

Overutilization of proton pump inhibitors and H₂ receptor antagonists in hospitalized medical patients

Proton pompa inhibitörleri ve H₂ reseptör antagonistlerinin iç hastalıkları servislerinde yatmakta olan hastalarda aşırı kullanımı

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SUMMARY

Objective: The aim of the study was to determine the frequency of the use of proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H₂RA), which are widely used drugs, in the medical wards.

Method: We retrospectively retrieved medical records of the patients who were hospitalized between January 1st and December 31th, 2010 in a tertiary care university hospital internal medicine wards and medical intensive care unit (MICU); one fourth of the cases who used a H₂RA or a PPI drugs were randomly selected for the study.

Results: In 2010, half of 4730 patients who admitted to internal medicine wards was ordered a H₂RA or a PPI. Of these, 556 patients (25.5%) were evaluated. Majority of the patient (76%) were on PPI. While 90.3% of the patients used a PPI in wards, 74.8% of the patients used a H₂RA in the MICU (p<0.001). Sixty-one percent (58/95) of patients who were transferred from the MICU to wards were switched from a H₂RA to a PPI without a specific reason. Before admission, 8% of patients was on PPI and 5% on H₂RA but at discharge, utilization significantly increased, 79% for PPI and 21% for H₂RA (p<0.001).

Conclusions: There is a high rate of acid suppressive therapy usage among hospitalized patients and similarly high rate of prescription at discharge. Further studies are required to evaluate the appropriateness of the utilization of these drugs.

Keywords : Proton pump inhibitor, histamine-₂ receptor antagonist, gastrointestinal prophylaxis, internal medicine

ÖZET

Amaç: Hastanede yatmakta olan hastalarda proton pompa inhibitörleri (PPI) ve histamine-2 reseptör antagonistlerinin (H₂RA) kullanıma sıklığı ve tercihine ilişkin veriler yoktur.

İç Hastalıkları servislerinde sık olarak kullanılan PPI ve H₂RA kullanım sıklıklarını belirlemektir.

Yöntem: Retrospektif olarak, 1 Ocak ve 31 Aralık 2010 tarihleri arasında bir üçüncü basamak üniversite hastanesinin İç Hastalıkları servislerinde ve yoğun bakım ünitelerinde (YBÜ) yatırılan hastaların tıbbi kayıtları incelendi; herhangi bir PPI veya H₂RA kullanımı olan olguların dörtte biri rastgele olacak şekilde seçildi.

Bulgular: 2010 yılında, İç Hastalıkları servislerinde yatırılan toplam 4730 hastanın yarısı bir H₂RA veya PPI kullanmıştı. Bunların içinden 556 (%25.5) olgu incelendi. Olguların büyük çoğunluğu (%76) PPI kullanmaktaydı. Servislerde, PPI olguların %90.3'ünde kullanılırken, YBÜ'de olguların %74.8'i H₂RA kullanmaktaydı (p<0.001). YBÜ'den servislere transfer edilen olguların %61'inde (58/95), herhangi özel bir neden olmadan, H₂RA kesilerek PPI kullanımına geçildiği görüldü. Hastaneye yatmadan önce olguların %8'i PPI ve %5'i bir H₂RA kullanırken, taburculuk sırasında %79 PPI ve %21 H₂RA olacak şekilde kullanım anlamlı şekilde artmıştı (p<0.001).

Sonuç: Hastanede yatmakta olan hastalarda ve taburcu edilirken verilen reçetelerde yüksek oranda asit baskılayıcı tedavi kullanılmaktadır. Bu ilaçların akılcı şekilde kullanıma durumlarını değerlendirmek için ileri araştırmalara ihtiyaç vardır.

Anahtar sözcükler: Proton pompa inhibitörü, histamine-2 reseptör antagonisti, gastrointestinal profilaksi, İç Hastalıkları, asit baskılayıcı tedavi

INTRODUCTION

Hospitalized patients with risk factors such as critical illness, prior gastrointestinal bleeding, coagulopathy, corticosteroid therapy, etc. are at increased risk of gastrointestinal bleeding^{1, 2}. Gastrointestinal bleeding prophylaxis with an acid suppressive drug is recommended for those patients who are hospitalized with various disease conditions and have the risk factors some of which are mentioned above. Moreover, increased incidence of gastric diseases and prescription of drugs with gastric side effects also lead to frequent use of acid suppressive therapy either as a proton pump inhibitor (PPI) or a histamine-2 receptor antagonist (H2RA)^{3,5}. However, beside clear indications for their use, irrational prescription of these drugs has been increasing^{6,7}. Overutilization of these drugs can lead to various acute and chronic adverse effects due to acid suppression and drug-drug interactions, and also a high financial burden⁸⁻¹⁰.

The primary aim of the study was to determine the frequency of the use of proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA) in the medical wards. The secondary aim was to determine the utilization patterns of these drugs.

MATERIAL AND METHODS

The study was performed retrospectively in a tertiary care university hospital internal medicine wards and medical intensive care unit (MICU). The medical records of the patients who were hospitalized between January 1st and December 31st, 2010 were retrieved. The frequency of the patients who used either an H2RA or a PPI any time during the hospital stay was calculated. Of those patients to whom these drugs were ordered, a random selection was performed and one fourth of the cases were included to create data set. Patients' demographic characteristics, H2RA or

PPI use, intensive care unit admission were recorded.

Statistical Analysis: Data were analyzed by *Statistical Package for the Social Sciences for Windows (IBM SPSS Statistics 17.0, Chicago, IL, USA)*. Numerical data was described as mean \pm standard deviation (SD) if normally distributed. Descriptive statistics were used for frequencies. Parametric variables were analyzed by chi square test in order to define the difference in between. $P < 0.05$ value was accepted as significant.

RESULTS

In 2010, a total of 4730 patients were admitted to internal medicine wards and either a H2RA or a PPI was ordered for 2177 (50.3%) of them. Of these patients, the hospital records of 556 patients (25.5%) were evaluated. The mean age of the patients were 57 ± 16.7 years and 54.7% of them were male. During the hospitalization period 123 patients (22%) were admitted to the MICU. The mean length of hospital stay was 22 ± 28.7 days (minimum 1- maximum 120 days).

In study population, 419 patients (76%) were on PPI rather than a H2RA (137 patients, 24%). While 90.3% (391/433) of the patients who were hospitalized in wards used a PPI rather than a H2RA, 74.8% (95/137) of the patients who were hospitalized in the MICU used a H2RA rather than a PPI ($p < 0.001$). Ninety-five patients were transferred from the MICU to internal medicine wards and 58 (61%) of them were switched from an H2RA to a PPI without a specific reason.

In the study population 173 patients (31%) had dyspnea as the most frequent complain at the time of hospital admission. The most frequent complains was shown in table 1. As shown in table 2, sepsis was the leading underlying disease in the H2RA group whereas in PPI group malignancy was the frequent underlying disease.

Table 1. Distribution of chief complains of study population at the time of hospital admission.

Chief complain	Number, (%)
Dyspnea	173 (31%)
General deterioration	85 (15%)
Fever	38 (7%)
Fatigue	26 (5%)
Gastrointestinal hemorrhage	23 (4%)
Abdominal pain	17 (3%)
Others	194 (35%)
Total	556 (100%)

Table 2. Distribution of underlying diseases in H2RA and PPI groups. Majority of patients have more than one disease so the percentages are presenting the ratio within the H2RA, PPI and total patient populations.

Disease	H2RA (n, %)	PPI (n, %)	Total (n, %)
Total study Population	137	419	556
Malignancy (total)	31 (22.6%)	160 (38%)	191 (34%)
Lymphoma	8 (5.8%)	46 (11%)	54 (9.7%)
Breast cancer	7 (5%)	42 (10%)	49 (10%)
Leukemia	6 (4%)	24 (5.7%)	30 (5%)
Lung cancer	5 (3%)	22 (5.2%)	27 (4.8%)
Gastric cancer	4 (2.9%)	11 (2.6%)	15 (2.7%)
Colon cancer	1 (0.7%)	7 (1.6%)	8 (1.4%)
Hepatocellular cancer	0 (0)	5 (1.2)	5 (0.8%)
Pancreas cancer	0 (0)	3 (0.7%)	3 (0.5%)
Hypertension	35 (25.5%)	149 (35.5%)	184 (33%)
Diabetes mellitus	44 (32%)	103 (24.5%)	147 (26.4%)
Chronic obstructive pulmonary disease	10 (7%)	60 (14%)	70 (12.5%)
Sepsis	60 (43.7%)	49 (11.6%)	109 (19.6%)
Hyperlipidemia	4 (2.9%)	36 (8.5%)	40 (7%)
Cardiovascular disease	6 (4%)	22 (5%)	28 (5%)
Pneumonia	25 (18%)	19 (4.5%)	44 (7%)
Renal failure	15 (11%)	89 (21%)	104 (18.7%)
Chronic renal failure	12 (8.7%)	58 (13.8%)	70 (12.5%)
Acute renal failure	3 (2%)	31 (7%)	34 (6%)
Hepatic disease (total)	14 (10%)	30 (7%)	44 (7%)
Chronic hepatitis B&C	7 (5%)	17 (4%)	24 (4%)
Hepatosteatosis	3 (2%)	10 (2.3%)	13 (2%)
Acute hepatitis	4 (2.9%)	3 (0.7%)	7 (1.2%)
Osteoporosis	9 (6.5%)	20 (4.7%)	29 (5.2%)
Hydatid cysts	1 (0.7%)	3 (0.7%)	4 (0.7%)

Before hospital admission 8% of patients were on PPI and 5% on H2RA, but during the hospital stay 76% received a PPI and 24% received an H2RA (Figure). At the time of admission, 23 (4%) patients had gastrointestinal hemorrhage and 5 (0.9%) had dyspepsia during hospital admission as indications for acid suppressive therapy. An esophagogastroduodenoscopy was performed in 36 (6.5%) patients during the hospital stay and

revealed one or more pathology in 29 (5.2%) patients. The rest of the acid suppressive therapy was deemed to be indicated for gastrointestinal bleeding prophylaxis during the hospital stay. However, at discharge PPI was prescribed for 79% of the patients and H2RA was prescribed 21% of the patients. It was noted that there was no recommendation about the time period for using these drugs in the discharge notes of patients.

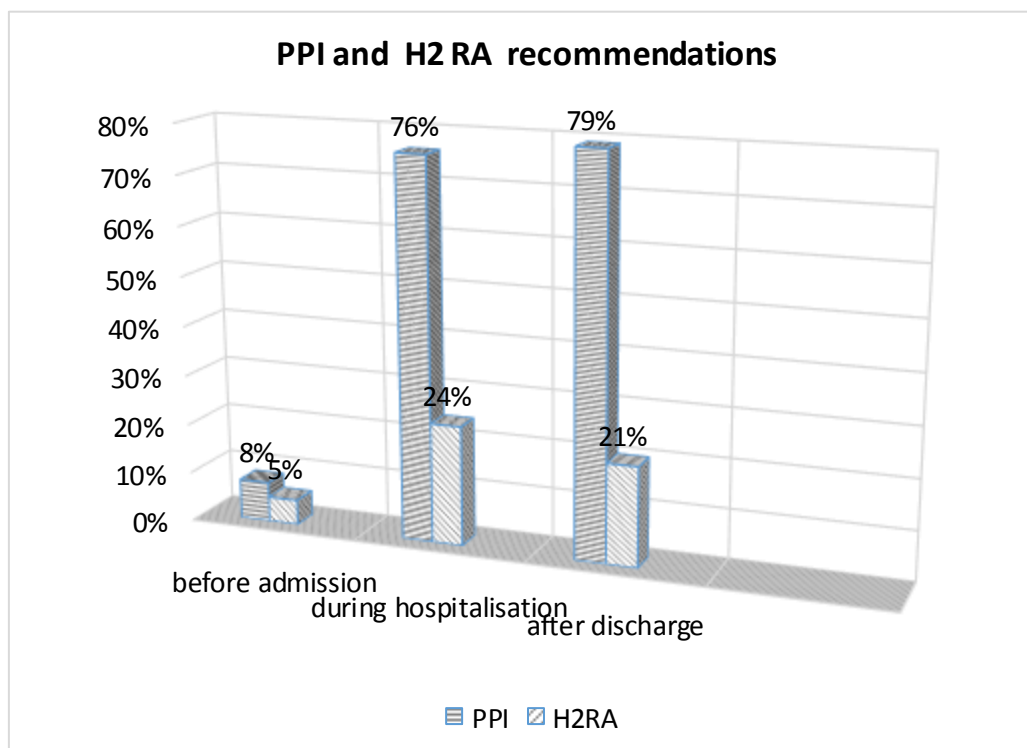


Figure. PPI and H2RA recommendation rates before hospital admission, during hospitalization and after discharge.

DISCUSSION

We showed that half of the patients admitted to the internal medicine wards and the MICU received an acid suppressive therapy during their hospital stay, mostly as a PPI. When the data of those patients who were ordered an acid suppressive therapy were analyzed, it was shown that only a minority of those has an indication for therapy and the rest were considered to receive it as prophylaxis. Moreover, the overutilization continued at the time of discharge: Although only 8% of the patients received a PPI at the time of admission, 79% were discharged with a PPI for an undefined time period.

Currently, H2RA and proton pump inhibitor drugs are recommended for the treatment of certain gastrointestinal diseases and for the prevention of gastrointestinal bleeding in some hospitalized patients with certain risk factors. International sepsis guidelines and American Journal of Health-

System Pharmacy (ASHP) recommends stress ulcer prophylaxis with H2RA for patients with sepsis, mechanical ventilation and coagulopathy in intensive care units.^{[1],[2]} Guidelines do not recommend stress ulcer prophylaxis in non-intensive care units. Although indications have been defined clearly, many patients receive unnecessary acid suppressive treatment and some of them are discharged with H2RA or PPI for an undefined period of time. American Journal of Health-System Pharmacy (ASHP) emphasized that 71% of the inpatients in internal medicine wards were treated with acid suppressive pharmaceuticals, which may increase adverse effects and cause drug interactions. Additionally, it was established that most of these patients (50%) continued using a PPI or a H₂ receptor antagonist after discharge from hospitals². Data from literature shows the use of acid suppressive therapy changes between 20-71% of patients in internal medicine wards and most of these (65-

81%) do not carry absolute indications^{6, 12-14}. Data from the USA showed that 68.8% of the discharged patients were inessentially prescribed a PPI, which accounts for a huge financial burden¹⁵.

In this study we also found that H2RA usage was higher than PPI in the MICU. This might be related to the implementation of well-defined stress ulcer prophylaxis recommendations for ICU patients, especially with after the 2008 recommendations of the Surviving Sepsis Campaign putting H2RA at the first place for patients with sepsis¹¹. However, doctors in the wards tended to use PPI more frequently with no specific reason. Also it was striking to see the switch from H2RA to PPI in 61% of patients who were transferred to wards from the MICU.

Proton pump inhibitors and H2RA drugs have been in use in medical practice over 25 years and they are mostly accepted as safe drugs, but as every pharmaceutical they are not totally innocent drugs. Especially PPIs might increase the risk of *Clostridium difficile* associated enterocolitis, ventilator associated pneumonia, acute interstitial nephritis, increased frequency of hip fractures, fundal gland polyposis, and vitamin B₁₂ deficiency¹⁶⁻²¹ and might have drug interactions especially with clopidogrel²². H2RA seems to be more safety drugs but they also have a wide variety of side effects changing from headache, nausea to serious allergic and anaphylactic reactions, movement disorders, hepatic dysfunctions, atrioventricular heart block, and interstitial nephritis rarely²³⁻²⁸. Off label use and polypharmacy should be avoided given the established and non-established adverse effects. When prescribing PPI and H2RA drugs at discharge, patients should be warned and drug interactions should always be considered. It is also a right approach to question for how long the patient has been using a PPI or an H2RA in order to stop the treatment when no more indicated.

The limitations of this study are its retrospective manner and the lack of documentation of gastrointestinal prophylaxis indications and adverse events associated with the drugs. Hence, we could not evaluate and comment on whether the prophylaxis indications were present or not, or whether inappropriate utilization has led to any additional medical conditions. But, at least we could conclude that only 13% of the patients who received an acid suppressive therapy during the hospital stay was using it at the time of admission. However, 99% of them were discharged with either a PPI or an H2RA with no specific

indication, no planned duration of treatment or no control recommendation.

CONCLUSION

In conclusion, there is a high rate of acid suppressive therapy usage among hospitalized medical patients and this leads to a similarly high rate of prescription at discharge. Further studies are required to evaluate the appropriateness of the utilization of these drugs.

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