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ORIGINAL PAPER

INAPPROPRIATE USE OF PPIS TO PATIENTS ADMITTED INTO A NON ICU GASTROENTEROLOGY DEPARTMENT

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Abstract. It is a fact that more frequent evidences are showing that proton pump inhibitors (PPIs) are used improperly. This contributes, on one hand, to the increase of the cost of health care services, and on the other hand, is impairing the safety and quality of patients' lives. The aim of this study was to identify whether, in a non ICU ward, PPIs are used with respect for the current clinical guidelines. The research is based on the assessment of therapeutic schemes of 98 patients which were hospitalized in a non-ICU ward, summarizing 236 days of treatment with PPIs. PPI administration was analyzed in related to indication, dose, route of administration and drug interactions. We also tried to determine if there is a potential cost of PPI therapy which could, potentially, be saved. We have found that that PPIs were unnecessarily administered in 8.05% of days, having inadequate doses in 21.61% of days, there have been interactions for 1.69% of days, and route of administration was inadequate for 10.17 % of days. By comparing the total cost with the potential total cost, the first was found as significantly higher. So, PPIs are being used inappropriately to some of the patients admitted to non-ICU ward. A solution for improving PPI therapy might be to include a clinical pharmacologist as part of the medical team and follow minimal prescribing rules.
Key words. Proton pump inhibitors, overprescribing, clinical pharmacologist, cost

Introduction

Discovery ATP-ase enzyme H+/K+ and introduction of the first proton pump inhibitor to treat disorders caused by stomach acid have marked a real success in gastroenterology [1, 2]. Currently, proton pump inhibitors are the most effective medication in reducing gastric acid secretion [3].

Proton pump inhibitors that have been used are derivatives of pyridyl-methyl-sulfinil benzimidazole and they act by inhibiting ATP-ase H+/K+, covalently binding to it. Through reaction between CO2 and H2O, under the action of carbonic anhydrase, H+ and HCO3_ are formed. ATP-ase H+/K+ perform the influx of H+ ions and efflux of K+ ions, and the H+ ion is coupled with Cl-introduced by ion exchange with HCO3_ [4, 5, 6].

PPI use is widespread and growing worldwide, with annual sales in excess over U.S. $ 25 billion [3]. In an era of heated controversy and debates on health reform-related costs in the healthcare system, it is important to address all sources of expenditure to the system. In particular, the efficacy and safety of PPI contribute to overuse this therapeutic class [7]. Studies conducted in the United States and Europe continues to report a PPI overprescribing both in hospital and ambulatory [8]. Approximately 50-60% of gastric acid secretion inhibitory medication prescribed for hospitalized patients is without adequate indication [9]. Here, clinical pharmacologist can have a positive impact. By including these specialists in medical team, may be reduced the cost of drug therapy and patient safety can be improved. In Romania, specializing in clinical pharmacology exists, but in hospitals there are no posts for this specialty. Consequently, clinical pharmacologists work either in research or in industry. This study intends to demonstrate the importance of including a clinical pharmacologist as part of medical teams as contributive solution to optimize and reduce costs of drug therapy for patients with digestive pathology.

Objectives

In this study we aim to evaluate the use of PPI in patients hospitalized in a clinic gastroenterology department, in terms of indications, dosage and administration. At the same time we assessed the extent to which clinical pharmacologist can help to improve prescribing therapeutic substances in this class.

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Method

Medical methodology

Medicinal therapies of 98 patients have been studied by a clinical pharmacologist. Patients were hospitalized in a department of gastroenterology, non-ICU, of Clinical Emergency County Hospital Cluj.

We considered proper use of PPIs:

A. Use as directed

Appropriate indications for PPI have been considered under the following conditions:

- Erosive esophagitis treatment;
- Treatment of symptoms of gastroesophageal reflux disease (GERD);
- Eradication of Helicobacter pylori (HP);
- Treatment of duodenal ulcer;
- Treatment of gastric ulcer;
- Treatment of Zollinger-Ellison syndrome;
- Treatment of ulcers induced by non-steroidal anti-inflammatory drugs (NSAIDs);
- Suspicion of bleeding in the upper gastrointestinal tract;
- Prevention of gastrointestinal bleeding ulcers;
- Prevention of ulcers caused by NSAIDs if:
  - The patient has a history of complicated ulcer;
  - Use several NSAIDs including aspirin;
  - The use of high doses of NSAIDs;
  - Concomitant use of anticoagulants;
  - Old age;
  - Concomitant use of corticosteroids. [7, 8, 10, 11].

B. Method of administration of PPIs: corresponding indication dose, frequency of administration, optimum route of administration, duration of therapy according to clinical guidelines: Order no. 1216/2010 for the approval of Medical Practice Guidelines for Specialty Gastroenterology, American College of Gastroenterology guidelines, monographs of each substance [8, 12, 13, 14, 15]. Most used PPI for the hospitalized patients were: omeprazole, pantoprazole, esomeprazole. These were administered either ways, orally or by parenteral use (iv).

Statistical Analysis

In order to prove the hypothesis of the study, two characteristics of the group have been considered. We aim to demonstrate that there is a potential cost of treatment that can be saved.

Characteristics of the study

a) Variable that measures the impact on patients exposed to PPIs.

- Usefulness of the drug - according to clinical guidelines.
- Dose - dose too high or too low relative to the patient's diagnosis.
- Possible interactions of PPI with other drugs administrated simultaneously.
- Untreated problem - there was a problem that required treatment with PPIs, but it was ignored.
- Route of administration - oral or parenteral (iv).

All the above variables are Boolean ones, having only two values 0 or 1, 1 representing the presence of medication error and 0 absence of it.

b) Variables that quantifies the effect of improper use of PPI therapy, quantifying the potentially cost saving.

- Potential cost saved achieved by assessing dose, route of administration, usefulness or interactions.
- Hospital cost: cost incurred by the hospital.
- Patient cost: cost incurred by the patient, deducted cost based on the patient's medical history in conjunction with price information published on the website of the Ministry of Health.
- Total Cost: The sum of hospital cost and patient cost.

All the above variables, related to costs, are quantitative ones.

Study sample

The 98 patients were treated with PPI during 236 days, on average 2.4 days / patient. Statistical unit of study (observation study) is "the day of hospitalization". A patient can produce multiple days of hospitalization, each day being measured using all variables described above. Day of hospitalization is the cost producer.

1. Method

1.1. Assumptions and descriptive results.

The metric of survey is represented by the comparison of the total cost of treatment with PPIs and total cost, excluding the potential cost savings. This test is designed to validate or invalidate working hypothesis. The metric will compare the actual cost versus actual cost less the amount that can be saved through proper use of PPIs (inappropriate use represents fundamental assumption we wish to be tested).

Type of test. Pair-test to compare differences between mean

Statistical hypothesis

H0 (null hypothesis): Average total cost equals average total cost potential.

H1 (alternative hypothesis): Average total cost is greater than average total cost potential.

Note. Given the alternative hypothesis formulation, unilateral paired t-test will be use. This choice is justified because the actual total cost is greater than the potential total cost as shown in Table I:

	Total cost	Potential total cost
Average	14.79	6.05
Standard deviation	23.17	11.49

Table I. Indicators for central tendency and deviation for Real Average Total Cost and Potential Average Total Cost

In accordance with clinical guidelines, either of the American College of Gastroenterology or those existing in Romania, of the 236 days of hospitalization in which the patients received PPIs, in 19 days the treatment was unnecessary, in 51 days doses of PPIs were inadequate (too big/too small), in 4 days were identified interactions between PPIs and medication given simultaneously, in 14 days there were problems that needed treatment with PPIs but they were ignored and in 24 days the administration route of PPIs was inadequate (see Table II).

Type of error	Presence of error	Absence of error
Unnecessary drug	19 days (8.05%)	217 days (91.95%)
Inadequate doses	51 days (21.61%)	185 days (78.39%)
Possible interactions	4 days (1.69%)	232 days (98.31%)
Problem untreated	14 days (5.93%)	222 days (94.07%)
Wrong route of administration	24 days (10.17%)	212 days (89.83%)

Table II. The incidence of medication errors, identified by groups of errors

1.2. Inferential results.

In the absence of no previous specifications, the standard 5% risk level (0.05) will be chosen.

Results of unilateral t test (one-tail) pairs are shown in Table III

	Total cost	Potential Total cost
Average	14.79	6.05
Dispersion (spread)	537.02	131.93
Standard deviation	23.17	11.49
Sample size	236	236
H0 (difference between actual average costs-potential)	0	
Statistical t (calculated)	7.62	
Theoretic t (unilateral)	1.652177009	
p-value, P(T<=t) (unilateral)	0.00 << 0.05	

Table III. Summary of statistical testing (unilateral)

Discussion

Due that PPIs is one of the most frequently prescribed medication, we considered important to evaluate the use of this therapeutic class, from the point of view of clinical pharmacologist. PPIs have been used to the 98 patients in 236 days and the medication errors were identified in 112 days, which means a summarized rate of 47.45%. A similar study on elderly patients highlighted a percentage of PPIs incorrect use of 61% [16].We present in Table IV some examples of errors.

The results are showing that the most common error encountered when using PPI medication is related to dose, 21.61% according to our study. This error can be avoided if it is taken into account the relevant specifications of the products monographs of the American College of Gastroenterology guidelines or those in Romania, where doses of PPIs are indicated for each part of the digestive pathology (gastro esophageal reflux disease, peptic ulcer, acute gastritis, etc.). In this, it is stated that, in patients with indication for PPIs therapy they are prescribed in minimum effective dose [17].

Wrong dose is coming on the second place, in descending order of frequency of occurrence, by wrong route of administration, unnecessary recommended drug, problem untreated and lowest frequency, drug interactions.

In the study there is a tendency to use PPI by injection against oral PPI although the efficacy of this class of drugs is the same regardless of the route of administration (oral or parenteral) and preparations administered parenterally cost is much higher than the oral (33 RON vs. 0.83 RON) [18]. A study in the UK shows that only 26.4% of the administered iv PPI are without prescription error (correct indication, correct dose, frequency of proper administration) [19]. Another study that has been conducted in a university hospital in the United States showed that 76% of the PPI administered iv. did not qualify for this route of administration [20].

For a correct use of PPIs in hospitalized patients would be useful associating a clinical pharmacologist to the medical team and following a few basic prescribing rules related to:

a) Drug indication: is the drug appropriate for the patient?

b) Similar drugs: is patient using a drug with the same action?

c) Dose: the dosing regimen is right? (dose, frequency of administration)?

Type of error	Example of error	Correcting the error
Unnecessary drug	Administration of pantoprazole and omeprazole together. Pantoprazole injectable, 2 x 40 mg/day, to a patient without digestive symptoms and no signs of gastrointestinal bleeding	Administration of a proton pump inhibitor alone. Minimum oral dose administration of PPI prophylactically until elucidate the diagnosis
Inadequate doses	Dose of pantoprazole 20 mg/day for peptic ulcer (diagnosis sustained by upper gastrointestinal endoscopy) or Controloc 2 x 40 mg/day prophylactic in patients with cirrhosis or chronic pancreatitis	Pantoprazole 40 mg/day for 4-8 weeks. Pantoprazole 20 mg/day
Wrong route of administration	Patient with dyspepsia receives injectable pantoprazole even though has in therapeutic plan also oral medication	Administration of pantoprazole or other PPI orally. The efficiency of PPI administered parenterally is the same as the ones being administered orally
Problem untreated	During hospitalization acute gastritis diagnosis is put both clinically and endoscopically, but patient remains without further treatment. Therapeutic recommendation is being offered only at discharge	Recommendation of antisecretory therapy immediately after diagnosis
Drug Interactions	Were administered omeprazole and sucralfate. There are possible interactions between the two medicinal substances, sucralfate activating it when the pH is below 4	Only the administration of PPI

Table IV. Examples of medication errors

d) Duration: duration of therapy is correct?

e) Cost: evaluating the cost / efficiency? [21, 22].

However, the prolonged use of PPIs has also potential side effects: vitamin B12 deficiency, iron deficiency, osteoporosis risk, risk of infections (e.g. Clostridium difficile infection), pneumonia, bone fractures, and their presence correlates with the rising cost from health system [7, 9, 23, 24, 25].

Conclusions

Based on data analysis we ordered, the study hypothesis is validated. Thus, the total cost can be accepted as being statistically significantly higher than the potential total cost. The source of this difference was found in the fact that PPIs are used inappropriately for hospitalized patients in non-ICU ward. This misuse has a particularly negative impact on treatment costs and, to a lesser extent, on patient safety.

Therefore, our recommendation is to include a clinical pharmacologist in medical team. As the owner of accumulation of information and knowledge, this kind of professional can optimize the cost, safety and quality of patients' life.

References

1. Shin JM,Vagin O, Munson K, Kidd M, Modlin IM, Sachs G. Molecular mechanisms in therapy of acid-related diseases. *Cell Mol Life Sci.* **2008; 65(2):264–281.**

2. Madanick RD. Proton pump inhibitor side effects and drug interactions:Much ado about nothing? *Cleveland Clinic Journal* **2011;1(78): 39-49.**

3. Ahrens D, Chenot JF, Behrens G, Grimmsmann T, Kochen M. Appropriateness of treatment recommendations for PPI in hospital discharge letters. *Eur J Clin Pharmacol* **2010; 66:1265–1271.**

4. Shin JM, Sachs G. Long lasting inhibitors of the gastric H,K-ATPase. *Expert Rev Clin Pharmacol.* **2009;2(5):461–468.**

5. Shin JM, Sachs G. Pharmacology of Proton Pump Inhibitors. *Curr Gastroenterol Rep.* **2008;10(6):528–534.**

6. Mejia A. Acid peptic diseases: pharmacological approach to treatment. *Expert Rev Clin Pharmacol.* **2009 ;2(3): 295–314.**

7. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therap Adv Gastroenterol.* **2012;5(4):219-32.**

8. Eid SM, Boueiz A, Paranji S, Mativo C, Landis R, Abougergi MS. Patterns and Predictors of Proton Pump Inhibitor Overuse among Academic and Non-Academic Hospitalists. *Intern Med* **2012;49: 2561-2568.**

9. Ali T, Roberts DN, Tierney WM. Long-term Safety Concerns with Proton Pump Inhibitors. *Am J Med.* **2009;122(10):896-903.**

10. Echevarría EM, Pereira JA, Torralba M, Arriola PG, Martín DP, Mateos J and Zapata R. Assessing the use of proton pump inhibitors in an internal medicine department. *Rev Esp Enferm Dig.* **2008;2(100):76-81.**

11. Nasser SC, Nassif JG, Dimassi HI. Clinical and cost impact of intravenous proton pump inhibitor use in non-ICU patients. *World J Gastroenterol.* **2010;16(8):982-6.**

12. *http://www.ms.gov.ro/index.php?pag=181&pg=2*

13. DeVault K, Kastell D. Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease. *Am J Gastroenterol* **2005;100:190-200.**

14. Lanza F, Chan F, Quigley E. Guidelines for Prevention of NSAID-Related Ulcer Complications.

Am.J.Gastroenterol **2009; 104:728 – 738.**

15. *http://www.drugs.com*

16. Hamzat H, Sun H, Ford J, MacLeod J, Soiza R, Mangoni A. Inappropriate Prescribing of Proton Pump Inhibitors in Older Patients: Effects of an Educational Strategy. *Drugs & Aging;* **2012:29(8):681-690.**

17. Heidelbaugh J, Metz D, Yang Y. Proton pu,p inhibitors: are they overutilised in clinical practice and do they pose significant risk? *Int J Clin Pract* **2012;66(6):582-591.**

18. Pang S, Graham D. A clinical guide to using intravenous proton-pump inhibitors in reflux and peptic ulcers. *Ther Adv Gastroenterol* **2010; 3(1): 11-22.**

19. Craig D, Thimappa R, Anand V, Sebastian S. Inappropriate utilization of intravenous proton pump inhibitors in hospital practice—a prospective study of the extent of the problem and predictive factors. *Q J Med* **2010; 103:327–335.**

20. Hoover JG, Schumaker AL, Franklin KJ. Use of intravenous proton-pump inhibitors in a teaching hospital practice. *Dig Dis Sci.* **2009;54(9):1947-52.**

21. Aronson JK. Medication errors: what they are, how they happen, and how to avoid them. *QJM.* **2009;102(8):513-21.**

22. Aronson JK. Balanced prescribing – principles and challenges. *Br J Clin Pharmacol* **2012;74(4):566–72.**

23. Coté GA, Howden CW. Potential adverse effects of proton pump inhibitors. *Curr Gastroenterol Rep.* **2008;10(3):208-14.**

24. Khalili H, Huang ES, Jacobson BC, Camargo CA Jr, Feskanich D, Chan AT. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. *BMJ.* **2012;344:e372.**

25. Durand C, Willet K, Desilets A. Proton Pump Inhibitor use in Hospitalized Patients: Is Overutilization Becoming a Problem? *Clinical Medicine Insights: Gastroenterology* **2012;5:65-76.**