ANADOLU UNIVERSITY
GRADUATE SCHOOL OF HEALTH SCIENCES

European Journal of Life Sciences 2023; 2: 25-30

Research Article

An observational study on drug interactions caused by proton pump inhibitors

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https://doi.org/10.55971/EJLS.1209405

Received: 24.11.2022
Accepted: 13.03.2023
Available online: 24.04.2023

ABSTRACT

Proton pump inhibitors (PPIs) are widely used to treat gastric acid-related diseases worldwide and in our country. The high reliability of PPIs also allows long-term use for appropriate indications in chronic diseases, which increases the possibility of drug-drug interactions. Therefore, it is clear that the usage of PPIs should be monitored in terms of drug-drug interactions to provide drug treatment success and patient safety. The ability of pharmacists, the closest health consultants, to identify these interactions during prescription fulfillment will significantly contribute to treatment success. Although many studies deal with the rational use of PPIs and drug interactions, the number of studies revealing observational drug interactions is minimal. This research aims to determine drug-drug interactions frequently encountered in community pharmacies for PPIs, which interact with many drug groups and are commonly prescribed. For this purpose, approximately 1700 prescriptions supplied by a selected community pharmacy, serving in Van, were examined. One hundred sixty-four of the prescriptions were evaluated by considering the study's limitations. Drug-drug interactions were checked by three different electronic database. It was determined that 73 of 164 prescriptions had interactions in at least one of the three databases. In 73 prescriptions, 86 drug interactions were observed. 34% of the interactions detected in the study were caused by lansoprazole.

Keywords: Comunity Pharmacy, Drug Interaction, Proton Pomp Inhibitors

1. INTRODUCTION

Proton Pump Inhibitors (PPIs) are widely used in treatment of gastro-oesophageal reflux disease (GERD), peptic ulcer, erosive esophagitis, Helicobacter pylori (HP) eradication, dyspepsia, and Zollinger-Ellison syndrome. In addition, PPIs are used to reduce the incidence of gastric ulcers due to non-steroidal anti-inflammatory drugs (NSAIDs) and to reduce the risk of gastrointestinal bleeding in intensive care patients [1]. The metabolization of the PPIs is made by hepatic cytochrome P450 (CYP) and enzymes (CYP2C19 and CYP3A4). Inhibitors and inducers of these enzyme groups can cause drug interactions with PPIs [2].

Despite the almost excellent safety profiles of the proton pump inhibitors group drugs, the treatment of patients should be monitored frequently, and caution should be exercised due to polypharmacy that may occur as a result of not being used in appropriate indications and using them for unnecessary long-term treatment. In this way, the most critical safety problem caused by excessive PPI use for a long time

is drug interactions [3]. As Johnson et al. stated, the most important reason that causes interactions in terms of PPIs is prescribing at high doses and for extended periods [4].

Encountering clinically relevant drug-drug interactions with PPIs is not common [2]. However, the ability of pharmacists, the closest health consultants, to identify these interactions during prescription fulfillment will significantly contribute to treatment success. Although many studies deal with the rational use of PPIs and drug interactions, the number of studies revealing observational drug interactions is limited. This research aims to determine drug-drug interactions frequently encountered in community pharmacies with PPIs, which interact with many drug groups and are commonly prescribed.

2. MATERIALS AND METHODS

Within the scope of this study, prescriptions containing proton pump inhibitors received between 15 December 2021 and 15 May 2022 at the "Bölge Pharmacy" serving in the Van were examined by the researchers in terms of drug interactions. In the study, the ICD-10 diagnostic code of the prescriptions, the specialty of the prescribing physician, the gender and age of the patient, how many items of medication were written on the prescription, whether there was a drug-drug interaction in the prescription, and if there was an interaction, which drugs were interacted with and the degree of interaction were collected. Potential drug interactions between prescription drugs were carried out in an electronic environment called Medscape, RxMediaPharma, and TEBRP programs.

Prescriptions containing at least one PPI and one different drug without PPI were included in the study. As a result of the evaluation with the pharmacist, it was determined that approximately 30-40 prescriptions meeting the relevant criteria were met monthly in the pharmacy. Additionally, in studies with similar study designs, the number of evaluated prescriptions was determined according to affiliated pharmacies' filling prescription rates, and almost 100-200 prescriptions were investigated. In this regard, 1700 prescriptions filled by the Bölge Pharmacy were evaluated. One hundred sixty-four prescriptions were evaluated by considering the study's inclusion criteria.

This study was conducted after Van Yüzüncü Yıl University Non-interventional Research Ethics Committee has approved the study ethically (Date:19/11/2021, Decision No: 2021/12-16).

3. RESULTS AND DISCUSSION

In the study, 164 prescriptions were evaluated, and 55 % were prescribed for women. The distribution of the prescribed physicians' specialty areas is given in Figure 1. It is seen that internal medicine specialists mainly prescribe PPIs and practitioners follow them. As presented in Öncü et al.'s study, it is known that internists frequently prescribe PPIs. It is also noteworthy that 55-80% of prescriptions do not have an appropriate indication for using PPIs [5].

Evaluated 164 prescriptions contain all PPIs available on Turkish pharmaceutical market (lansoprazole, pantoprazole, esomeprazole, omeprazole and rabeprazole). The distribution of prescribed PPIs is illustrated in Figure 2.

As can be seen from Figure 2, the most prescribed PPI was lansoprazole and followed by pantoprazole. In this study, prescription rate of the esomenprazole was low, in contrast to Arı et al. [6].

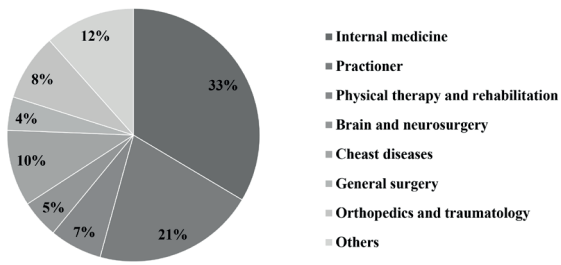

Figure 1. Prescribed physicians' specialty areas

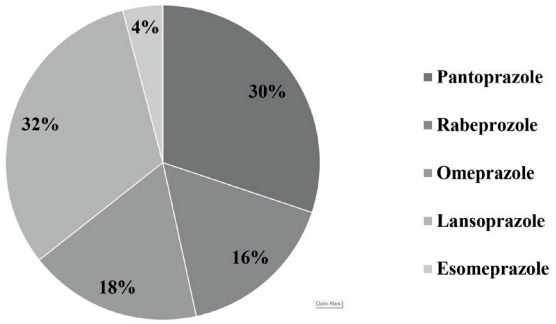

Figure 2. Distribution of the prescribed PPIs

Additionally, ICD-10 codes of these 164 prescriptions were evaluated. 60% of them had gastroesegial reflux, 18% had peptic ulcer, 8% had irreparable bowel syndrome, 4% had dyspepsia, 4% had indigestion, 1% had helicobacter pylori code.

It was determined that 73 of 164 prescriptions had interactions in at least one of the three databases. In 73 prescriptions, 86 drug interactions were observed. As stated in various literature, the findings obtained from the databases show differences. In Table 1, interactions with lansoprazole are presented.

34% of the interactions detected in the study were caused by lansoprazole. In light of the information presented in Table 1, interactions with lansoprazole were seen differently in the three databases. Among the interactions, only lansoprazole and methotrexate interaction were detected by three databases. The most common interaction between lansoprazole and acetaminophen was seen at a minor level. Table 2 summarizes detected interactions with pantoprazole.

28% of the interactions detected in the study were caused by pantoprazole. According to Table 2, no interactions were detected by Medscape; however, 24 "minor" level interactions were found by TEBRP. Only pantoprazole and rifaximin interaction was detected by RxMediaPharma and TEBRP similarly. Table 3 outlines interactions with esomeprazole.

Parallel to the prescription rate, only 7% of interactions are related to esomeprazole. Table 3 indicates that interactions caused by esomeprazole were detected only by TEBRP and were minor. Interactions with omeprazole are given in Table 4.

14% of the interactions detected in the study were caused by omeprazole. Table 4 outlined that interactions were generally at a minor level. Only interaction with ciprofloxacin (prescribed for Helicobactor pylori) was detected as monitor closely in Medscape. Lastly, interactions with rabeprazole are presented in Table 5.

Rabeprazole caused 17% of the interactions in the study. The only interaction with cefpodoxime is detected as monitor closely in Medscape. Other interactions were detected only in TEBRP and were minor.

Table 1. Interactions with lansoprazole

Drug pairs	Frequency	Medscape	RxMediaPharma	TEBRP
Lansoprazole-diclofenac	1	No interactions	No interactions	Minor
Lansoprazole-methotrexate	1	Monitor Closely	Minor	Minor
Lansoprazole-bethametazon	1	No interactions	No interactions	Minor
Lansoprazole-dextromethorpan	1	No interactions	No interactions	Minor
Lansoprazole-clarithromycin	2	Monitor Closely	No interactions	Minor
Lansoprazole-ibuprofen	3	No interactions	No interactions	Minor
Lansoprazole-prednisolone	1	No interactions	No interactions	Minor
Lansoprazole-ciprofloxacin	3	No interactions	No interactions	Minor
Lansoprazole-sucralfate	3	Minor	No interactions	Minor
Lansoprazole-acetaminophen	10	No interactions	No interactions	Minor
Lansoprazole-Vitamin D	3	No interactions	No interactions	Minor

Table 2. Interactions with pantoprazole

Drug pairs	Frequency	Medscape	RxMediaPharma	TEBRP
Pantoprazole-metilprednisolone	1	No interactions	No interactions	Minor
Pantoprazole-amoxicillin	1	No interactions	No interactions	Minor
Pantoprazole-ciprofloxacin	1	No interactions	No interactions	Minor
Pantoprazole-rifaximin	1	No interactions	Minor	Minor
Pantoprazole-diclofenac	3	No interactions	No interactions	Minor
Pantoprazole-bethametazon	1	No interactions	No interactions	Minor
Pantoprazole-metoprolol	1	No interactions	No interactions	Minor
Pantoprazole-ibuprofen	1	No interactions	No interactions	Minor
Pantoprazole-Vitamin D	3	No interactions	No interactions	Minor
Pantoprazole-famotidine	4	No interactions	No interactions	Minor
Pantoprazole-domperidone	2	No interactions	No interactions	Minor
Pantoprazole-acetaminophen	5	No interactions	No interactions	Minor

Table 3. Interactions with esomeprazole

Drug pairs	Frequency	Medscape	RxMediaPharma	TEBRP
Esomeprazole-Vitamin D	2	No interactions	No interactions	Minor
Esomeprazole-amoxicillin	2	No interactions	No interactions	Minor
Esomeprazole-diclofenac	1	No interactions	No interactions	Minor
Esomeprazole-ibuprofen	1	No interactions	No interactions	Minor

Table 4. Interactions with omeprazole

Drug pairs	Frequency	Medscape	RxMediaPharma	TEBRP
Omeprazole-piroxicam	1	No interactions	No interactions	Minor
Omeprazole-acetaminophen	1	No interactions	No interactions	Minor
Omeprazole-Vitamin D	1	No interactions	No interactions	Minor
Omeprazole-lidocaine	1	Minor	No interactions	Minor
Omeprazole-etodolac	2	No interactions	No interactions	Minor
Omeprazole-flurbiprofen	1	No interactions	No interactions	Minor
Omeprazole-acetylsalicyclic acid	1	No interactions	No interactions	Minor
Omeprazole-ciprofloxacin	1	Monitor Closely	No interactions	Minor
Omeprazole-rifampicin	2	No interactions	No interactions	Minor
Omeprazole-doxycycline	1	No interactions	No interactions	Minor

As Özdemir et al. stated, PPIs are frequently used to prevent complications related to NSAIDs, but side effects associated with concomitant use are also encountered [7]. The findings obtained in the present study also support this.

Findings from this study, similar to [8-10], suggest that omeprazole and its isomer, esomeprazole, are unlikely to cause major drug interactions especially in the treatment of Helicobacter pylori.

TEBRP was the one that gave the most interaction warnings among these three databases. In TEBRP, it was observed that all of the interactions were at the "minor" level. In the research conducted in Medscape, six interactions were detected, of which four were at the "monitor closely" level and two at the "minor" level. Two interactions at the "minor" level were detected in the search performed with RxMediaPharma. This situation is similar to many studies in the literature dealing with the consistency

Table 5. Interactions with rabeprazole

Drug pairs	Frequency	Medscape	RxMediaPharma	TEBRP
Rabeprazole-acetaminophen	3	No interactions	No interactions	Minor
Rabeprazole-ibuprofen	2	No interactions	No interactions	Minor
Rabeprazole-cefpodoxime	1	Monitor Closely	No interactions	Minor
Rabeprazole-domperidone	5	No interactions	No interactions	Minor
Rabeprazole-rifampicin	1	No interactions	No interactions	Minor
Rabeprazole-trimethoprim	1	No interactions	No interactions	Minor
Rabeprazole-azelastine	1	No interactions	No interactions	Minor
Rabeprazole-Vitamin D	1	No interactions	No interactions	Minor

of databases in detecting drug interactions [11-13]. However, it should be noted that the difference observed in this study is much more than in the literature. For this reason, it is vital to use more than one database to determine drug interactions in order to prevent possible adverse events and increase patient safety.

From a different point of view, when the interaction of PPIs is evaluated from an economic perspective, it can be said that there are some changes from the relevant literature. In a study conducted by Bilgener on PPI use between 2006 and 2011, it was emphasized that omeprazole was less costly among PPI, but physicians prescribed more expensive PPI [14]. Özdemir et al. also support this situation, in contrast a change in preference for omeprazole was found [7]. It is seen that the most preferred group after lansoprazole and pantoprazole is omeprazole (18%). However, it should be noted that the decrease in the use of lansoprazole, as stated in Bilgener [14], continues.

4. CONCLUSION

From the research that has been carried out, it is possible to conclude that PPIs appear relatively far from major drug interactions. On the other hand, however, due to the frequent prescription and irrational use of PPIs, healthcare professionals, especially pharmacists, need to be able to detect interactions caused by PPIs. It was determined that the interactions were mostly between PPIs and NSAIDs, vitamin D, and acetaminophen which are not clinically critical.

The main limitation of the observational result is evaluating only prescribed PPIs. However, it should be noted that this group is also assessed as OTC. Therefore, more deep studies should be conducted. Community pharmacists play an essential role in preventing prescribed interactions. Problems arising from drug interaction can be minimized by working in cooperation with physicians and pharmacists and allocating more time to pharmaceutical care services. In this regard, pharmacists should be a guide for patients. To increase the safety of PPIs in drug interactions, it is thought that pharmacists who have adopted themselves as lifelong learners, good healthcare providers, and good researchers will take an active role in the field. For this aim, preparing guidelines and disease algorithms will be helpful, especially for newly graduated pharmacists, and will positively affect the patients' treatment processes.

Acknowledgements

This study was created by expanding the graduation project that the first author completed at Van Yüzüncü Yıl University Faculty of Pharmacy under the supervision of the corresponding author. The initial findings of the study were presented at the "1. Ulusal ve Sosyal Eczacılık Kongresi" on 7-8 September 2022.

The authors would like to thank Pharm. Volkan AKTAŞ for providing the data used in the study.

Ethical approval

The study was approved by the Van Yüzüncü Yıl University Non-interventional Research Ethics Committee (Protocol no. 2021/12-16 / 19.11.2021).

Author contribution

Concept: BA, MA; Design: BA, MA; Supervision: MA; Materials: BA, MA; Data Collection and/or Processing: BA; Analysis and/or Interpretation: BA, MA; Literature Search: BA, MA; Writing: BA, MA; Critical Reviews: MA.

Source of funding

This research received no grant from any funding agency/sector.

Conflict of interest

The authors declared that there is no conflict of interest.

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