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ORIGINAL ARTICLE / ÖZGÜN MAKALE

DETECTING DRUG-DRUG INTERACTIONS INDUCED BY ANTACIDS ENCOUNTERED IN A COMMUNITY PHARMACY: AN OBSERVATIONAL STUDY

BİR TOPLUM ECZANESİNDE KARŞILAŞILAN ANTİASİTLER KAYNAKLI İLAÇ ETKİLEŞİMLERİNİN TESPİTİ: GÖZLEMSEL BİR ÇALIŞMA

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ABSTRACT

Objective: *This study aimed to reveal drug-drug interactions (DDIs) due to antacids through programs used to detect DDIs.*
Material and Method: *Within the scope of this study, 207 prescriptions containing at least one antacid and a drug from a different pharmacological group were evaluated in terms of DDIs. Evaluations were made on the prescriptions received in a community pharmacy serving in Van, Türkiye. Three different DDI checking programs were used for this evaluation.*
Result and Discussion: *Antacid-induced DDIs were detected in 64 of the prescriptions. Interactions occurred between 52 active ingredient pairs, and it was revealed that DDIs were most common between calcium carbonate and famotidine. This interaction is minor and has been detected by only one database. Another common interaction was found between the calcium carbonate and cholecalciferol (Vitamin D) pair, and this interaction was reported as Level 2 and should be closely monitored in two different databases. As a result, DDIs induced by antiacids generally were found to be at moderate levels. However, it is seen that three DDI checking programs used in the study provide different results in detecting DDIs.*
Keywords: *Antacids, community pharmacy, drug-drug interactions, observational study*

ÖZ

Amaç: *Bu çalışma, ilaç-ilaç etkileşimlerini (DDIs) tespit etmek için kullanılan programlar aracılığıyla antiasitler nedeniyle oluşan DDI'leri tespit etmeyi amaçlamaktadır.*
Gereç ve Yöntem: *Bu çalışma kapsamında en az bir antiasit ve farklı farmakolojik gruptan bir ilaç içeren 207 reçete DDI açısından ele alınmıştır. Bu doğrultuda, Van'da hizmet veren bir toplum eczanesinde karşılanan reçeteler değerlendirilmiştir. Bu değerlendirmeler için üç farklı DDI kontrol programı kullanılmıştır.*
Sonuç ve Tartışma: *Reçetelerin 64'ünde antiasit kaynaklı DDI tespit edilmiştir. 52 aktif madde çifti arasında etkileşim meydana gelmiş olup, DDI'ların en yaygın olarak kalsiyum karbonat ve famotidin arasında olduğu ortaya konulmuştur. Bu etkileşimin minor düzeyde olup, yalnızca bir veritabanı tarafından tespit edilmiştir. Diğer bir sık karşılaşılan etkileşim ise kalsiyum karbonat ve kolekalsiferol (Vitamin D) çifti arasında bulunmuştur. Bu etkileşim Düzey 2 ve yakından takip*

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edilmesi gerekir olacak şekilde iki farklı program tarafından tespit edilmiştir. Sonuç olarak antiasitlerin neden olduğu DDI'ların genel olarak orta düzeyde ciddiyete sahip olduğu bulunmuştur. Ancak çalışmada kullanılan üç DDI kontrol programının DDI'ların tespitinde farklı sonuçlar verdiği görülmüştür.
Anahtar Kelimeler: *Antiasitler, gözlemsel çalışma, ilaç-ilaç etkileşimleri, toplum eczanesi*

INTRODUCTION

Antacids are alkaline substances generally used to neutralize excess acid in the stomach and alleviate dyspepsia symptoms [1,2]. They are widely used in the treatment of gastro-oesophageal reflux disease (GERD), duodenal and gastric ulcers, peptic ulcer, erosive esophagitis, Helicobacter pylori (HP) eradication, and dyspepsia [3,4].

In clinical practices, it is known that drug-drug interactions (DDIs) are very common, which may lead to synergistic or antagonistic medication responses in many cases. Since minor DDIs generally do not have a significant effect on clinical outcomes, no change in treatment is required in such cases. However, in moderate and serious interactions, many precautions must be taken, such as a dosage change, a change in the active ingredient, or closer patient monitoring [5]. Sadowski and Gugler and Allgayer put forth that DDIs caused by antacids do not cause serious health problems. Still, DDIs are common because patients generally do not consider antacids as a drug [6,7].

Unlu revealed that the most preferred drug for GERD in Turkey is PPIs, followed by antacids. Antacids can be included in the group of active substances that rarely may cause serious DDIs [8]. Ogava and Echizen revealed that antacid use is becoming increasingly common, and this increases the possibility of DDIs [9]. However, it is known that the ions of antacids containing calcium, magnesium, and aluminum are chelating agents, and they bind many drugs, such as digitoxin, tetracycline, indomethacin, aspirin, cimetidine, ranitidine, famotidine, theophylline, etc. Antacids also reduce the bioavailability of barbiturates, sulfonamides, and penicillin [2]. Maton and Burton stated that most antacids, except sodium bicarbonate, can reduce drug absorption through adsorption or chelation of other drugs [3]. Antacid-induced drug interactions can be prevented by rescheduling drug administration times. To avoid undesirable interactions, antacids are usually used two hours before or after taking any medication [4].

To the best of the author's knowledge, a limited number of studies have been conducted on detecting DDIs induced by antacids at the community pharmacy level. Therefore, this study aimed to detect the frequency of DDIs caused by prescribed antacids and their severity level with the help of three different national and international DDI checking programs.

MATERIAL AND METHOD

Prescriptions containing antacids received between 20 November 2022 and 20 April 2023 at a predetermined community pharmacy serving in the Van City center were examined by the researchers in terms of DDIs within the scope of this study. Firstly, the ICD-10 diagnostic code, the specialty area of the prescribing physician, the gender and age of the patient, and the number of items written on the prescription were obtained from prescriptions. Then, prescriptions were evaluated for possible DDIs. If a DDI was detected in the prescription, the degree of the DDI was also determined with the help of electronic DDI checker programs. The literature recommends evaluating data from at least three programs to get more reliable information in such studies [10,11].

For this reason, two of the programs to be used in the study were determined to be “Medscape” and “Drugs.com,” which are frequently preferred databases in the literature. In addition, “RxMediaPharma® Interactive Drug Information Resource,” commonly used in community pharmacies in Türkiye, has been included as the third program. A brief piece of information about these programs was given as follows.

1. RxMediaPharma: In RxMediaPharma, interaction levels are considered at three levels: Level 1 (high interaction), Level 2 (medium interaction), and Level 3 (low level of interaction).
2. Medscape: Medscape is a free online resource and divides drug-drug interactions into four groups: contraindicated, serious-use alternative, monitor closely, and minor.

3. Drugs.com: Drugs.com is a free online resource that evaluates drug interactions under four groups: major, moderate (recommended for use only in special cases), minor, and unknown.

Prescriptions containing at least one antacid and one different drug without antacids were included in the research. As a result of the evaluation with the concerned pharmacist, it was determined that approximately 60-70 prescriptions meeting the relevant criteria were met monthly at this 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, prescriptions that meet the study criteria were considered among all prescriptions filled at the relevant pharmacy during the research period.

The obtained data was subjected to descriptive statistical analysis via Microsoft Excel.

RESULT AND DISCUSSION

During the research period (20 November 2022 and 20 April 2023), 1128 prescriptions were filled at the corresponding community pharmacy. It was determined that approximately 18% of these prescriptions met the study's inclusion criteria. Hence, 207 prescriptions were evaluated in detail in terms of DDIs. 58% of these prescriptions were for women and 67% for patients over 40. The distribution of the prescribed physicians' specialty areas is given in Figure 1.

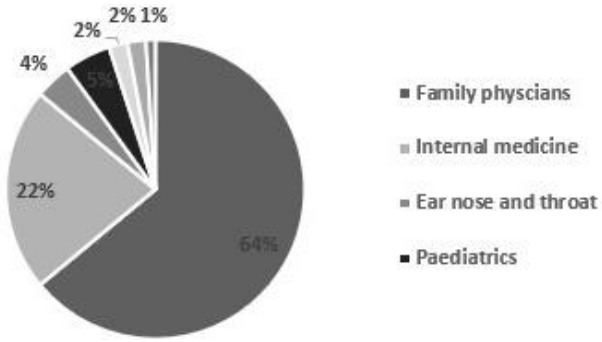

Figure 1. Prescribed physicians' specialty areas

According to Figure 1, family physicians mainly prescribe antacids, and internal medicine specialists follow them. Prescriptions were also evaluated in terms of diagnosis according to ICD-10 codes. It was determined that antacids were mainly prescribed for diagnosing K21, which refers to GERD (77%). When the antacids in the prescriptions were examined, it was seen that the most prescribed antacid was Calcium Carbonate. Figure 2 shows the distribution of them.

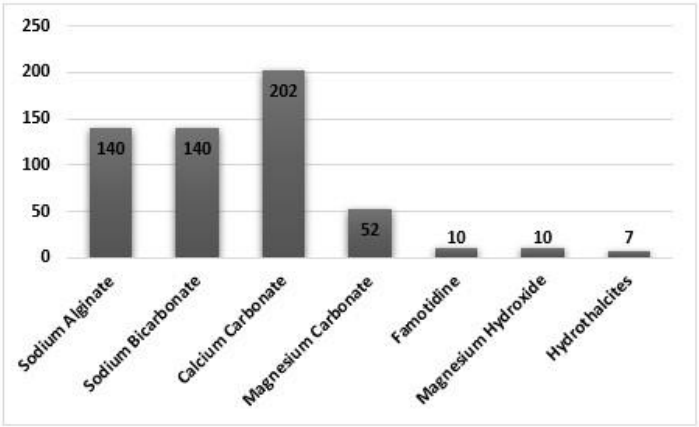

Figure 2. Distribution of prescribed antacids

While prescriptions were considered in terms of DDIs, an interaction was supposed to exist if a DDI was detected in any of the three databases. In this context, it was determined that 64 out of 207 prescriptions had DDIs. These 64 prescriptions were evaluated in more detail, and it was determined that sodium bicarbonate, calcium carbonate, magnesium carbonate, and famotidine caused 116 DDI cases. These cases were detected between 52 different active substance pairs. As stated in various literature, the findings obtained from three databases showed differences.

Table 1 presents the frequencies of DDIs encountered based on calcium carbonate due to the research conducted in three databases.

Table 1. Interactions with calcium carbonate

Pairs	Frequency	RxMediaPharma	Medscape	Drugs.com
Calcium carbonate-ferrous sulfate	2	Level 2	Minor	Moderate
Calcium carbonate-ramipril	4	No interactions	Monitor Closely	Minor
Calcium carbonate-metoprolol	3	No interactions	Monitor Closely	Moderate
Calcium carbonate-nitrofurantoin	4	No interactions	Monitor Closely	No interactions
Calcium carbonate-famotidin	10	No interactions	No interactions	Minor
Calcium carbonate-acetyl salicylic acid	5	No interactions	No interactions	Moderate
Calcium carbonate-amlodipin	2	No interactions	No interactions	Moderate
Calcium carbonate-ciprofloxacin	4	Level 2	Monitor Closely	Moderate
Calcium carbonate-lactulose	4	No interactions	Monitor Closely	Minor
Calcium carbonate-bisoprolol	1	No interactions	Monitor Closely	Moderate
Calcium carbonate-diltiazem	1	No interactions	Monitor Closely	Moderate
Calcium carbonate-levothyroxine	6	Level 2	Monitor Closely	Moderate
Calcium carbonate-sucralfat	3	No interactions	No interactions	Moderate
Calcium carbonate-cholecalciferol	8	Level 2	Monitor Closely	No interactions
Calcium carbonate-itraconazole	1	Level 2	Monitor Closely	Moderate
Calcium carbonate-azithromycin	2	No interactions	Monitor Closely	No interactions
Calcium carbonate-ferrous II glycine	1	No interactions	Monitor Closely	Moderate
Calcium carbonate-pancreatin	1	No interactions	No interactions	Moderate
Calcium carbonate-ibandronic acid	2	Level 2	Monitor Closely	Moderate
Calcium carbonate-allopurinol	1	No interactions	Monitor Closely	No interactions
Calcium carbonate-cefuroxime	3	Level 2	Monitor Closely	Moderate
Calcium carbonate-bisacodyl	4	Level 2	No interactions	Moderate
Calcium carbonate-ferrous II fumarate	2	Level 2	Monitor Closely	Moderate
Calcium carbonate-nebivolol	2	No interactions	Monitor Closely	Moderate
Calcium carbonate-hydrocortiazide	3	No interactions	No interactions	Moderate

It was determined that 61.3% of the interactions detected in the study were caused by calcium carbonate. In the light of Table 1, it was determined that the active ingredients ciprofloxacin, levothyroxine, itraconazole, ibandronic acid, cefuroxime, and ferrous II fumarate interact with calcium carbonate in all three databases.

The two active substances that have been found to interact most with calcium carbonate are famotidine and cholecalciferol. However, it is necessary to look at these interactions in more detail. Because there are products in the pharmaceutical market that contain these active substances in combination, Therefore, concerning cholecalciferol, it should be noted that the concurrent use of cholecalciferol with calcium salts is generally beneficial. Since vitamin D helps the absorption of calcium salts from the intestines, it is seen that these two active ingredients are used in combination in many preparations [12]. However, this combination may cause hypercalcemia in some patients. Concerning interaction with famotidine, although it has been detected by one of the databases, current studies mostly show that antiacids have no significant effects on famotidine's pharmacokinetics [13]. In

this context, it is thought that an interaction was detected between this active ingredient pair because the reference used in the database is not up-to-date.

The interaction between calcium carbonate and levothyroxine can be considered the most severe calcium carbonate-related interaction among the prescriptions evaluated within the scope of this study. In this interaction, which was detected in 6 different prescriptions, calcium carbonate reduces the gastrointestinal absorption of levothyroxine, negatively affecting levothyroxine's treatment success [14,15]. Thus, it is generally recommended to leave a two-hour break between the use of these two active substances to prevent interaction. Prescribing calcium carbonate and levothyroxine together is a common situation, and studies in the literature reveal that patients are generally unaware of the interaction between these two active substances and misuse them, which negatively affects treatment success [16,17]. In this context, pharmacists must inform patients about how to avoid this DDI.

Another vital interaction originating from calcium carbonate is with acetylsalicylic acid. In this study, this interaction was detected in all five prescriptions. This interaction must be considered, especially for hemodialysis patients [18].

Table 2 presents the frequencies of DDIs encountered based on sodium bicarbonate.

Table 2. Interactions with sodium bicarbonate

Pairs	Frequency	RxMediaPharma	Medscape	Drugs.com
Sodium bicarbonate-ferrous II sulfate	2	Level 2	Monitor Closely	Moderate
Sodium bicarbonate-ramipril	3	No interactions	Monitor Closely	Minor
Sodium bicarbonate-acetylsalicylicacid	1	No interactions	No interactions	Moderate
Sodium bicarbonate-famotidine	1	No interactions	No interactions	Minor
Sodium bicarbonate-pseudoephedrine	5	Level 1	Monitor Closely	Moderate
Sodium bicarbonate-lactulose	1	No interactions	Monitor Closely	Minor
Sodium bicarbonate-ciprofloxacin	3	Level 2	Monitor Closely	Moderate
Sodium bicarbonate-allopurinol	1	No interactions	Monitor Closely	No interactions
Sodium bicarbonate-cefuroxim	3	Level 2	Monitor Closely	Moderate
Sodium bicarbonate-bisacodyl	3	Level 2	Monitor Closely	Moderate
Sodium bicarbonate-nebivolol	2	No interactions	Monitor Closely	No interactions
Sodium bicarbonate-ferrous II fumarate	1	Level 2	Monitor Closely	Moderate
Sodium bicarbonate-nitrofurantoin	1	No interactions	Monitor Closely	No interactions
Sodium bicarbonate-metoprolol	1	No interactions	Monitor Closely	No interactions

Interactions with sodium bicarbonate 21.7% of the DDIs detected in the study were caused by sodium bicarbonate. It has been determined that the active ingredients ramipril, pseudoephedrine, ciprofloxacin, cefuroxime, and bisacodyl interact with sodium bicarbonate in three databases.

When the study findings are examined, it is possible to say that interactions caused by sodium bicarbonate are more serious. For example, dosage adjustments must be made if sodium bicarbonate and pseudoephedrine are used together. In this study, this interaction was detected in 5 prescriptions.

Table 3 presents the frequencies of drug-drug interactions encountered based on magnesium carbonate.

17% of the interactions detected in the study were due to magnesium carbonate. It has been determined that the active ingredient ciprofloxacin interacts with magnesium carbonate in three drug interaction databases. Similar to calcium carbonate, magnesium carbonate has interaction with famotidine and cholecalciferol. Different studies have reported that interactions between ciprofloxacin and antacids affect the absorption level, and the success of treatment is negatively affected [19,20].

As a result, it is clear that the selected three programs' results are different from each other in general. Three programs showed that out of 52 active substance pairs in which interactions were detected, 14 of them had interactions in common. RxMediaPharma detected 20 of them, Medscape detected 34 of them, and Drugs.com detected 42 of them. When looking at the interaction levels, it is seen that 5 of the interactions detected by RxMediaPharma are Level 1, and 15 are Level 2. It was determined that 33 of the interactions detected by Medscape were in the "Monitor closely" class, and 1

was in the "Minor" class. It was revealed that 32 of the interactions detected by Drugs.com were at the "Moderate" level, and 9 of them were at the "Minor" level.

Table 3. Interactions with magnesium carbonate

Pairs	Frequency	RxMediaPharma	Medscape	Drugs.com
Magnesium carbonate-sucralfate	1	No interactions	No interactions	Moderate
Magnesium carbonate-famotidine	3	No interactions	No interactions	Minor
Magnesium carbonate-acetyl salicylic acid	2	No interactions	No interactions	Moderate
Magnesium carbonate-amlodipine	1	Level 1	No interactions	No interactions
Magnesium carbonate-ciprofloxacin	1	Level 2	Monitor closely	Moderate
Magnesium carbonate-lactulose	2	No interactions	Monitor closely	Minor
Magnesium carbonate-bisoprolol	1	No interactions	Monitor closely	Minor
Magnesium carbonate- itraconazole	1	Level 2	No interactions	Moderate
Magnesium carbonate- azithromycin	1	No interactions	No interactions	Moderate
Magnesium carbonate- ferrous II glycine	3	Level 2	No interactions	Moderate
Magnesium carbonate- magnesiumoxide	1	No interactions	No interactions	Moderate
Magnesium carbonate-ibandronicacid	2	Level 2	No interactions	Moderate
Magnesium carbonate-cholecalciferol	3	No interactions	No interactions	Moderate

From the outcome of this observational study, it is possible to conclude that DDIs induced by antiacids generally were found moderate level. However, three DDI checking programs used in the study provide different results in detecting DDIs. This situation can lead to inconsistent results for pharmacists and other healthcare professionals and poses a risk to patient safety. In this context, in light of the findings of this study, to minimize this risk, it may be recommended that community pharmacists check the interactions from several programs instead of using a single program when detecting DDIs by combining their medical knowledge. Moreover, when the issue is considered in terms of the evaluation of health technologies, it is seen that there is a need to create a standard in such programs.

This observational study has possible limitations. The first one is evaluating only prescribed antacids. However, it should be noted that antacids also can be sold in community pharmacies without a prescription in Türkiye. Secondly, the data of this study only comes from one community pharmacy. Thus, to increase the generalizability of the results, more in-depth studies, where data is gathered from different pharmacists, will be needed in this area. Also, it should be noted that two international (free) and one national (not free) DDI checking programs were used in the study, so the generalizability of the results may also be increased by adding more programs.

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AUTHOR CONTRIBUTIONS

Concept: D.G., M.A.; Design: D.G., M.A.; Control: M.A.; Sources: D.G., M.A.; Materials: - ; Data Collection and/or Processing: D.G.; Analysis and/or Interpretation: D.G., M.A.; Literature Review: D.G., M.A.; Manuscript Writing: D.G., M.A.; Critical Review: M.A.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

This study was conducted after Van Yüzüncü Yıl University Non-interventional Research Ethics Committee approved the study ethically (Date:18/11/2022, Decision No: 2022/11-26).

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