Gastric acid suppressors on inpatients in a Brazilian hospital: overuse and underuse

Supressores ácidos gástricos em pacientes de um hospital nacional:

utilização abusiva e subutilização

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RESUMO

Investigou-se o perfil de utilização dos medicamentos omeprazol e ranitidina em hospital escola do Brasil. O uso de omeprazol e ranitidina foi avaliado através da seleção de 220 pacientes adultos e idosos de um hospital em São Paulo no período de 6 meses. Os dados foram obtidos de prescrições e prontuários médicos e analisados conforme literatura médica e os protocolos hospitalares educativos. Estudos anteriores demonstraram uso indevido de terapia supressora ácida comprovando uma tendência à altos índices de prescrição de inibidores de secreção gástrica em pacientes hospitalizados. Nesse estudo, omeprazol ou ranitidina foram prescritos para 44% dos pacientes. De todas as prescrições contendo omeprazol ou ranitidina, 63% foram de não indicação para uso e a maioria dos pacientes desse grupo eram idosos. Dentre os pacientes em uso de supressores gástricos, 15% dos casos possuía interação medicamentosa. A porcentagem de uso abusivo de supressores ácidos nesse estudo foi similar às apresentadas em estudos similares realizados em outros países. Notavelmente uma alta incidência de sub utilização desses medicamentos também foi observada, 41% dos casos no grupo de não utilização. Os resultados sugerem que a existência de protocolos hospitalares não exime a necessidade de estratégias adicionais para promover o uso racional de medicamentos.

PALAVRAS-CHAVE: Omeprazol, Ranitidina, Antiácidos, Uso Indevido de Medicamentos sob Prescrição, Interações de medicamentos.

ABSTRACT

We investigated the usage profile of the medicaments omeprazole and ranitidine in a school hospital in Brazil. The use of omeprazole and ranitidine was evaluated throughout a random selection of 220 adults and elderly inpatients of a hospital in São Paulo during a 6 months period. The data were obtained from prescriptions and medical records and analyzed according to medical literature and the hospital educational protocols. Earlier studies demonstrated misuse of acid suppressive therapy verifying a trend toward high prescription of inhibitors of gastric secretion in hospitalized patients. In this study, omeprazole or ranitidine was prescribed for 44% of the patients. Of all prescriptions containing omeprazole or ranitidine, 63% had no indication of use and most of the patients of this group were elderly. In the usage group 15% of the cases had drug interactions. The frequency of abusive use of acid suppressors observed was similar to that found in resembling studies performed in other countries. Notably a high incidence of under-utilization of these drugs was also observed, 41% of the cases in the non-usage group. The results suggest that the existence of written protocols does not preclude the need of additional strategies to promote rational medicine use.

KEYWORDS: Omeprazole, Ranitidine, Antacids, Prescription drug misuse, Drug interactions.

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INTRODUCTION

Drugs to reduce gastric acid secretion or acid suppressors such as proton pump inhibitors (PPIs) and histamine-2 receptors antagonists (H₂RAs) are largely prescribed for hospitalized patients in several countries and this prescription is commonly inappropriate. The use of any type of medication potentially exposes the patient to side effects and increases the risk of drug interaction; therefore, the inappropriate drug utilization must be avoided (Nardino *et al.*, 2000; Sebastian *et al.*, 2003, Parente *et al.*, 2003; Scagliaini *et al.*, 2005; Grube *et al.*, 2007).

In Brazil the differences between the two classes of acid-suppressors (PPIs and H_2RAs) regarding effectiveness and tolerance have already been evaluated, but there is no data regarding acid suppressors usage and prescription practices (Meneghelli *et al.*, 2010). In the USA, the misuse of this therapeutic class was already determined in some studies suggesting educational interventions and guidelines for appropriate prescription (Nardino *et al.*, 2000; Heidelbaugh *et al.*, 2009; Hwang *et al.*, 2007). In addition, proton pump inhibitors class is the third one sold in North America and was responsible for 13 billion dollars profit in 2009 (Pallarito, 2009). The popularization of acid-suppressive therapy in hospitals happened after studies indicated a significant reduction on the risk of gastric bleeding in critically ill patients with the use of acid suppressors (Faisy *et al.*, 2003; Stollman *et al.*, 2005). This specific clinical condition characterized by bleeding of the gastrointestinal tract in extreme stress situations, such as sepsis and severe burns, is called stress ulcer and the prescription of an acid suppressor is used with a prophylactic aim.

Although the use of acid suppressors in prophylaxis may be beneficial in some cases, it is important to avoid misuse, once the risks can outweigh the prophylaxis benefits. In 1999 a guideline for stress ulcer prophylaxis was published by the American Society of Health Systems Pharmacists (ASHP) to help physicians select patients with indication for ulcer prophylaxis. For the prescription of acid suppressors, the patient's age, previous diseases and susceptibility to any of the side effects should be considered (Nardino *et al.*, 2000; Parente *et al.*, 2003).

Despite the risk of side effects, there is also the risk of interaction with food or other medicines; therefore, the prescription of a drug must be carefully analyzed for a rational drug use (Fabricant, 1987). Omeprazole and clopidogrel must be avoided, there are evidences that show a competitive hepatic metabolism reducing the pharmacologic effects of the antiplatelet and increasing the risk of thrombosis (Gurbel *et al.*, 2008). The concurrent use of omeprazole or ranitidine with ferrous sulfate and warfarin is considered of moderate severity. The absorption of ferrous sulfate can be reduced according to gastric pH, causing an increase on the plasma's warfarin level with a consequent risk of intoxication. The concomitant use of phenytoin or digoxin with omeprazol also increases the risk of intoxication (Micromedex®).

Medical protocols that contain updated clinical information have been recommended as guides to help physicians in the decision of drugs indications. Because Brazil lacks information about acid-suppressive treatment and this therapy misuse is world widely discussed as an important health issue, we determined the usage of omeprazole and ranitidine in a school hospital in one of Brazil's largest cities, São Paulo. The evaluation of prescription appropriateness was based on the hospital protocols and on information of the medical databases Micromedex® and UpToDate®.

MATERIALS AND METHODS

Location and study design

The study was conducted in a teaching hospital, the University Hospital of the University of São Paulo (HU-USP), which is a 258-bed community hospital in Brazil. Adults and elderly patients from the general medical clinic of the hospital were randomly selected during a 6 month period, from May to October 2010. The 220 selected patients were assessed for the usage and indication of omeprazole and ranitidine. Patients were excluded from the study if readmitted during the survey period.

Prescriptions and medical records were analyzed to collect data throughout a form. The patient's admission diagnoses, clinical evolution, and exam results were observed to evaluate whether the prescription of an acid-suppressor could be justified. ''Usage'' was characterized as the presence of omeprazole or ranitidine in the prescription regardless the dosage. ''Indication'' was defined when the medical record or the admission diagnoses were in agreement with the hospital protocols of indication for omeprazole or ranitidine or in agreement with the medical literature not included in the hospital protocols, but included in the medicine leaflets and in medical databases (Micromedex®; UpToDate®).

The hospital protocol lists ranitidine as the preferred acid suppressor for the prevention of stress ulcer and omeprazole as the most indicated medication for the prevention of gastric bleeding from ulcer caused by non-steroid anti-inflammatory drugs and low platelets levels. Accepted indications were the indications from the hospital protocols and from medical literature such as ulcer, esophagitis, stress ulcer prophylaxis, use of high doses of non-steroid anti-inflammatory, among others. Any other use despite the indication of the hospital protocols and medical literature was characterized as not indicated.

The potential drug interactions with these two acid suppressors were also collected from the prescriptions. The frequency of the following medicines prescribed with omeprazole was analyzed: clopidogrel, digoxine, warfarin, ferrous sulfate and phenytoin. For ranitidine, the occurrence of simultaneous prescription with warfarin or with ferrous sulfate was considered potential drug interactions. The selection of these medicines to evaluate drug interaction was based on the availability of the medicines in the hospital pharmacy and the severity of the effects in the occasion of a drug interaction according to previously cited medical databases.

The prescription of omeprazole and clopidogrel together was classified as non-indication of omeprazole, even though the clinic situation justified the use of an acid suppressor. This decision was based on studies results that point this drug interaction as high risk (Micromedex®) and on informative of the World Health Organization (WHO) that does not recommend this simultaneous usage. Therefore, in these cases ranitidine would be the best option.

Gender, age and reason of hospital admission were assessed. The patients were divided in the "usage" and "indication" groups to establish the frequency of incorrect prescription of omeprazole and ranitidine. The unnecessary usage of the acid suppressor or the lack of an acid suppressor in the patient's treatment was characterized as a faulty prescription.

Population Characteristics

In this randomized study, 220 patients from the general medical clinic were recruited. There was a predominance of men (55%) and most of the patients were elderly, age of 60 or more (55%). Cardiovascular and respiratory affections were the most common hospital admission reasons (Table 1).

Table1: Demographic features of the medical clinic selected patients. São Paulo, 2010.

	Nº of Patients (N=220)	% of Population
Age (years) 18 - 40	34	16%
41 - 59	65	29%
60 - 80	88	40%
81 or more	33	15%
Affected System		
Cardiovascular	66	30%
Respiratory	61	28%
Urinary	25	11%
Tegumentary	22	10%
Digestive	11	5%
Immunologic	11	5%
Nervous	9	4%
Endocrine	5	2%
Others*	10	5%

^{*}Unknown reasons of hospital internment

Statistical analysis was performed using two software: Microsoft Excel® version XP and OpenEpi® version. The results for utilization and indication of omeprazole or ranitidine were expressed in percentage. The chi-squared test was used to compare the prescription of omeprazole and ranitidine between the groups of adults and elderly. The results were considered statistically significant when p < 0.05.

Ethics

The research was submitted and approved by the Ethics in Research Committee of the Faculty of Pharmaceutical Sciences (protocol CEP/FCF/TCC/17 and approval CEP/37/2010) and by the Ethics in Research Committee of the University Hospital (protocol CEP-HU714/07D), both belonging to the University of São Paulo.

RESULTS

Patients were grouped according to whether or not there was omeprazole or ranitidine in their prescription. For each group the indication of use was assed considering the hospital protocols and other medical literature (Table 2).

Table 2: Usage and non usage groups of omeprazole and ranitidine and indication or no indication of use in the patient's groups. São Paulo, 2010.

	Medicine Usage		Medicin	Medicine Non Usage	
	Indication	No indication	Indication	No indication	
Omeprazole	24	42	31	72	
Ranitidine	12	20	20	12	
Group Subtotal		98*		123	
Total of patients			220		

Indication according to Micromedex®, UptoDate® and medicine leaflets *Patients subtotal of usage exceeds 97 patients, because 1 patient was undergoing the acid-suppressive treatment with omeprazole and ranitidine.

Overall, 44% (97/220) of the patients were undergoing acid suppressive therapy. From the usage group: 65 patients used omeprazole, 31 ranitidine and 1 both drugs. The patient receiving both medicines appears in the group of no indication for omeprazole and for ranitidine as well. The number of patients that used these medicines before hospital admission is unknown.

According to the data presented in Table 2, it is clear that most patients receiving omeprazole or ranitidine had no indication of use. Comparing the medicines, omeprazole was more frequently prescript without indication. Needlessly, 42 and 20 patients received omeprazole and ranitidine, respectively. This represents an overuse of 63%. Five patients were evaluated as having no indication for omeprazole, once they were also receiving clopidogrel and this combination is not advised for safety reasons (Gurbel *et al.*, 2008; WHO). As a substitute to prevent gastric bleeding, ranitidine was considered indicated.

In addition, one other interesting finding is related to the higher prevalence of acid suppressor use in elderly patients (121/220) (p<0,05). More than half of the elderly patients 52% (63/121) had an acid suppressor prescribed. From the elderly using an acid suppressor, 40 patients did not have indication for such therapy.

Besides overuse, sub utilization was also noticed in patients with clear indication to receive acid suppressive therapy. In the Non Usage group, 31 patients had indication to receive omeprazole and 20 to receive ranitidine.

As already mentioned, the concurrent use of omeprazole and clopidogrel must be avoided according to the Food and Drug Administration (FDA). Despite the omeprazole – clopidrogrel interaction, other potential drug interactions with omeprazole and ranitidine were detected in the studied population (Table 3).

Table 3: Number of potential drug interactions detected on the patient's prescriptions of the usage group of omeprazole or ranitidine. São Paulo, 2010.

Omeprazole					
Clopidogrel	5				
Ferrous Sulfate	1				
Phenytoin	3				
Digoxin	0				
Warfarin	3				
Ranitidine					
Ferrous Sulfate	2				
Warfarin	1				
Total	15				

Fifteen patients were under risk of an adverse drug interaction and 12 of these patients didn't even have indication of treatment with an acid suppressor. Thus, for these patients the simple suspension of omeprazole or ranitidine from the prescription would eliminate the risk of this type of drug interaction.

DISCUSSION

This study evidences misusage of acid suppressors in the hospital inpatients; both overuse and underuse were observed. The usage profile of acid-suppressors, mainly overuse, was a much discussed issue. Similar studies from other countries reported usage of acid suppressors among inpatients from 32% to 71% and overuse from 42% to 90% (Nardino *et al.*, 2000; Sebastian *et al.*, 2003, Parente *et al.*, 2003; Scagliaini *et al.*, 2005; Pham *et al.*, 2006; Gingold *et al.*, 2006; Naunton *et al.*, 2000; Walker & Mcdonald 2001; Niklasson *et al.*, 2003). Therefore, this Brazilian study with 44% of usage and 63% of overuse follows the world's patterns (Figure 1).

Figure 1: Acid-suppressors usage profile results from similar studies conducted in different countries

Country	Year of publication	Patients	Inpatients using acid- suppressive therapy	Overuse of acid- suppressive therapy	Reference
U.S.A	2000	n=200	54%	65%	NARDINO et al
Ireland	2003	n=272	32%	63%	SEBASTIAN et al
Italy	2003	n=799	47%	68%	PARENTE et al
Italy	2005	n=834	59%	42%	SCAGLIAINI et al
U.S.A	2006	n=213	71%	90%	PHAM et al
U.S.A	2006	n=179	50%	91%	GINGOLD et al
Australia	2000	n=200	a	63%	NAUNTON et al
United Kingdom	2001	n=85	a	67%	WALKER et al
Sweden	2003	n=301	44%	59%	NIKLASSON et al
Brazil ^b	2010	n=220	44%	63%	

^a 100% The study selected patients undergoing acid-suppressive therapy ^bThis study.

It is known that multiple factors can influence the usage of medicines in populations, such as market price, the offer or lack of medicines, the powerful pharmaceutical marketing and prescription practices. The great challenge, according to the World Health Organization is to rationalize this use, considering effectiveness, safety and costs of the treatment (WHO). The rationalization will provide safety for the patient and better application of hospital financial resources (Heidelbaugh *et al.*, 2006). A trained multidisciplinary team inside the clinic can also help decide the need of a certain prescription improving the rational use of medicines.

Prophylactic acid suppression is commonly used for prevention of gastrointestinal mucosa damage in patients with high risk of bleeding, major trauma, severe head injury, multiple organ failure, severe burns, and major surgical procedures (Navab & Steingrub,1995). In recent years, the practice of stress ulcer prophylaxis has become increasingly common in general medical clinic patients. However, there is little to no evidence on the literature to support this widespread use and not all patients reach criteria to receive acid suppressive prophylaxis (Ali & Harty, 2009; Janicki & Stewart, 2007). While many practitioners view acid-suppressive therapy to be harmless, its use is not risk-free. The inappropriate prescribing and the excessive use of acid suppressors (especially the class of proton pump inhibitors) is associated with increased risk for pneumonia, interstitial nephritis, *Clostridium difficile* colitis and fractures (Laheij *et al.*, 2004; Torpey *et al.*, 2004; Dial *et al.*, 2005; Gray *et al.*, 2010).

Regarding the simultaneous use of omeprazole or ranitidine with drugs that could interact with the acid-suppressor, it's always important for the physician to analyze the risks and the benefits of the concomitant prescription. This study emphasizes that almost no patients with potential drug interaction had the indication for an acid-suppressive therapy. It was observed, during the study, the suggestion of clinical pharmacists to the medical team to change some prescriptions with the intention of avoiding potential drug interactions. This finding is on conformity with some studies that state that the clinical pharmacist plays an important role in medical error interception (Miller *et al.*, 2011; Pantawalla *et al.*, 2012).

The conduct of the study in only one hospital and the sample size could be considered possible biases for the results found for the hospital usage of acid suppressive medicaments. Future studies performed in other hospitals and different locations in Brazil can increase the sample size and present more accurate results regarding the prescription practices of omeprazole and ranitidine in the country.

CONCLUSION

Although the acid suppressive therapy overuse was expected in our population, this study brings a new contribution regarding these medicines profile usage, the underuse. Forty-one percent of the patients not undergoing an acid suppressor therapy had use indication. Most of the underuse cases had indication for prevention of injury of the gastric mucosa caused by non-sterol anti-inflammatories, a common use of acid-suppressors indicated by the hospital protocol. The underuse was unexpected and not previously described (Nardino *et al.*, 2000; Sebastian *et al.*, 2003, Parente *et al.*, 2003; Scagliaini *et al.*, 2005; Grube *et al.*, 2007). Further studies in Brazil and in other countries should consider the occurrence of this important health issue creating strategies to identify it and tackle it.

To increase medical knowledge and promote rational drug use, some actions are recommended. Among the past years, medical and health centers implemented the idea of having guidelines and protocols to improve the assertiveness of the medical team regarding prescriptions and medical use (Lillis & Lord, 2011; Chua *et al.*, 2009). However, it is notable that the existence of a protocol itself, such as the case of this study, doesn't assure ration prescription results. There must be an effective strategy aimed at the divulgation of the protocol and at the importance of following it. Furthermore, continuous learning practices and multidisciplinary team dialogues in order to prevent medication errors are of high importance in the hospital and clinic environments (Pantawalla *et al.*, 2012; Miller *et al.*, 2011; Esmaily *et al.*, 2010).

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