Using proton-pump inhibitors among hemodialysis patients - single academic dialysis center's preliminary experience

Rakowska M.[1,A-E*], Brzósko S.[2,A,B,C,E,F], Dąbrowska E.[1,B,C,D], Jabłońska E.[1,B,C,D], Szczykowska J.[1,B,C,D], Prusator P.[1;B C,D], Kwaśniewska A.[1,B,C,D], Naumnik B.[2,A,E,F]

1. Students' Scientific Society, Medical University of Białystok, Białystok, Poland
2. 1st Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Białystok, Białystok, Poland

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ABSTRACT

Introduction: Proton-pump inhibitors (PPIs) are a class of drugs which decrease gastric acid production, their overuse is becoming increasingly common.
Purpose: The aim of this study was to evaluate medical indications for PPIs in a cohort of prevalent hemodialysis (HD) patients and their awareness about the medical effects of these drugs.
Materials and methods: The study was performed in 78 HD patients enrolled in a chronic dialysis program in a single academic dialysis unit. The study was based on medical history obtained from the patients (survey about drugs they take with intention of revealing PPIs, indications for the treatment, their awareness of the mechanism of action of these drugs).
Results: 46 patients (59%) took or have been taking PPIs. Almost half (49%; n=22) had no clear medical indications for the drugs. Prescription of PPIs without medical indications was more common among nephrologists (27%), when compared with gastroenterologists (5%; $p<0.05$). Only 29% (n=13) of patients taking PPIs were aware of the mechanism of action of the drugs.
Conclusions: Results of this study reveal the problem of PPI overuse among HD patients. Gastroenterologists usually prescribed PPIs according to medical indications. Lack of patients' knowledge about the indications for PPI therapy is overwhelming.
Key words: Proton-pump inhibitors, hemodialysis, overuse, side effects, nephrology

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***Corresponding author:**
Maja Rakowska
1st Department of Nephrology and Transplantology with Dialysis Unit
Medical University of Białystok
Żurawia 14, 15-540 Białystok, Poland
Tel./Fax: +4885 743 4586; e- mail: rakowska.maja@gmail.com

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INTRODUCTION

Proton pump inhibitors (PPIs) are among the most commonly used medications for the treatment of upper gastrointestinal disorders [1], and one of the most frequently prescribed classes of drugs in the world [2], because of their high effectiveness in decreasing gastric acid production and seemingly low toxicity. Their safety profile makes overuse of these drugs an increasingly common custom [3]. Many patients receive PPIs for unapproved or inappropriate indications. Those include: nonspecific abdominal symptoms without acid-related disease features, prescription with a low dose of NSAIDs in asymptomatic or low risk patients "just in case," but the most common reason for long-term therapy is its continuation although the problem had already been resolved [4].

With the advent of over-the-counter omeprazole, self-directed PPI therapy is now widely available, though this increases the potential for its inappropriate use. The risk of a minor symptomatic adverse effect from PPIs (nausea, diarrhea, or headache) is low, approximately 1-3%, with no significant differences noted between the PPIs [5]. Serious adverse events are rare, with case reports of interstitial nephritis induced by omeprazole [6] and hepatitis with omeprazole and lansoprazole [7,8]. Nevertheless, there have been emerging concerns with reports of potential long-term adverse effects associated with the use of PPIs. These include alteration of absorption of vitamin B12, especially in elderly patients [9], hypomagnesemia [10], increased risk of osteoporotic fractures [11], and effect on pharmacokinetics, pharmacodynamics and drug interactions [12].

A recently performed retrospective study, based on a population of 99,269 patients showed that long-term use of PPIs is associated with increased risk of developing chronic kidney disease and death [13]. Overuse of PPIs is also of concern in hemodialysis (HD) patients. End stage kidney disease patients, in an HD program, commonly suffer from many comorbid diseases like arterial hypertension, ischemic heart disease, chronic heart failure, and diabetes mellitus. This makes them medically prone to taking many different, potentially interacting, drugs.

The aim of the present study was to evaluate the prevalence of PPI use and the medical indications for their prescription among a cohort of chronic HD patients. Secondarily, the study was to assess patients' awareness about the medical effects of these drugs.

MATERIALS AND METHODS

The study was performed in 78 prevalent HD patients being treated in the 1st Department of Nephrology and Transplantation with Dialysis Unit at the Medical University of Bialystok. All patients were fully informed about the aim of the study and gave their consent. Patients were on a conventional maintenance HD program (three times a week, 4-4.5 hours per HD session).

The study was based on the medical history taken individually from the patients (survey about drugs they take with intention of revealing PPIs, medical indications for the treatment, their awareness of the mechanism and effects of action of this class of medication). Information obtained this way was verified and complemented by a review of medical documentation. The collected information included: clinical characteristic of the patients (age, sex, and etiology of chronic kidney disease) as well as medications prescribed and their quantity. In the case of treatment with PPIs: the type of drug prescribed, information who prescribed the therapy (gastroenterologist, nephrologist, or other specialist), medical indications for and the duration of therapy were retrieved. Finally patients' awareness of indications, mechanisms and effects of action of this class of medications were verified.

Interpretation of the proper indications for PPI administration were limited to cases of:

- Barrett's esophagus
- esophageal peptic stricture
- GERD / esophagitis / dyspepsia
- ulcer healing and/or *Helicobacter pylori* eradication
- upper GI bleed (including varices)
- Zollinger-Ellison syndrome
- short bowel syndromes
- peptic ulcer disease prophylaxis for patients taking NSAID / aspirin / steroid/ clopidogrel; according to bleeding risk assessment.

Descriptive statistics of variables are expressed as mean ± SD and numbers (%). Chi^2 test was used to compare variables as appropriate. Differences were regarded as statistically significant when $p< 0.05$. Statistical analysis was performed with the use of Statistica 9.0 (StatSoft, Inc. Tulsa, Okla., USA).

RESULTS

Seventy eight patients participated in the study. Patients' mean age was 65±15 years, and 53% were male (n=41). The etiology of kidney disease was as follows: diabetic nephropathy 19% (n=15), autosomal dominant polycystic kidney disease 18% (n=14), glomerulonephritis 17% (n=13), hypertensive nephropathy 9% (n=7), and other or unknown (n=22).

Forty-six of the examined patients (59%) were treated with PPIs. Most PPI users were administered omeprazole (n=30; 65%); pantoprazole was selected in eleven (24%) patients (Table 1).

Table 1 Frequency and type of PPI administration in the studied group

Proton pump inhibitor	N	%
Omeprazole	30	65
Pantoprazole	11	24
Others	5	11
Total	46	100

Almost half (n=22; 48%) of the patients taking PPIs had no medical indications for this therapy. Prescription of PPIs without accepted medical indications is more common among nephrologists and other physicians when compared with gastroenterologists ($p<0.05$). Generally, gastroenterologists prescribed PPIs according to the accepted medical guidelines (Table 2).

Table 2 Prescribing PPIs in accordance with medical guidelines

Specialist	Accordance with medical guidelines	
	Yes (n)	No (n)
Nephrologists	4	6
Other physicians	6	15
Gastroenterologists	13	1

Results of the study revealed that 28% (n=13) of the patients taking PPIs were familiar with the mechanism of action of the drugs. A total of 47% (n=21) of patients taking PPIs were on chronic therapy (regular schedule), while 27% (n=12) took the drug as a rescue therapy ("as needed"), related to the presence of symptoms. Patients on chronic treatment were more often the ones treated according to the medical guidelines ($p<0.05$) when compared with others. The study showed that 15% (n=7) of patients took PPIs at an inappropriate time.

Figure 1 depicts the daily pill burden for HD patients. It ranges from 1 to 15 different drugs per day with an average of 6, as shown in the study. However, there is no relation between taking PPIs and the daily pill burden among HD patients.

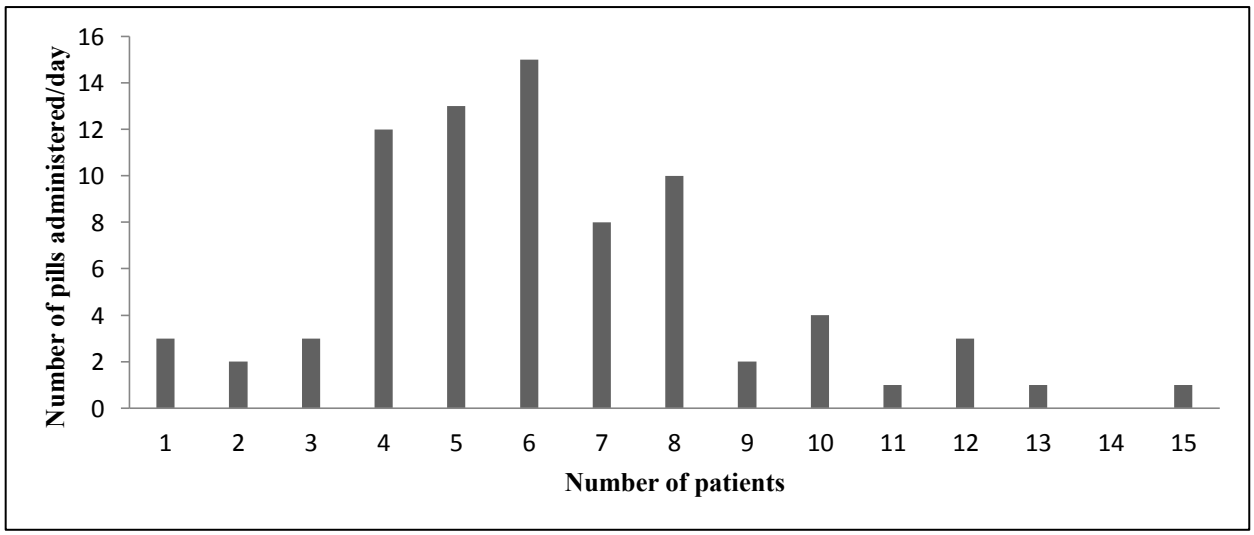

Figure 1 Daily pill burden among HD patients

DISCUSSION

The present study shows that the majority (59%) of the examined HD patients currently take or have been taking PPIs, which is a common phenomenon [3,4] both in the general and the chronic kidney disease population [14]. Noteworthy is the fact that long term PPI therapy increases the risk for enteric infections - *Clostridium difficile* [15], *Campylobacter, Salmonella* [16]. There is also

evidence of an increased risk of osteoporosis and bone fractures, nutritional deficiencies of vitamin B12, iron [17], and impaired calcium and magnesium absorption [18,19] related to PPI therapy. Recent studies have suggested that avoidance of PPIs may prevent the development of dementia [20].

Although omeprazole is the most popular PPI among the examined patients, pantoprazole seems to be safer, because of a reported lower risk of drug interactions [21,22]. Furthermore, pantoprazole has no influence on the pharmacodynamics or pharmacokinetics of drugs like: carbamazepine, diazepam, diclofenac, digoxin, ethanol, gliben-clamide, metoprolol, nifedipine, phenpro-coumon, phenytoin, theophylline, or warfarin [21].

According to our study, the main indication for prescribing PPIs was the prophylaxis or treatment of peptic ulcer disease. Gastroenterologists were the physicians most commonly prescribing PPIs in accordance with the medical guidelines.

As the study shows, almost half of HD patients taking PPIs had no medical indication for it. Similar studies consistently present that PPIs are overprescribed in both primary and secondary medical care [23]. A total of 40% of examined patients admitted a lack of awareness of the mechanism of action of PPIs; they described them mostly as "protective." Our findings are consistent with studies reporting a lack of knowledge concerning this group of drugs among patients in general practice [24]. This phenomenon might be caused by poor patient-doctor communication. We should also consider a patient's personality and age [24], which make a physician's efforts even harder.

The results of the present study indicate that a substantial number of patients take the drug at a wrong time or manner – occasional use. Some patients took PPIs at night, in contrast to the recommendation of a once-daily morning dosage [25] prior to a meal [26]. Furthermore, many of them were not aware of this importance. PPI failure is a frequent problem in gastroenterology clinics and at the primary care level as well [27]. Patients' knowledge about the treated disorder and prescribed drug is crucial to successful treatment [24]. One quarter of the examined patients had admitted to taking the drugs "as needed," however occasional use of PPI does not provide appropriate acid inhibition or clinical response [28,29].

A high daily pill burden increases the problem of lack of compliance. The more pills are prescribed, the more possible it is to skip portions of drugs by patients [30]. HD patients are a specific group suffering from comorbidities in many ways. Not only do they take many drugs, but also they are cared for by several specialists. These factors could make adhering to medical recommendations a problem for patients. Better communication might also prevent drug interactions, caused by insufficient awareness about the medications prescribed by other specialists. All of these arguments clearly point out that information about treatment should be more transparent and abundant, which leads to the fact that doctors should dedicate more time and patience to it.

This study has potential limitations, such as a relatively small number of examined patients and gaps in their medical documentation. We are aware that a larger trial is needed in order to draw a final conclusion.

CONCLUSIONS

The results of this study reveal the problem of PPI overuse among HD patients. They often do not know when to take the drug or how the drug works. Among the medical specialists, only gastroenterologists prescribe PPIs according to the accepted guidelines, whereas other doctors mostly prescribe PPIs without clear medical indications. The most popular PPI used in the HD population is omeprazole. There is a necessity to develop communication skills among doctors to improve patient adherence to their recommendations and improve the effectiveness of treatment.

Conflicts of Interest

The authors declare no conflicts of interest.

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