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Original Research Article

## Use of proton pump inhibitors in dialysis unit in tertiary care hospital: a pharmaco-epidemiological study

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### ABSTRACT

**Background:** Proton pump inhibitors (PPI) are generally thought to be safer drug with fewer adverse effects. Though this class of the drug is thought to be well tolerated, a detail study about actual use of these agents in nephrology department is still awaited in many parts of India. There had been case reports and case series which were reporting PPIs producing acute interstitial nephritis progressing to acute renal failure. The risk of PPI treatment in haemodialysis patients remains unexplored. The aim of the study was to evaluate a drug utilization of PPI in patient undergoing haemodialysis procedure.

**Methods:** In this study every day visit to the dialysis units of the hospitals was carried out. After taking consent from the patients, the information from the case-report form was noted like; age, sex, diagnosis, laboratory reports and drug prescribed. No personally identifiable information about patient or physician was collected. After this an interview of patients was taken.

**Results:** In this study, out of 126 patients 76.6% were male and 23.4% were female. Out of these 126 patients 88.89% patients were on PPI. Nearly 54% were using PPI for more than six months. Nearly 29% patients were using PPI for more than 12 months.

**Conclusions:** As many case-reports and studies are suggesting, there is co-relation of PPI and acute interstitial nephritis from this study we suggest that especially in nephrology unit patients', more caution must be exercised while using PPI.

**Keywords:** PPI, Drug utilization study, Dialysis, AIN, ARF

### INTRODUCTION

The principal aim of drug utilization research is to facilitate the rational use of drugs in populations. Without knowledge of how drugs are being prescribed and used, it is difficult to point out or make comment on rational drug use or to suggest measures to improve prescribing habits. Though drug utilization research in itself does not necessarily provide answers, but it contributes to rational drug use in important ways as how drugs are being used like, (prevalence, incidence, extent of use) at a particular moment and/or in a particular area (eg. in a country, region, community or hospital). Researchers can evaluate as what extent of drugs (properly used, overused or

underused), the pattern or profile of drug use, and can compare the observed patterns of drug use (for the treatment of a certain disease with current recommendations or guidelines).<sup>1</sup>

Proton pump inhibitors (PPIs) are generally well tolerated. PPI generally thought to be safer drug with fewer adverse effects, which are similar to the placebo with less than 5% incidence ratio, so PPIs are the most commonly used drug worldwide.<sup>2</sup> Several drug utilization studies were carried out in India, which show that the use of proton pump inhibitors varies from 45-85% in different conditions.<sup>3-7</sup> In 82.96% of patients suffering from chronic renal disease PPI were used.<sup>8</sup> Another study of intravenous PPI

utilization shows in 89% internal medicine ward patients and 34.04% patients in surgery ward PPI were used.<sup>9</sup>

Though this class of the drug is thought to be well tolerated there had been case reports and case series which were reporting PPIs producing acute interstitial nephritis (AIN) progressing to acute renal failure (ARF). The first report of omeprazole induced AIN was reported in 1992 while that of pantoprazole and lansoprazole were reported in 2004, simultaneously similar reports of all PPI are coming.<sup>10</sup> The risk of PPI treatment in hemodialysis patients remains unexplored.<sup>11</sup> The aim of the study was to evaluate drug utilization of PPI in patient undergoing haemodialysis procedure.

## METHODS

This observational study was conducted in the dialysis units of Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital, Sangli and Government Medical College, Miraj. Study was conducted from 1<sup>st</sup> January 2015 to 31<sup>st</sup> March 2015. The patient undergoing dialysis and giving consent to involve in the study such patients were selected. After taking consent from the patients, the information from the case-report form was noted like; age, sex, diagnosis, laboratory reports. No personally identifiable information about patient or physician was collected. Along with this information, the patient's prescription was also noted from case report form. After this an interview was taken by asking following questions to the patient- (a) when the dialysis process done first? (b) how many times you have gone through this procedure of dialysis? (c) after how many days you have to do another procedure of dialysis (d) which drugs you take before, during and after the procedure of dialysis? (e) if the prescription contains any PPI then, from how many days you are taking these drugs continuously? (f) in between two different dialysis procedures do you suffer from any gastritis or GIT related problems? If yes, which drug you take to get relief from that.

## RESULTS

The average age of patients was 47.04±14.75 (mean±SD) (range 19-77 years). In this study we observed that out of 126 patients 76.6% were male and 23.4% were female. Out of these 126 patients 88.89% patients were on PPI (Table 1).

Only 3% patients were on NSAIDs and paracetamol was the commonest used NSAID. 11.11% prescriptions contained antimicrobial agents; in this amoxicillin in combination with clavulanic acid was the most commonly used combination. Nearly 33.33% patients were using FDC of PPI out of which domperidone+PPI was the commonest used FDC (Figure 1).

We observed that nearly 54% patients in dialysis unit were using PPI for more than last six months. While 35%

patients taking PPI from last 1 to 6 months. Nearly 29% patients were taking PPI for more than 12 months. Out of these, 2 patients each took PPI for more than 30 months and 42 months. It ranges from 1-43 months. Most of the patients from study group were undergoing dialysis for twice a week. It was good to note that 98% patients did not consume any OTC drug without physicians' advice. Amongst all these patients 16% patients were newly diagnosed, and they had undergone the dialysis procedure less than 10 times. 12% patients had done dialysis in between 51-60 times. One of them had it done for 1040 times (Figure 3).

**Table 1: Demographic data**

Age group (years)	No. of patients			Percentage (%)
	Total	Male	Female	
11-20	5	3	2	3.55
21-30	21	17	4	14.89
31-40	26	18	8	18.44
41-50	28	23	5	19.86
51-60	34	26	8	24.11
61-70	24	19	5	17.02
71-80	3	2	2	2.13
<b>Total</b>	141	108 (76.60)	33 (23.40)	100.00

**Table 2: Frequency of dialysis.**

Duration in between two dialysis	No. of patients	Percentage (%)
<b>One per week</b>	01	0.79
<b>Two per week</b>	124	98.41
<b>One per week for one year than two per week</b>	01	0.79
<b>Total</b>	126	100.00

**Table 3: Number of patients having dialysis for less than year.**

Duration on dialysis (months)	No. of patients	Percentage (%)
<b>0-1</b>	17	13.49
<b>1-2</b>	10	7.94
<b>2-3</b>	08	6.35
<b>3-4</b>	05	3.97
<b>4-5</b>	03	2.38
<b>5-6</b>	06	4.76
<b>6-7</b>	08	6.35
<b>7-8</b>	08	6.35
<b>8-9</b>	05	3.97
<b>9-10</b>	04	3.17
<b>10-11</b>	04	3.17
<b>11-12</b>	10	7.94
<b>Total</b>	88	69.84

**Table 4: OTC PPI consumption by dialysis unit patients.**

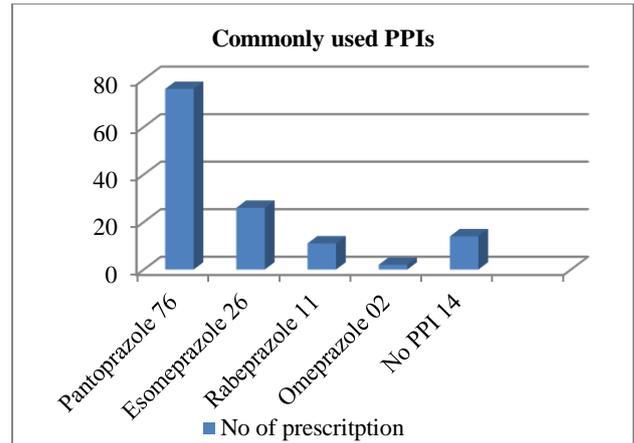
OTC consumption of PPI	No. of patients	Percentage (%)
No	123	97.62
Yes	03	2.38
	Ranitidine=01	
	Omeprazole=01	
	Ranitidine+omeprazole= 01	
<b>Total</b>	<b>126</b>	<b>100</b>

**Table 5: Use of PPI in patient having dialysis more than 200 time.**

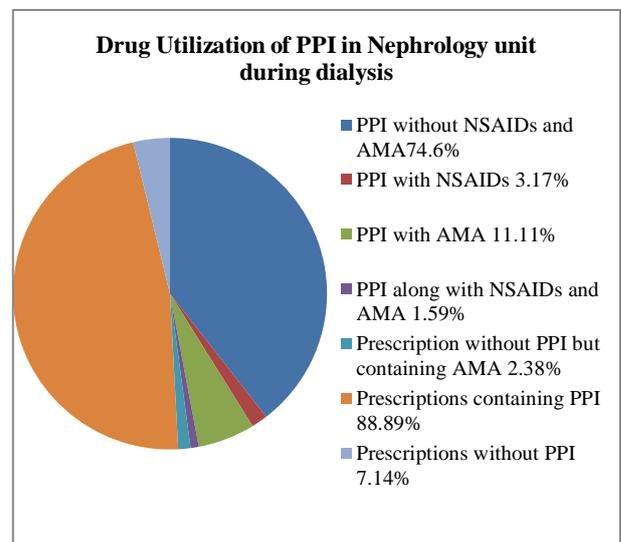
No. of dialysis for more than 200 times	Duration of PPI months
208	24
216	37
224	>3
224	25
224	26
242	>6
250	>18
260	>27
270	6
270	43
312	>6
338	>12
364	>12
374	43
936	>36
1040	>24

**Table 6: Use of PPI in patient having dialysis less than 10 times.**

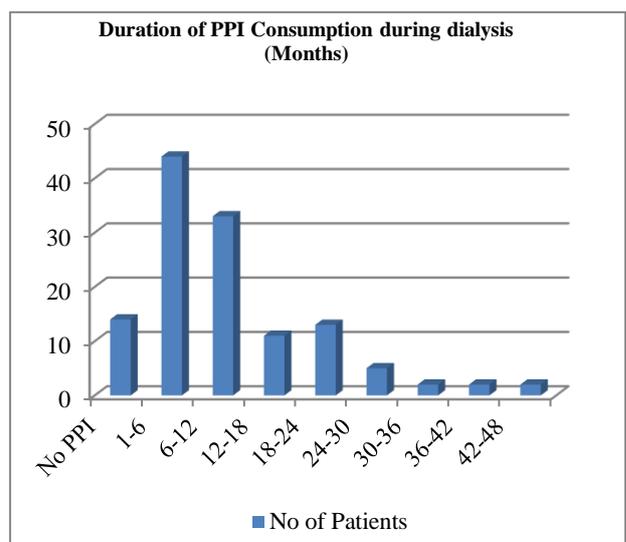
No. of dialysis for less than 10 times	Duration of PPI months
3	10 days
4	15 days
4	2
4	2
5	1
6	20 days
6	2
8	15 days
8	1
8	1
8	1
8	1
8	1
8	2
9	1
9	3



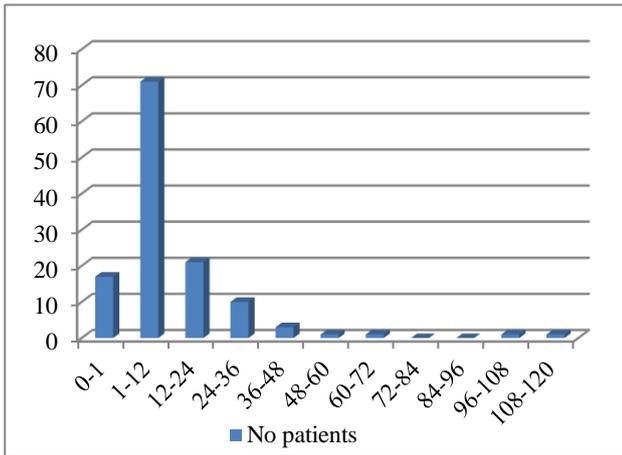
**Figure 1: Commonly used PPIs.**



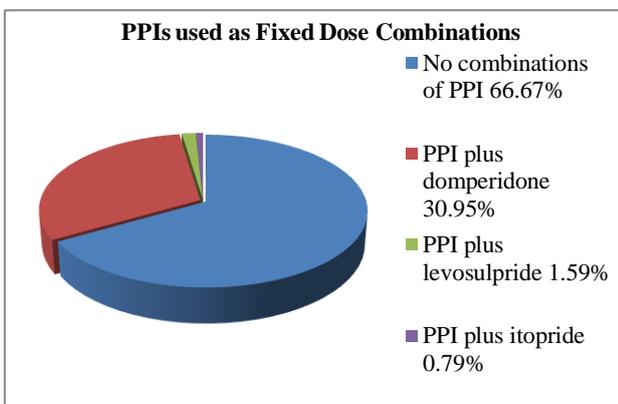
**Figure 2: Utilization of PPI in dialysis patients.**



**Figure 3: Duration of PPI consumption during dialysis.**



**Figure 4: Duration of dialysis in months.**



**Figure 5: PPIs as fixed dose combinations.**

**DISCUSSION**

Chronic renal failure is a worldwide public health problem, there is still increase in incidence and prevalence observed because of co-morbidities resulting in polypharmacy. So, we had planned drug utilization of PPI in patient undergoing dialysis procedure in the nephrology department. We wanted to know, if there is positive correlation between PPI and AIN, then what is the burden of PPI in ‘nephro-compromised’ patients.

Our study shows nearly 89% burden of PPI in study population. (Figure 1)

A study by Tamilselvan et al observed 82.96% patients who were treated for CKD were on PPI.<sup>8</sup> This is nearly equal to our study. But a study done by Soumya Santra et al observed 98% patients with CKD were on antiulcer agents like PPI and H2 blockers, but they fail to explain the distribution of these two classes.<sup>12</sup> Angel et al observed that 79.2% patients were on PPI in haemodialysis patients.<sup>11</sup> Another study was done by Misra et al and Erdem et al done a study to find out relation of PPI with serum magnesium in haemodialysis patients where they observed 55% and 72% patients were on PPI respectively.<sup>13,14</sup>

Only 3% patients were on NSAIDs and paracetamol was the commonest used NSAID. 11.11% prescriptions contained antimicrobial agents, in this amoxicillin in combination with clavulanic acid was the most commonly used combination (Figure 2). It is nearly similar to Lee et al who observed 7.1% patients with CKD stage 3-4 and 6.6% pts with CKD-5 end stage renal diseases were using NSAIDs.<sup>15</sup> Santra et al also found that 58% patients were on AMA while 30% patients were on NSAIDs, this is very high as compared with our study. But there are very less studies on the drug utilization in chronic kidney disease patients.<sup>12</sup>

In this study we asked five questions regarding use of PPI, we observed that nearly 54% patients in dialysis unit were using PPI for more than last six months. While 35% patients taking PPI from last 1 to 6 months. Nearly 29% patients were taking PPI for more than 12 months. Out of these, 2 patients each took PPI for more than 30 months and 42 months. It ranges from 1-43 months. (Table 5)

Such kind of findings were observed in study of Misra et al where patients consume PPI for 4 to 25 months.<sup>13</sup> In study done by Lee et al observed that CKD patients are taking PPI for a much longer duration compared to non-CKD patients (range 63-273 days vs 56-176 days respectively).<sup>15</sup> In another study of Erdem et al patients with haemodialysis were using PPIs for average of 42.5±35 months (range 3-144 months) which is very high.<sup>14</sup> But it may be harmful because by the Sampathkumar et al the average age of PPI induced AIN was 52.5±18 years while duration of PPI consumption before diagnosis of AIN was 1-8 weeks.<sup>16</sup> In other study of Ray et al in patients diagnosed with PPI induced AIN the age varied from 61-87 and duration of PPI varied from 10 days to 26 months.<sup>17</sup> In these two examples we have to think about one point that, in both studies one patient had developed PPI induced AIN within 10 day of PPI use.

Most of the patients from study group were undergoing dialysis for twice a week (Table 3). Nearly 98% patients did not consume any OTC drug without physicians advice. (Table 4)

Nearly 16% patients were newly diagnosed, and they had undergone the dialysis procedure less than 10 times. 12% patients had done dialysis in between 51-60 times. There was one patient who had done this procedure for more than 1040 times. It is also observed that in patients having multiple dialysis sessions PPI were still in use in large extent. (Table 4, 5)

When we think about the duration of months of dialysis, we observed that nearly 70% patients started this therapy one year (12 months) before. While 30% patients were following this therapy for more than 12 months. There was one patient who had been undergoing dialysis for nearly 10 years (Figure 4).

Nearly 33.33% patients were using FDC of PPI out of which domperidone+PPI was the commonest used FDC (Figure 5).

After comparing the use of PPI and PPI co-prescribed AMA and NSAIDS in drug utilization studies we found that, since patients undergoing dialysis are known to suffer from hyperacidity, gastric problem and symptoms like heart burn due to multiple causes, including the underlying disease process which had mandated dialysis. Hence statistically significant use of PPI was expected. We have received similar results in our nephrology unit. This is similar to the study of Tamilselvan et al and Santraet al.<sup>12</sup>

Our earlier experimental study had postulated a possible connection between use of PPI and AIN.<sup>18</sup> Based on such similar studies and other reports FDA has included this statement in his latest report in view of this information extensive use of PPI in dialysis patients is a potential problem in the nephrology unit. Multicentric as well as continuous follow-up studies might be needed before conclusive guidelines for contraindications are formed.

## CONCLUSION

As PPIs follow hepatic metabolism and no dose modification is required in patients with kidney disease, the use of PPI will be observed more. But as many case reports and studies are reports suggesting, we also found that there is probable co-relation of PPI and higher number of dialysis session. Acute interstitial nephritis can be a contributing factor for this observation (as experimental study have demonstrated such effect). We suggest that especially in nephrology unit patients, more caution must be exercised while using PPI.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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