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Original Research

Indication of acid suppression therapy and predictors for the prophylactic use of proton-pump inhibitors vs. histamine-2 receptor antagonists in a Malaysian tertiary hospital

Ai L. OH, Andrew G. TAN, Hui S. PHAN, Basil C. LEE, Nafisah JUMAAT, Soo P. CHEW, Siok H. WONG, Shee H. TING, Theebaa SUBRAMANIAM.

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ABSTRACT[*]

Background: Proton-pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA) are common acid suppressants used in gastrointestinal disorders. The trend of usage in Malaysia has changed from predominantly H2RA to PPI from 2007 to 2008, 3.46 versus 2.87 and 2.99 versus 3.24 DDD (Defined Daily Dose)/1000 population/day respectively. This raises concerns as PPI overutilization amounts to higher cost expenditure and are associated with various untoward consequences such as *Clostridium difficile*-associated diarrhea, pneumonia, and osteoporosis.

Objectives: To evaluate the indication of acid suppression therapy (AST) and to look for predictors associated with the prophylactic use of PPI as compared to H2RA.

Methods: Data collection was conducted via a standardized surveillance form over a 2-month period in the general medical wards of Sarawak General Hospital. All patients who received at least one dose of PPI or H2RA in any dosage form were included in the study. Appropriateness of prophylaxis was determined using current available guidelines. Selected risk factors were analysed using simple logistic regression to look for predictors associated with the choice of PPI in prophylactic AST.

Results: Out of 212 cases in the present cohort, about three quarters (75.5%, n=160) of acid suppressants were given as prophylaxis. Over half of these did not have appropriate indications for prophylactic AST (58.1%, n=93). Among all cases given prophylactic AST, 75.0% (n=120) of them were given PPI. Renal insufficiency was identified as the only predictor associated with the use of prophylactic PPI in preference to H2RA (OR=2.86, 95%CI 1.21:6.72, p=0.011).

Conclusion: Inappropriate prophylactic AST is a major concern and may even be underestimated due to the lack of appropriate guidelines. More data is required to guide the selection between PPI and H2RA, specifically the more cost-effective use of H2RA in patients with lower gastrointestinal risk or in whom PPI has no clear advantage.

Keywords: Proton Pump Inhibitors; Histamine H2 Antagonists; Inappropriate Prescribing; Malaysia

[*]**Ai Ling OH**. Department of Pharmacy, Sarawak General Hospital. Sarawak (Malaysia). ohailing79@yahoo.com
Andrew Gerald Hua Kiong TAN. Department of Pharmacy, Sarawak General Hospital. Sarawak (Malaysia). andrewgtan@gmail.com
Hui Sieng PHAN. Department of Pharmacy, Sarawak General Hospital. Sarawak (Malaysia). hsphan@hotmail.com
Basil Choong Lin LEE. Department of Pharmacy, Sarawak General Hospital. Sarawak (Malaysia). baslee90@yahoo.com
Nafisah JUMAAT. Department of Pharmacy, Sarawak General Hospital. Sarawak (Malaysia). nafisah.jumaat@gmail.com
Soo Piing CHEW. Department of Pharmacy, Sarawak General Hospital. Sarawak (Malaysia). ezvic2@hotmail.com
Siok Hui WONG. Department of Pharmacy, Sarawak General Hospital. Sarawak (Malaysia). kaylawng@hotmail.com
Shee Hui TING. Department of Pharmacy, Sarawak General Hospital. Sarawak (Malaysia). tshui1025@gmail.com
Theebaa SUBRAMANIAM. Department of Pharmacy, Sarawak General Hospital. Sarawak (Malaysia). jyshetha_87@yahoo.com

INTRODUCTION

Proton-pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA) are two classes of drugs widely used as gastric acid suppressants. These are indicated in the management of several acid-related gastrointestinal disorders, including treatment of hypersecretory conditions, duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), heartburn, upper gastrointestinal bleeding, Zollinger-Ellison Syndrome and Helicobacter pylori eradication, in addition to stress ulcer prophylaxis and drug-induced peptic ulcer prophylaxis.[1]

It has become apparent that the use of acid suppressants has shifted away from the H2RA to the more potent PPI. The usage of acid suppression therapy (AST) has consistently been predominated by PPI over H2RA in Australia and the Nordic countries from 2004-2008.[2,3] The widespread use of PPI as the more prescribed acid suppressant is likely attributable to its superior efficacy over H2RA in preventing ulcer re-bleeding.[4]

In Malaysia, we saw a lag in the trend towards more PPI usage compared to other countries. According to the Malaysian Statistics on Medicine 2005-2008, H2RA dominated the treatment of acid related disorders in 2005, 2006 and 2007 with 2.73, 2.94 and 3.46 Defined Daily Dose (DDD)/1000 population/day respectively, followed very closely by PPI with 2.42, 2.21 and 2.99 DDD/1000 population/day respectively. PPI usage in the private sector was greater than in the public sector then. However, in 2008, the more commonly prescribed acid suppressant had shifted from H2RA (2.87 DDD/1000 population/day) to PPI (3.24

DDD/1000 population/day), which was mainly contributed by the increasing PPI use in the public sector.[5]

Concerns have been raised with regards to the possibility of overutilization of PPI where studies have emerged with reports claiming up to 68% of hospital inpatients did not have appropriate indication for PPI therapy in developed countries such as US, Australia, New Zealand, Italy, and Ireland.[6-10] This is particularly alarming especially since PPI is accounted for significant cost expenditure as they are more expensive than H2RA. PPI therapy is also associated with various adverse drug reactions such as *Clostridium difficile*-associated diarrhea, pneumonia, and hip fracture, to name a few.[11]

Cost consideration has always been of paramount importance in healthcare. In 2012 alone, our institution spent a remarkable MYR 1.334 million on PPI, compared to just close to MYR 70,000 on H2RA. The cost of oral esomeprazole, pantoprazole and omeprazole (unit dose of 40mg) were MYR 1.80, MYR 0.40 and MYR 1.00 respectively; compared to their parenteral counterparts MYR 22.75, MYR 12.40 and MYR 6.66 respectively. Oral and parenteral ranitidine (unit dose of 150mg) cost MYR 0.13 and MYR 0.96 respectively in 2012.

In view of the worrying possibility of PPI overutilization, we seek to explore the indications for the prescribing of acid suppressants and their appropriateness, in addition to looking at predictors of prophylactic PPI versus H2RA usage in our hospital. To the best of our knowledge, this is the first of such initiatives in Malaysia.

METHODS

Study design and ethical consideration

This prospective observational study was conducted over a 2-month period from April to May 2013 in the general medical wards of Sarawak General Hospital (SGH). The research has been approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia with the registration ID NMRR 13-900-15967.

All patients who were admitted into the general medical wards during the duration of the study and had received at least one dose of PPI or H2RA in any dosage form were included.

Data collection

A standardized surveillance form was designed to facilitate data collection by pharmacists of respective wards. Data collected included patient's demographic characteristics, the type of acid suppressant initiated during admission, concurrent medications and medical conditions, and the indication for AST.

Medication charts of all patients in the wards were reviewed to identify patients who were prescribed with PPI or H2RA. Patients who were admitted and discharged before they could be screened by any pharmacist were excluded. A thorough review of the case notes, clinic cards and medication charts were subsequently carried out to extract information regarding concomitant medications and underlying medical conditions. Patients were interviewed to obtain additional information only if documentations were lacking. All acid suppressants used for treatment purposes were deemed appropriate whereas for prophylactic use, appropriateness was determined based on guidelines outlined below. Prescriber's verification was obtained in case of unclear indication stated in the clinical case notes.

Guidelines recommendation

The approved indications for PPI and H2RA were based on the information in the Malaysia Ministry of Health (MOH) drug formulary and product inserts. These include treatment of peptic ulcer disease (PUD), gastritis/esophagitis, upper gastrointestinal bleeding (UGIH), gastro-esophageal reflux disease (GERD), Zollinger-Ellison syndrome and *Helicobacter pylori* eradication.

For prophylactic AST, we used the American Society of Health-System Pharmacists (ASHP) guideline, Surviving Sepsis Campaign guideline and American College of Cardiology Foundation/American College of Gastroenterology / American Heart Association (ACCF/ACG/AHA) guidelines to determine the appropriateness.

There was no guideline on acid suppressant for stress ulcer prophylaxis (SUP) in general medicine patients to date. As such, we utilized the most established guideline for SUP in intensive care patients by ASHP.[12] Although the ASHP recommends H2RA to be the preferred choice of stress ulcer prophylaxis due to the lack of data with PPI at that time (1999), we took into consideration a recent systematic review and meta-analysis in 2013 which showed PPI to be more effective than H2RA in stress ulcer prophylaxis.[13] Hence we considered patients who fulfilled the ASHP criteria for stress ulcer prophylaxis as appropriate use of acid suppressants be it PPI or H2RA. The ASHP guideline can be referred to Table1.
Another guideline for SUP was the Surviving Sepsis

Table 1. ASHP therapeutic guidelines on stress ulcer prophylaxis (SUP) (1999)[12]

• Mechanical ventilation > 48 hours • Coagulopathy (platelet count < 50,000/mm3, INR > 1.5) • History of GI ulceration/bleeding ≤ 1 year before admission • Thermal injury (> 35% BSA) • Multiple trauma (injury severity score > 16) • Severe head or spinal injury • Perioperative transplant period • Low intragastric pH • Major surgery (lasting > 4hours) • Acute lung injury	Two or more of the following: • Sepsis syndrome • ICU stay > 1 week • Occult bleeding ≥ 6 days • High dose corticosteroid (250 mg of hydrocortisone equivalent) • Hepatic failure • Renal insufficiency • Hypotension • Anticoagulant

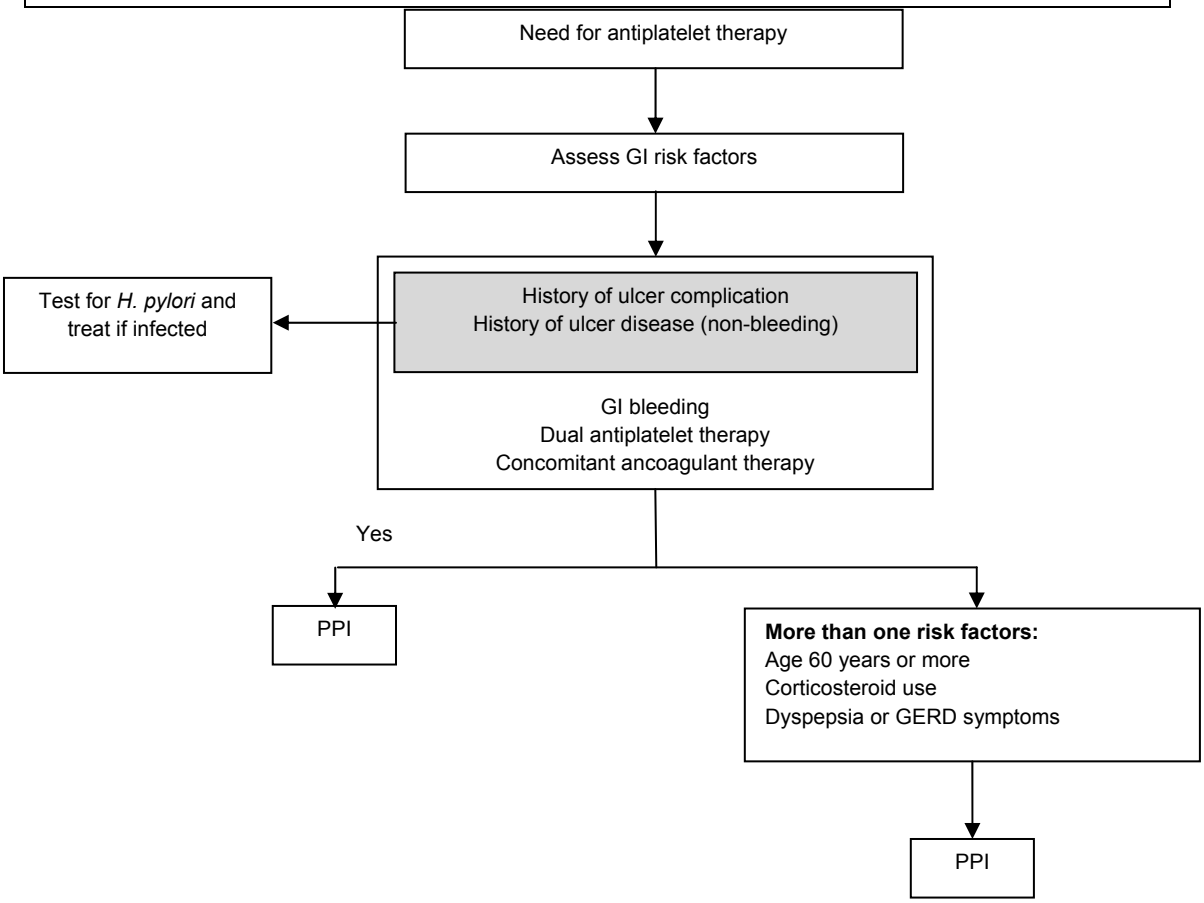

Figure 1. ACCF/ACG/AHA expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy (2008),[15]

Campaign guideline, which recommends a H2RA or PPI to be given in patients with severe sepsis/septic shock who have bleeding risk factors, though no specific risk factors are listed. A PPI is preferred to a H2RA when SUP is indicated.[14]

In addition to SUP, prophylactic AST can also be given for other indications such as gastrointestinal ulcer prophylaxis in patients on antiplatelet therapy. We adopted the ACCF/ACG/AHA 2008 guideline for this indication, the algorithm for which can be found in Figure 1.[15]

AST prophylaxis was only deemed appropriate if the patient fully met either the ASHP guidelines for SUP or the ACCF/ACG/AHA guidelines. Fulfilling part of each guideline did not justify use of AST.

Data Analysis

All data were analysed using SPSS (SPSS Inc., Chicago, IL) version 17.0. Descriptive statistics and logistic regression were used in the data analysis. The level of significance was set at $p<0.05$.

The predictors for PPI versus H2RA use in ulcer prophylaxis were analysed using simple logistic regression. Factors that were tested included risk factors for stress ulcers that we felt could have contributed to the preference for prescribing PPI. These were age >60 years old, sepsis, renal insufficiency, hepatic illness, history of peptic ulcer, GERD, coagulopathy, mechanical ventilation, antiplatelet, anticoagulant and steroid use.

RESULTS

A total of 212 patients were included in this study with the mean age of 54.2 (SD=20.2). Figure 2 showed approximately three quarters (75.5%, n=160) of the cohort were given acid suppressants as prophylaxis with the remainder (24.5%, n=52) intended for treatment. PPI (80.8%, n=42) was more commonly prescribed over H2RA (19.2%,

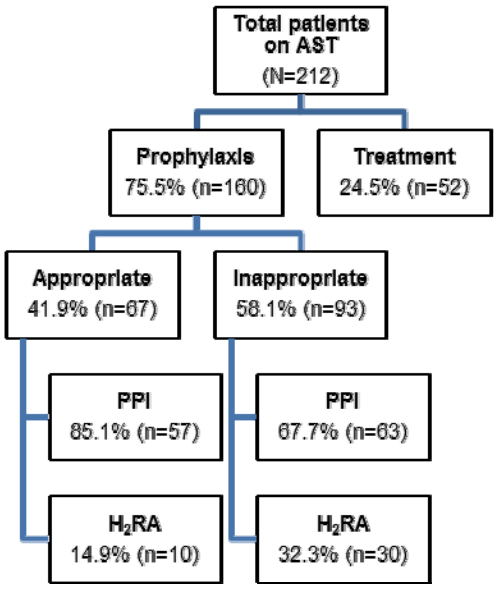

Figure 2. Indication of acid suppression therapy (AST)

Table 2. Risk factors present in patients given inappropriate AST prophylaxis (n=93)

Risk Factors	Number (%)
1 medication (Antiplatelet / Anticoagulant / Cortisosteroid)	38 (40.9%)
2 medications (Corticosteroid + Antiplatelet / Anticoagulant)	6 (6.5%)
1 medication (Antiplatelet / Corticosteroid) + 1 SUP risk	9 (9.7%)
1 SUP risk (sepsis/renal)	22 (23.7%)
No risk factors	18 (19.4%)

n=10) for the treatment of acid-related disorders. Among cases where acid suppressants were used for prophylaxis, over half (58.1%, n=93) were deemed inappropriate, of which about two thirds were prescribed a PPI (67.7%, n=63). It was also important to note that in patients who were appropriately prescribed acid suppressants, 85.1% (n=57) of them received a PPI.

Table 2 showed a breakdown of risk factors that were present in those deemed to have been inappropriate prescribing of acid suppressants. The risk factors selected here were based on those from the ASHP and ACCF/ACG/AHA prophylaxis guidelines. These patients either did not fully fulfil the criteria for prophylaxis in either guideline (80.6%, n=75) or had no risk factor at all (19.4%, n=18).

The choice for prescribing PPI in all prophylactic use amounted to three quarters (75.0%, n=120) of all cases (derived from Figure 2). The predictors for the choice of PPI over H2RA were displayed in Table 3. Renal insufficiency was the only statistically significant, independent predictor of the choice of prophylactic PPI over H2RA (OR=2.86, 95%CI=1.21:6.72, p=0.011). Hepatic illness, history of peptic ulcer, and GERD were also among factors tested. However, the analyses were invalid as there were nil samples in the H2RA group. In our sub-analysis, we found that patients who had fulfilled 2 or more risk factors, PPI was more commonly prescribed for prophylaxis compared to H2RA (OR=3.72, 95%CI=1.76:7.85, p<0.001).

DISCUSSION

Inappropriate PPI prescribing had been noted in the hospitalized patients in the USA (65%), Australia (63%), New Zealand (40%), Italy (68%) and Ireland (33%).[6-10] A similar situation was also apparent in our setting, whereby 52.5% of all prophylactic PPIs prescribing were unnecessary according to guidelines used in this study. What was of greater concern was the alarming rate of overall inappropriate prophylactic use of acid suppressants (58.1%), which we felt could be largely explained by the lack of guidelines for such indications in patients who are not critically ill. Applying the ASHP guidelines for intensive care patients in less critically ill patients could have arguably led to an underestimation of inappropriateness. This is because we should expect a higher threshold for AST prophylaxis in such patients. There is a desperate need for validated guidelines for gastric ulcer prophylaxis in non-critically ill patients.

Despite our national formulary restriction of PPIs to specialists only, the use of PPI continued to rise. The alarming upward trend of PPI use as the most prescribed acid suppressant has been largely due to the increasing numbers of evidence-based trials which support the use of PPI over H2RA in a number of acid-related disorders such as, bleeding peptic ulcer and erosive esophagitis with promising outcomes.[4,16] Its advantage over H2RA in the treatment of acid-related disorders could have been extrapolated to prophylactic use. Several recent meta-analyses looking at SUP in critically ill patients have shown contradicting results when comparing the 2 groups of acid suppressants, with 2 of 3 meta-analyses demonstrated superiority of PPI.[13,17,18] We also felt that the increase in PPI use could be attributed to the generic availability of omeprazole and pantoprazole. In order to illustrate this claim more clearly, the cost of a 40mg dose of generic parenteral pantoprazole in our hospital was only 48% of its patented counterpart in 2012. All other PPI formulations were only available in generic except esomeprazole.

Out of 93 cases of inappropriate prophylactic acid suppressant use, 19.4% had no risk factors identifiable based on current guidelines. The remainder which consisted of either 1 or 2 risk factors also did not fulfil criteria for use of AST. A study conducted in Florida had also identified frequent prescribing of acid suppressants in low risk patients as determined by consensus review.[19] It went on to suggest that prescribing pattern with regards to overuse of acid suppressants have not changed much since 2000. A hint of defensive prescribing might have been suggested, but this remained to be proven.

Our results showed renal insufficiency to be the only significant predictor for the choice of PPI over H2RA. This can be partially explained by the increased gastrointestinal (GI) symptoms, multiple-drug regimens and also a higher prevalence of superficial gastritis, duodenitis and peptic ulcer in

Table 3. Univariate analysis of predictors associated with the prophylactic use of PPI over H_2RA (n=160)

Risk Factors	Odds Ratio	95%CI	p-value
Age ≥ 60	1.61	0.77 : 3.36	0.198
Sepsis	1.32	0.46 : 3.79	0.603
Renal insufficiency	2.86	1.21 : 6.72	0.011
Coagulopathy	3.94	0.49 : 31.49	0.124
Mechanical ventilation	1.24	0.49 : 3.14	0.644
Antiplatelet use	0.96	0.44 : 2.10	0.920
Anticoagulant use	1.34	0.50 : 3.58	0.547
Corticosteroid use	1.52	0.63 : 3.63	0.338
*Hepatic illness, history of peptic ulcer and GERD results were invalid as there was nil sample in the control group for these risk factors.			

this group of patients.[20-22] The additional benefit of no renal dose adjustments required for PPI could be another contributing factor. As much as one would like to think that AST is appropriately indicated in all patients with renal insufficiency, concerns have been raised over the issue.[21]

Limitations

Several limitations of the study had been identified. Firstly, we failed to distinguish whether patients were initiated on or merely continued on AST from past medication history. Instead we assessed the appropriateness of the AST based on patient's clinical status and medical history at the point of admission. Although these patients might have been inappropriately maintained on AST prophylaxis even prior to admission, this was not an objective of our study.

Inevitably we faced difficulties obtaining complete history and information regarding the indication of the acid suppressants being prescribed in some cases. This led to us consulting the patient and/or prescriber for additional information. When both failed to justify the need for prophylactic AST based on guidelines considered in this study, we labelled it as inappropriate use. Though some might argue that this could have contributed to overestimation of inappropriateness, our counter-argument would be that neither patient nor prescriber could at that point satisfy the criteria for appropriateness even if patients actually had an unknown indication for AST. If any overestimation were to occur, we expected it to be minimal.

A third limitation was that we did not take into account of the change in pattern (step-up or step-down) of AST prescribing during the same admission. A single patient would have been seen by several doctors starting from the Emergency & Trauma Department, and later ending up in the Medical Wards. Inevitably so, the patient's clinical condition and fulfilment of criteria for prophylactic AST would also have varied throughout the entire admission. Failure to correct our findings for this "varying appropriateness" could unfortunately contribute to some inaccuracy.

CONCLUSIONS

Inappropriate prophylactic acid suppression therapy is a major concern and may even be underestimated due to the lack of appropriate guidelines. More data is required to guide the selection between PPI and H2RA, specifically the more cost-effective use of H2RA in patients with lower gastrointestinal risk or in whom PPI has no clear advantage.

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CONFLICT OF INTEREST

No conflict of interests to declare.

INDICACIÓN DEL TRATAMIENTO DE SUPRESIÓN ÁCIDA Y PREDICTORES DEL USO PROFILÁCTICO DE INHIBIDORES DE LA BOMBA DE PROTONES VS. ANTAGONISTA DE RECEPTORES DE HISTAMINA-2 EN UN HOSPITAL TERCIARIO MALAYO

RESUMEN

Antecedentes: Los inhibidores de la bomba de protones (PPI) y los antagonistas de los receptores de histamina-2 (H2RA) son antiácidos comunes que se usan en desordenes gastrointestinales. La tendencia de uso en Malasia ha cambiado de la predominancia de H2RA a PPI entre 2007 y 2008 de 3,46 vs. 2,87 y 2,99 vs. 3,24 DDD (Dosis Diarias Definida)/1000 habitantes/día, respectivamente. Esto preocupa ya que la sobre-utilización de PPI produce mayores costes y están asociados a varias consecuencias indeseadas como diarrea asociada a *Clostridium difficile*, neumonía, y osteoporosis.
Objetivos: Evaluar la indicación del tratamiento de supresión ácida (AST) y buscar predictores asociados con el uso de PPI comparados con H2RA.
Métodos: Se recogieron datos mediante un formulario de vigilancia estandarizado durante 2 meses en los servicios de medicina heneral del Hospital General de Sarawak. Todos los pacientes que recibieron, al menos una dosis de PPI o de H2RA en cualquier forma fueron incluidos en el estudio. La adecuación del tratamiento fue determinada usando las guías disponibles actualmente. Se analizaron los factores de riesgo usando una regresión logística simple para buscar predictores asociados con la elección de PPI en AST profiláctica.
Resultados: De los 200 casos presentes en la cohorte, cerca de tres cuartos (75,5; n=160) de los antiácidos fueron usado como profilácticos. Más de la mitad de ellos no tenían una indicación apropiada para AST profiláctica (58,1%, n=93). Entre todos los casos con AST profiláctica, el 75,0% (n=120) eran PPI. La insuficiencia renal fue el factor asociado con el uso de profilaxis con PPI en preferencia a los H2RA (OR=2,86; 95%CI 1,21:6,72, p=0,011).
Conclusión: La AST profiláctica inadecuada es una gran problema y podría estar subestimada debido a la ausencia de guías apropiadas. Se requieren más datos para guiar la selección entre PPI y H2RA, específicamente el uso más coste-efectivo de los H2RA en pacientes con riesgo gastrointestinal bajo, o en los que no hay una clara ventaja de los PPI.

Palabras clave: Inhibidores de la Bomba de Protones; Antagonistas de los Receptores Histamínicos H2; Prescripción Inadecuada; Malasia

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