lazarus et al and Xie et al reported similar findings that males are a risk factor for CKD and AKI.[19,21] Other authors showed similar results that male patients are more vulnerable to renal diseases.[20,22] Also in this study, it was observed that 56% patients were males and 44% were females. This shows that male patients are more prone to renal dysfunction than female patients. Moreover, the present study also suggests that rural patients are more likely to be affected by renal dysfunction compared to urban patients. Also, the study found that alcoholics and smokers are likely to be prone to renal dysfunction. Similar results were obtained by Benjamin Lazarus et al. and Yan Xie et al that smoking is a risk factor for renal CKD.[19,21] In the present study, all the patients showed a normal range of vital signs such as pulse, systolic BP, and diastolic BP. However Lazarus et al and Xie et al showed that increased BP is a risk factor for renal disease.[19,21] Xie et al study showed a significantly elevated risk of doubling S. creatinine levels.[21] Another study reported that S. creatinine is a risk factor for kidney disease progression and ESRD.[23] A study reported that PPIs users had an increased risk for double levels of creatinine and also showed associated with a significant increase in s. creatinine which further leads to kidney dysfunction.[20] In contrast to these study, our study showed no significant risk of renal dysfunction when patients s. creatinine levels were considered. For the S. blood urea test, the maximum number of patients showed values between 31-35 mg/dl while 0.8% of patients have s. blood urea values ≤15 mg/dl. Thus, in contrast to Sowjanya et al documented that PPIs users with increased BUN have no significant impact on renal dysfunction and also reported that PPIs users had an increased risk for double levels of creatinine and BUN compared to non-PPIs users.[20] The observation demonstrates that there may be some risk factors in causing renal disease with the increase in BUN levels. A recent study shows that there are no significant differences in BUN levels.[24] The MDRD equation was used to calculate the eGFR values.[20] The generated value showed that 76.8% of the patients have an eGFR value in grade 1 kidney function, 22.4% were in grade 2 kidney function and 0.8% showed grade 3 kidney function. The study shows that PPIs use has a significant association with renal dysfunction. Lazarus et al in the ARIC study, eGFR show that there is a risk of renal dysfunction in PPIs users.[19] Similar to this study, Yan Xie et al. showed the impact on CKD and ESRD.[21] Other authors reported that PPIs users have a higher risk of developing renal diseases.[20] The S. electrolytes such as Na+, K+ and Cl- levels have been determined to check their impact on kidney functions when different dosages of PPIs were given to patients. In this study, there was no significant change in the S. electrolytes of the patients. In this study, the maximum number of patients were in the normal FBS range; one major reason may be due to comorbid conditions which

were excluded from the study. A short course of PPIs use may be another reason.

Also, the present study shows the association between the duration of PPIs use and the severity of renal dysfunction. The study shows that 56 patients who were prescribed PPIs for 1-3 weeks showed mildly reduced kidney function, and 2 patients who were on PPIs for >2-3 weeks showed grade 3 kidney function. Therefore, it can be stated that there is a significant association between the duration of PPIs use and eGFR (p value 0.013) and it was obtained that all groups irrespective of the duration of PPIs use, patients in the age group >50 years showed grade 2 kidney function.

Klepser et al showed a positive association between PPIs user patients and AKI.[25] Antoniou et al reported that there was thrice more risk of AIN amongst the PPIs user patients.[26] Lazarus et al showed a high risk of PPIs use and more than 1.5 times more risk of CKD.[19] The authors established that PPIs use was more common among patients with CKD, and showed that the chances of CKD were 1.88 times higher among patients on PPIs.[27] Arora et al. found that PPI user patients are at higher risk of incidence of CKD, and higher mortality.[28] Gulipalli Sowjanya et al carried out a study to show that PPIs use is related to a high risk of the development of renal disease.[20] Wu et al documented a significant association between AKI or CKD events and PPIs, including dexlansoprazole, lansoprazole, pantoprazole, omeprazole, esomeprazole, and rabeprazole.[29] Also, in our study, patients were prescribed different dosages of PPIs. This study shows that 74% of the total patients were on pantoprazole (40 mg) out of which 141 patients showed grade 1 kidney function and 4.8% of patients were on pantoprazole (80 mg), amongst them, only 9 patients showed grade 1 kidney function. In the study, patients prescribed omeprazole and rabeprazole were less compared to pantoprazole. This study established that most of the patients who are on PPIs with lesser dosages showed normal kidney function rather than higher dosages. The results obtained in the present study is similar to Lee et al and Leonard et al.[30,31] A possible limitation of the current study is the sample size, which might be larger. Multicentre research can be conducted in this regard so that more information about PPIs on renal dysfunction could be obtained.

CONCLUSION

PPIs are the most commonly prescribed drug by clinicians, and found a significant association between PPIs use and renal dysfunction. PPIs use in the elderly population has shown a 4-fold increased risk of developing renal dysfunction.

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