

# The impact of an education program on the appropriate prescription of proton pump inhibitors in hospitalized internal medicine services patients

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## ABSTRACT

The objective of this study was to determine the effect of an education program on physicians' knowledge, appropriate prescribing, and administration of proton pump inhibitors (PPIs) in hospitalized internal medicine patients. This quasi-experimental, prospective study was conducted in a university hospital over a period of three months, and included patients who received PPIs before (1 month) and after (1 month) the education program. A questionnaire was used to assess physicians' knowledge before and after the education program. In this study, a total of 215 patients and 32 physicians participated. The rate of appropriate PPI prescribing for indication and administration route increased from 46.4% to 49.5% and from 48.2% to 51.5%, respectively, after the education program ( $p > 0.05$ ). The mean number of correct answers on the knowl-

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(Received 20 Jun 2023, Accepted 13 Jul 2023)

edge questionnaire increased by 5 out of an average of 10 correct answers before the education to 15 correct answers after the education ( $p=0.001$ ).

**Keywords:** proton pump inhibitors, education, internal medicine, pharmacists, medication review

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## INTRODUCTION

Proton pump inhibitors (PPIs) are medications that are used to treat a variety of gastrointestinal (GI) conditions, including peptic ulcer disease, gastroesophageal reflux disease, GI hemorrhages, dyspepsia, *Helicobacter pylori* eradication, Zollinger-Ellison syndrome (ZES), erosive gastritis, and esophagitis<sup>1,2</sup>. PPIs are sometimes prescribed without a clear indication or for unnecessarily long periods of time, which is referred to as overuse<sup>3</sup>.

It is common for patients hospitalized in internal medicine departments to receive acid suppression therapy (AST). It has been observed that proton pump inhibitor (PPI) treatment often begins during a hospital stay and continues after the patient is discharged. However, the inappropriate use of PPIs has been linked to increased medication costs and an increase in undesirable side effects<sup>1,4</sup>.

There is a high rate of inappropriate use of PPIs in hospitalized patients, according to several studies. De Rijdt et al. found that 43% of non-critical patients in their study were prescribed long-term AST without a proper indication<sup>1</sup>. Other studies have also found high rates of inappropriate AST use, including 69.2% in a study by Nachnani et al., 44% during hospitalization and 47% after discharge in a study by Sheik-Taha et al., and 69% of patients receiving PPI treatment in a study by Nasser et al. who did not have a valid indication for PPI use<sup>5-7</sup>.

Another important issue regarding the inappropriate use of PPIs concerns the route of administration. In 2004, two hospital reports on PPI use indicated that 56% of patients receiving intravenous (IV) PPIs had inappropriate indications, most of which were indications for stress ulcer prophylaxis (SUP). On the other hand, oral PPIs have several advantages over IV formulation, including lower cost, less use of hospital resources, and fewer complications associated with IV administration<sup>7,8</sup>. Currently, IV PPIs are approved by the US Food and Drug Administration (FDA) to treat ZES patients with pathological hypersecretory conditions who cannot tolerate oral medications due to complicated erosive esophagitis. In practice, the use of IV PPIs is much more common. The decision to administer IV PPI depends on several factors such as the patient's

ability to swallow, gastric motility, intestinal transit, and permeability<sup>9</sup>. Given the potential complications and cost, IV PPIs should be considered among inappropriate uses in cases where oral PPIs could be used instead.

The aim of this study is to improve the knowledge of physicians regarding the appropriate use of PPIs in terms of indications and administration route, following an educational program on PPI prescribing in the internal medicine services.

## **METHODOLOGY**

This study, which was a prospective, quasi-experimental design, was conducted at a university hospital between October 1, 2019, and January 15, 2020. The study was divided into two parts: a pre-education phase (October 1-30, 2019) and a post-education phase (December 15, 2019-January 15, 2020). During both periods, the researchers evaluated the treatment of patients hospitalized in the internal medicine services and assessed the appropriateness of PPI use. The study included adult patients who were admitted to the internal medicine services and used PPIs for any reason during their hospitalization. The goal was to include at least 200 patients in the study without any sampling, based on the number of hospitalized patients in the relevant services for the periods in which the study was conducted.

The patient's demographic information such as age, gender, comorbidities, reason for hospitalization, total hospital stay, recent hospitalization history in the last six months, smoking, and alcohol use were collected using a "Patient Profile Registration Form" Information regarding the patient's medication use and results of biochemical laboratory tests were obtained from the patient's medical records.

The appropriateness of the indication and method of administering PPIs was assessed by a clinical pharmacist and a gastroenterology specialist, using evidence-based criteria from previous studies<sup>4,9-13</sup>. To evaluate the appropriateness of the indication and administration route of PPIs, the medical records and drugs of inpatients were examined. The appropriateness of the indication was evaluated by considering accompanying risk factors (such as the use of non-steroidal anti-inflammatory drugs [NSAIDs], systemic corticosteroids, antiplatelet, and anticoagulant drugs) and information from the package insert of PPIs. When evaluating the appropriateness of the administration route, factors like tolerance of oral medications, pathological hypersecretion states, swallowing ability and gastric motility were taken into consideration.

In the second part of the study, an educational program was organized by gas-

troenterology specialists for internal medicine residents, lasting one hour. The program covered general information about PPIs, including mechanism of action, appropriate indications, recommended treatment duration, potential side effects, contraindications, drug interactions, common inappropriate uses, safety concerns, and options for administration route (IV or oral). The education was concluded with case studies and discussion. On the same day, a questionnaire which included a knowledge test was administered to the physicians, both before and after the education.

The questionnaire given to the participating physicians consisted of three sections and a total of 34 questions. The questionnaire, which was created by the authors, was self-structured and had 11 questions in total, with the first section asking about sociodemographic information and the second section containing general questions about PPI use (such as frequency of prescribing PPIs for hospitalized and discharged patients and recognizing adverse effects caused by PPIs). The third section, which evaluated the education, had 23 questions about PPIs, covering topics such as indications, side effects, safety, and drug interactions.

The primary outcome of this study is to enhance the knowledge level of internal medicine residents on the appropriate use of PPIs through education, and as a result, to decrease the inappropriateness of PPIs prescribed to patients in terms of indication and administration.

### **Statistical Analysis**

As the data collected did not follow a normal distribution, non-parametric statistical tests were used for the analysis. The chi-square test was used to analyze categorical variables, while the Mann-Whitney U test was used for nonparametric numerical values. The McNemar-Bowker Test was used to compare the responses to the questionnaire before and after the education. The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0. (Armonk, New York: IBM Corp.). The results were considered statistically significant at a 95% confidence interval, with a  $p < 0.05$ . There was no missing data in the study.

### **RESULTS and DISCUSSION**

During the study period, 302 patients were admitted to the internal medicine services. A total of 215 patients who used PPIs during their hospitalization were included in the study, 112 in the pre-education period and 103 in the post-education period. Eighty-seven patients (28.8%) were not included as they did not use PPIs during the study period. Thirty-two physicians participated in the

education on appropriate PPI prescribing. The patients included in the study were 54% male, and 80,6% of the physicians participating in the education were female. There was no significant difference in sociodemographic characteristics between the patients included in the study before and after the education. Table 1 shows the sociodemographic information of the patients who were evaluated for PPI appropriateness in the first period of the study.

**Table 1.** Sociodemographic characteristics of patients\*

	<b>Before Education (n=112), n (%)</b>	<b>After Education (n=103), n (%)</b>
<b>Age, Median (IQR)</b>	64.50 (52.25-74.75)	64.00 (47.00-75.00)
<b>Gender</b>		
<b>Male</b>	60 (53.6)	56 (54.4)
<b>Female</b>	52 (46.4)	47 (45.6)
<b>Smoking</b>	17 (17.5)	23 (24.0)
<b>Alcohol</b>	3 (3.1)	1 (1.0)
<b>History of hospitalization in the last 6 months</b>	29 (61.7)	39 (61.9)

IQR: Interquartile range \*There was no statistically significant difference in terms of sociodemographic characteristics.

The appropriateness of PPI uses for patients participating in the study was evaluated in terms of indication and administration route. When compared to before and after the education, the results for PPI appropriateness were not found to be statistically significant ( $p > 0.05$ ). When all periods were evaluated, it was determined that PPI was used with an inappropriate indication at a rate of 47.9% and by an inappropriate administration route at a rate of 49.7%. Other comparisons of PPI use before and after education are shown in Table 2.

**Table 2.** Comparison of PPI use appropriateness in the pre-and post-education periods

	Total	Before Education	After Education	p value
<b>PPI indication compliance at admission, n (%)</b>	103 (47.9)	52 (46.4)	51 (49.5)	0.651
<b>PPI administration route compliance at admission</b>	107 (49.7)	54 (48.2)	53 (51.5)	0.635
<b>Prognosis, n (%)</b> <b>Intensive Care Unit</b> <b>Death Discharge</b>	15 (6.9) 3 (1.4) 197 (91.6)	10 (8.9) 1 (0.9) 101 (90.2)	5 (4.9) 2 (1.9) 96 (93.2)	0.422
<b>Total number of days using PPI, Median (IQR)</b>	10 (7.00-14.00)	10 (7.00-14.00)	10 (6.00-14.00)	0.810
<b>Total length of stay in hospital, Median (IQR)</b>	11(8.00-17.00)	10 (8.00-17.00)	12 (8.00-18.00)	0.297

IQR: Interquartile range, PPI: Proton pump inhibitor

Before the education, the physicians participating in the survey were asked 5 general questions about the use of PPIs. According to their responses, the physicians reported that they frequently initiate PPI treatment (46.9%) in hospitalized patients. When it comes to patients who were already taking the drug at home, physicians stated that they mostly did not evaluate the appropriateness of indication (71%) or the duration of treatment. They also frequently prescribed PPIs at discharge. The distribution of other responses to the general questions about the use of PPIs is shown in Table 3.

The accuracy of the answers on the questionnaire given after the education were compared to the answers given before the education. The median (interquartile range) of correct answers before and after the education were 10 (8-11.25) and 15 (13-17) respectively. The mean number of correct answers increased by 5 (from 10 to 15) after the education, which was found to be statistically significant ( $p=0.001$ ).

The questionnaires conducted before and after the education on PPIs were grouped into 4 categories. According to the group of questions, there was an average increase of 22.6% in correct answers for indication questions, 19,1% for interaction questions, 17.8% for side-effect questions, and 23.6% for safety questions. The comparison of the questionnaire questions before and after the education according to their categories is shown in Table 4.

In this study, the appropriateness of PPI treatment in terms of indication and administration route for patients admitted to internal medicine services was evaluated and the impact of education on these usage rates was assessed. It was determined that approximately half of the patients had inappropriate PPI use and administration route rates when all periods were evaluated.

**Table 3.** Distribution of physicians' opinions about PPI use before education

Questions	Answers	The number of participants, n (%)
<b>How often do you start PPI treatment for your hospitalized patients?</b>	Rarely	3 (9.4)
	Sometimes	14 (43.8)
	Often	15 (46.9)
<b>In what percentage of patients do you start PPI treatment?</b>	≤30%	6 (18.8)
	31-59%	9 (28.1)
	60-89%	12 (37.5)
	≥90%	5 (15.6)
<b>How often would you evaluate the appropriateness of indication and treatment duration in a patient with PPI among the medications used at home?</b>	Never	4 (12.5)
	Sometimes	23 (71.9)
	Always	5 (15.6)
<b>How often do you write PPI treatment in the discharge prescription?</b>	≤30%	5 (15.6)
	31-59%	17 (53.1)
	60-89%	7 (21.9)
	≥90%	3 (9.4)
<b>Have you observed any PPI-related adverse reactions in your patients?</b>	Yes	8 (25.0)
	No	24 (75.0)

PPI: Proton pump inhibitor

Pham et al. reported that while the rate of PPI use was 29% at hospital admission, this rate increased to 71% by the time of discharge, and that PPI use was prescribed for appropriate indications in only 9.9% of patients<sup>2</sup>. A 7-month retrospective review of a large teaching hospital in Australia found that only 37% of the inpatient population used PPIs for indications deemed acceptable by the

Australian Pharmaceutical Benefits Program<sup>12</sup>. Other studies also support the findings of this study regarding the inappropriate use of acid suppressants. Walker et al. reported that 67% of PPIs were prescribed for unapproved indications in their study involving hospitalized patients<sup>13</sup>. Other studies have reported rates of inappropriate PPI use as high as 57% and 60%<sup>14,15</sup>. Our findings, along with previous studies, suggest that the prescribing of acid-suppressing drugs is relatively common and often inappropriate. The rates of inappropriate PPI use reported in these studies were found to be higher than in this study. The differences in these rates may be due to variations in the guidelines, consensus, and sources used to evaluate indication appropriateness.

In this study, physicians reported that their PPI prescribing habits at hospital admission were moderate to high. The habit of prescribing PPIs without considering appropriate indication criteria at admission leads to high rates of inappropriate use<sup>16</sup>. A review reported that prophylaxis for gastro-duodenal ulcers in patients without risk factors, prophylaxis for stress ulcers in non-intensive care units, patients receiving steroid therapy alone without risk of gastric ulcers, and excessive treatment of functional dyspepsia are the main causes of inappropriate use of PPIs<sup>15,17</sup>. However, the development of stress ulcers is rare in general hospitalized patients, and guidelines recommend this practice only for intensive care patients<sup>18</sup>.

**Table 4.** Distribution of the number of participants who answered the survey questions correctly before and after the education

Category of Questions	Participation (n)		Correct answer (%)		p value
	Before	After	Before	After	
<b>Indication Questions</b>					
Injectable PPI is always preferred for hospitalized patients	23	26	76.7	96.3	NS
There is no need for PPI use in a patient over 65 years of age who is taking low-dose aspirin for cardiovascular prevention	10	13	33.3	48.1	NS
A PPI should be added to the discharge prescription of a patient using steroids long term	6	18	20	66.7	NS
A PPI should be added to the discharge prescription of a patient using NSAIDs	11	19	36.7	70.4	NS
A PPI should be added to the discharge prescription of a patient with a history of ulcer	27	22	90	81.5	NS

Barret's esophagitis, idiopathic Helicobacter pylori/NSAID (-) ulcers, Zollinger-Ellison syndrome, NSAID use with a high risk of GI bleeding are examples of short-term PPI use indications	10	13	33.3	48.1	NS
Helicobacter pylori eradication, stress ulcer prophylaxis, functional dyspepsia, peptic ulcer treatment and maintenance are examples of long-term (PPI indications)	7	13	23.3	48.1	NS
The most effective medication group for the initial treatment of GERD is PPIs	26	27	86.7	100	NS
Patients using steroids (if they are not using NSAIDs), patients with portal hypertensive gastropathy and acute pancreatitis can be given as examples of patients who need to use PPIs for stress ulcer prophylaxis	4	13	13.3	48.1	0.011
PPI can be used for stress prophylaxis in patients outside the intensive care unit	7	15	23.3	55.6	0.0001
<b>Average</b>	13.1	17.9	43.6	66.2	
<b>Interaction Questions</b>					
It is recommended that a patient using omeprazole and levothyroxine take both drugs together on an empty stomach	25	22	83.3	81.5	NS
PPIs may increase the absorption and serum concentration of digoxin	17	22	56.7	81.5	NS
PPIs can increase the toxicity of warfarin and phenytoin	15	23	50	85.2	NS
PPIs can decrease serum concentrations of diazepam, theophylline, methotrexate	0	5	0	18.5	NS
<b>Average</b>	14.2	18	47.5	66.6	
<b>Advers Effect Questions</b>					
Clostridium difficile infection is not associated with PPI use	18	24	60	88.09	0,042
It was observed that the risk of osteoporosis did not increase in patients receiving long-term PPI therapy	22	24	73.3	88.9	NS
One of the conditions associated with the use of PPIs is the increased risk of community-acquired pneumonia	1	6	3.3	22.2	0,021
It is accepted that there is a relationship between PPI use and dementia	5	6	16.7	22.2	NS
In chronic PPI use, magnesium, calcium and B12 levels should be monitored once a year	24	27	80	100	NS
<b>Average</b>	14	17.4	46.6	64.4	
<b>Safety Questions</b>					
PPI use in pregnant women is safe	9	16	31	59.3	NS

Long-term use of PPIs may delay the diagnosis of gastrinoma in the patient	23	21	76.7	77.8	NS
Long-term use of PPI can be stopped suddenly	5	13	16.7	48.1	NS
The use of PPIs is considered safe in patients with cirrhosis	13	21	43.3	77.8	NS
<b>Average</b>	12.5	17.7	41.9	65.7	

GERD: Gastroesophageal reflux disease, GI: Gastrointestinal, NS: Not significant, NSAID: Non-steroidal anti-inflammatory drug, PPI: Proton pump inhibitor

Another issue of concern regarding the inappropriate use of PPIs in this study is the unnecessary use of IV PPIs in patients who are able to take them orally. Approximately half of the patients had such an inappropriate route of administration. IV PPIs are more expensive compared to oral PPIs and have only a few absolute indications. More than half of the hospitalized patients prescribed IV PPIs could have taken oral PPIs instead<sup>19</sup>. Recent studies have shown that IV PPI preparations are associated with gastric hypersecretion and ZES associated with neoplastic conditions, severe non-variceal upper GI bleeding cases that cannot take oral medication, GI bleeding with the risk of recurrent continuous bleeding, and high rates of GI bleeding in intensive care units without access to enteral nutrition or without oral intake. Its use in risky patients is considered appropriate<sup>20</sup>. Inappropriate use of IV PPI has been observed in various studies, especially in cases with no high suspicion of upper GI bleeding<sup>20-22</sup>. Lai et al. reported inappropriate IV PPI use at 74.5%, and Alsultan et al. reported as high as 71.7%<sup>20,23</sup>. Alsultan et al. also noted differences between consultants, specialists, and practitioners in the inappropriate prescribing of IV PPI<sup>20</sup>. These rates are considerably higher than the rates found in our study.

In this study, the impact of education on PPI use was evaluated. The education was evaluated by a knowledge test containing 23 questions about PPIs, including indications, side effects, drug safety, and drug interactions. The physicians' knowledge level was found to have increased by an average of 5 correct answers after the education, with the largest increases observed in questions about PPI safety and indications. However, this statistically significant increase in the level of knowledge did not provide a positive change in the PPI prescribing habits of physicians in the post-training period. Previous studies have also attempted to reduce inappropriate PPI use through different methods. Odenthal et al. implemented a program led by a clinical pharmacist, which included patient education and follow-up, in a family medicine clinic to reduce inappropriate PPI use. The clinical pharmacist evaluated PPI-using patients through visits to determine whether the PPIs used were candidates for discontinuation. Of the

patients followed up on, 86% successfully discontinued the use of PPIs. This suggests that a program led by a clinical pharmacist, which includes detailed discontinuation instructions, patient education, and follow-up, can be effective in avoiding the prescribing of long-term PPI therapy<sup>24</sup>. In a study conducted at a university hospital in France, the prescribing of PPIs was analyzed over a period of three years, during which 132.890 prescriptions were evaluated. Out of these, 701 (4.6%) were identified as problems with PPIs. The most commonly reported issues were the lack of proper indications (24.4%) and inappropriate routes of administration (19.8%). To address these issues, recommendations were made to discontinue the drug or adjust the dosage in 40.5% of cases. The primary intervention was to discontinue the use of PPIs due to their inappropriate use. Through these pharmaceutical interventions during prescription analysis, the use of PPIs was optimized. The study highlights the importance of communication strategies to improve the education and practice of healthcare professionals, especially through the actions of pharmacists<sup>25</sup>.

In this study, it was found that a one-day training program alone did not significantly decrease the rate of PPI use for inappropriate indications or administration. This may be due to the passive nature of the intervention and the need for more comprehensive and long-term approaches, such as implementing a national guideline, incorporating appropriate instructions for use into electronic systems, and providing continuing education for physicians and medical personnel, as previous studies have shown to be effective in reducing inappropriate PPI use<sup>26-29</sup>. It is important to note that continuing education is crucial in ensuring that physicians and medical personnel adopt generally accepted principles and use PPIs in a balanced manner<sup>10</sup>.

One of the strengths of this study is that it demonstrated the effectiveness of a one-day education program in significantly increasing the knowledge level of physicians about PPIs. However, the study also has limitations, such as being dependent on the information present in medical records, which may be incomplete, and not reflecting the long-term impact of education. Additionally, the study was conducted in a single center academic tertiary hospital with a relatively small sample size, making it difficult to generalize the results to other hospitals and internal medicine services.

In conclusion, our study highlights the need for improvement in the appropriate prescribing and administration of PPIs among internal medicine residents. The results showed that a one-day education program can increase the knowledge level of physicians about PPIs, but this increase was not reflected in their prescribing and administration habits. To address this issue, hospitals should

implement guidelines on the use of PPIs, provide regular education to physicians by experts, and monitor the long-term effects of these interventions. Additionally, implementing controlled policies such as formulary restriction, restricting IV PPI administration to specific indications, and including drug discontinuation orders for certain indications may also help improve the appropriate use of PPIs.

#### **STATEMENTS OF ETHICS**

Approval from the ethics committee was obtained for this study on July 26, 2019, with the approval number 09.2019.686 from Marmara University Faculty of Medicine Clinical Research Ethics Committee.

#### **CONFLICT OF INTEREST STATEMENT**

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, shareholding, and similar situations in any firm.

#### **AUTHOR CONTRIBUTIONS**

Design: YEA, CE; Acquisition of data: YEA, CE, ÇK, AA, TKY; Analysis of data: YEA, CE, MS, BO, OCÖ; Drafting of the manuscript: YEA, MS; Critical revision of the manuscript: YEA, MS, OCÖ; Statistical analysis: YEA, MS; Technical or financial support: YEA, CE, ÇK, AA, TKY; Supervision: YEA, CE, ÇK, AA, TKY; Other (specify): YEA, CE, ÇK, AA, TKY.

#### **FUNDING SOURCES**

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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