

COMPARATIVE STUDY BETWEEN THE SALES OF ANTIULCER DRUGS H2 ANTAGONISTS AND PROTON PUMP INHIBITORS

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Abstract

Gastric ulcer is a frequently encountered disease, currently existing a great number of antiulcer drugs on the pharmaceutical market. The purposes of the study were to analyse the sales of the products containing active pharmaceutical ingredients (APIs) from the pharmacological classes of proton pump inhibitors (PPIs) and H2 antagonists, their comparison, highlighting the best-selling drugs of the two pharmacological classes, by underling the factors that influence them. There were analysed the quantitative sales of the products containing the common international names (INNs) from the two classes of antiulcer drugs studied, during a period of time of two years. The necessary data for the study were collected from community pharmacies, using pharmacies' management software, the methods used in the research being: retrospective analysis, sampling method, comparison method and descriptive methods. The results showed that from the total quantities of medicines issued in the pharmacies analysed (48164 units), the PPIs represent 84.91% (40895 units), while H2 antagonists represent only 15.09% (7269 units). The best-selling common international name (INN) of the PPIs class was omeprazole (20634 units, 50.46%) and the best-selling INN of H2 antagonists class was ranitidine (5897 units, 81.13%). The ranking of the pharmacies analysed, in terms of sales of antiulcer drugs was conducted taking into account: regime of drug release, existence of generic drugs, pharmacies' location and schedule, and presence or absence of medical institutions near the pharmacies.

Rezumat

Ulcerul gastric este o afecțiune frecvent întâlnită, în prezent existând pe piața farmaceutică un număr mare de medicamente antiulceroase. Scopul și obiectivele cercetării au fost analizarea vânzărilor produselor conținând substanțe active din clasele inhibitorilor pompei de protoni (IPP), respectiv antihistaminicelor H2, compararea acestora, reliefaarea celor mai bine vândute medicamente din cele două clase farmacologice, evidențiind factorii care le influențează. S-au analizat vânzările cantitative ale produselor conținând substanțele active din cele două clase de medicamente antiulceroase studiate, pe o perioadă de timp de doi ani. Datele necesare studiului au fost colectate din farmacii comunitare, folosind programele informatice de gestiune farmaceutică, metodele utilizate în cercetare fiind: analiza retrospectivă, metoda eșantionării, metoda comparației și metode descriptive. Rezultatele obținute au arătat că din cantitățile totale de medicamente eliberate în farmaciile analizate (48.164 unități), IPP reprezintă 84,91% (40.895 unități), în timp ce antihistaminicele H2 reprezintă doar 15,09% (7.269 unități). Cea mai bine vândută substanță activă din clasa IPP a fost Omeprazol (20.634 unități, 50,46%), iar cea mai bine vândută substanță activă aparținând clasei antihistaminicelor H2 a fost Ranitidina (5.897 unități, 81,13%). Clasamentul farmaciilor analizate din punctul de vedere al vânzărilor de medicamente antiulceroase a fost realizat luând în considerare: regimul de eliberare, prezența genericilor, amplasarea și orarul farmaciilor, dar și prezența sau absența unor instituții medicale în apropierea farmaciilor.

Keywords: antiulcer drugs, H2 antagonists, proton pump inhibitors (PPIs), pharmaceutical market

Introduction

According to research conducted on the global pharmaceutical market [9], the hierarchy of the best-selling pharmacological classes in the world highlights the importance of the antiulcer drugs worldwide; they topped the 13 of the first 20 pharmacological classes [8]. Top 10 the best-selling drugs in the world includes an antiulcer drug (on 9th place), a representative of the proton pump inhibitors class [7]. The class of antiulcer drugs includes three

subclasses, which are considered as three different generations used in the treatment of ulcer.

H2-antagonists class comprises the first-generation antiulcer drugs, placed on the market between 1970 and 1980 which treat ulcers by blocking the action of histamine at the gastric level. H2 antihistamine medications include a series of molecules, from which the most common are: cimetidine, famotidine, ranitidine and nizatidine. H2 blockers had noteworthy success in many countries through the companies

Smith-Kline (cimetidine) and Glaxo (ranitidine - sold under the trade name "Zantac®"). The representatives of this class remained the top-selling drug until the late 1980s when a new generation of antiulcer drugs was introduced in the pharmaceutical market: the proton pump inhibitors (PPIs).

Drugs from the class of proton pump inhibitors do not block the action of histamine at gastric level, instead, blocks the acid secretion for a long time. This class includes omeprazole, lansoprazole, pantoprazole and rabeprazole – one of the most widespread representatives – and is considered an upper class compared to the H₂-antagonists class. Omeprazole, under the trade name "Lossec®" (or "Prilosec®") of the producer Astra Zeneca, was the bestselling drug worldwide for many years.

The third class includes cytoprotective medication (e.g. prostaglandins) less used to prevent or treat ulcers.

Antiulcer drugs were market leaders in the world's top of drug sales for several years, from 1990 to 2003 [6].

Gastric ulcer is a condition frequently encountered also at national level, which is why currently, on the pharmaceutical market in Romania, there is a large number of antiulcer drugs. The research objectives were to analyse the quantitative sales of the medicinal products containing INNs from the classes of proton pump inhibitors (PPIs) and H₂-antagonists and highlighting the best-selling drugs of the two pharmacological classes.

The present paper constitutes a market study on the sales of drugs containing active pharmaceutical ingredients from the two representative classes of the antiulcer drugs. Based on the gathered data and the centralized results were evidenced different aspects which influence the marketing of medicines in the market studies.

Materials and Methods

The research was conducted by analysing the quantitative sales of medicinal products that contain active substances (INNs) of the two analysed classes of antiulcer drugs, approved by the National Agency for Medicines and Medical Devices and included in the Index of medicinal products for human use [10], during a period of two years, between 01.10.2012 and 01.10.2014. The necessary data for the study were collected from community pharmacies from Cluj-Napoca, Romania, using the pharmaceutical management software programs (Pharmec®, Netfarm, Dataklas for retail). The collected data were centralized and processed using Microsoft Office Excel 2010.

The methods used in the research are described below.

The retrospective analysis: in this type of study, the data are collected from the past, from a previously

established moment till the time of the research. In this case, the study was conducted on a specified timeframe, a period of two years relevant for the study carried out.

The sampling method implies that the sample selected should be representative for the target population on which the study is conducted and to which the obtained results will be extrapolated. In the present case, for the research carried out the *simple random sampling* was used. There were taken into consideration representative criteria for interpreting the results, namely: location of the pharmacies, schedule of the pharmacies, the presence of hospitals or medical centres close to the pharmacies, access zone (public transportation, pedestrian area, periphery, residential area – neighbourhood).

Sample representativeness. In the present research, data were collected from 15 community pharmacies from Cluj-Napoca, Romania, representing 10.63% of the total of 141 existing pharmacies in the city at the time of the survey [5] and the margin of error was calculated, in order to verify that the sample selected is representative for the study [1, 2-6, 12, 13].

The acceptable level for the margin of error must be less than 5% and the value obtained in the present study, 2.77%, is accepted the sample being representative. Thus, the 15 pharmacies analysed constitute a representative sample for the total of 141 existing pharmacies in Cluj-Napoca, Romania, and the results obtained from the research can be applied to any of the 141 community pharmacies, with a margin of error of 2.77%.

The comparison method: the obtained data were processed and interpreted according to the same criteria and taking into account the same parameters so that the results should be viable.

Descriptive methods: there were collected and analysed the obtained data, there were observed the outcomes and the particularities of the results dependent of the criteria and the conclusions were drawn [1].

Results and Discussion

All the authorized products in Romania containing substances belonging to PPIs and H₂-antagonists pharmacological classes were centralized and the results of the market study on the quantitative sales of the products containing exclusively the INNs of the two classes of antiulcer drugs are presented below.

Global analysis of the quantitative sales of the drugs from the classes H₂-antagonists and PPIs pharmacological classes

After collecting and processing the results of the study conducted retrospectively over the two years, 48164 units released from the analysed pharmacies (units represent the number of boxes) of antiulcer

drugs were totalled, including both H2-antagonists and PPIs.

Figure 1 presents the shares of the two classes of antiulcer drugs from the total sales recorded in the

community pharmacies, in a quantitative manner and regarding the percentages view.

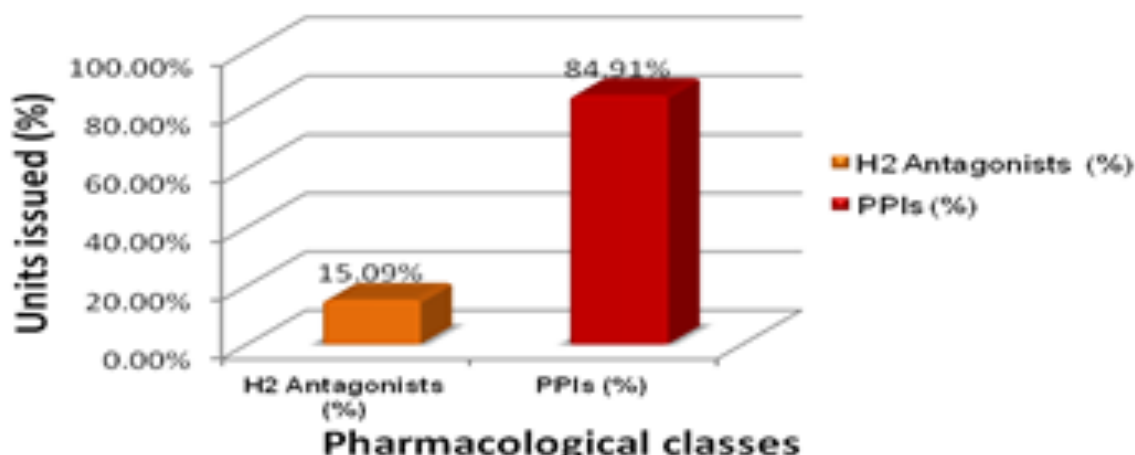


Figure 1.

Quantitative sales (%) of H2 antagonists and PPIs

Thus, H2 antihistamines class represents a percentage of 15.09% of sales (7269 units), while the PPI class is the sales leader with a percentage of 84.91% (40895 units). These results can be justified as follows: the class of proton pump inhibitors is considered upper the class of H2 antihistamines due to the mechanism of action; in the PPIs class, there are on the market much more generic products containing substances from this class and which are much more affordable to the patients for whom they are prescribed or recommended.

Further, it has been researched each class of drugs, both in terms of quantity and percentage, to highlight the sales leader in each class of antiulcer drugs.

Regarding the percentage of sales for each class of antiulcer drugs, in Figure 2 the results illustrates that in the case of H2-antagonists, from the total of 7269 units sold, a percentage of 81.13% (5897 units) is represented by ranitidine, followed by famotidine with 18.78% (1365 units) and cimetidine holds only 0.10% (7 units) of the total sales.

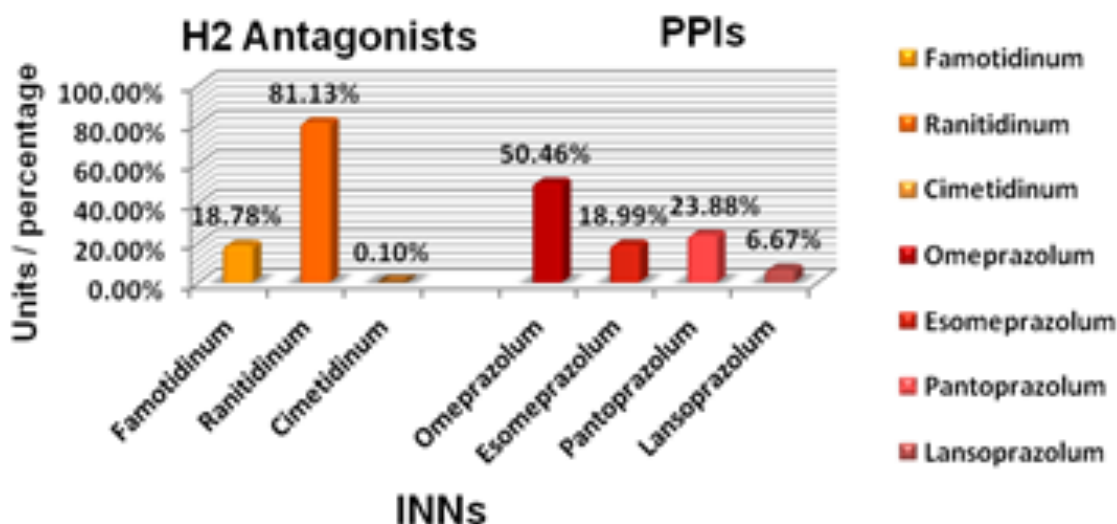


Figure 2.

Quantitative sales (%) of INNs in the two pharmacological classes of antiulcer drugs

The sales results are influenced by the pharmaceutical products containing active substances from H2-antagonists class. Thus, ranitidine is present in Romania under various trade names, produced by

national companies and due to this fact the costs are reduced. The products are manifold and is also available as OTCs, so a medical prescription is not necessary for the lowest concentration (75 mg),

leading the patients to the opportunity of choosing the product as their needs.

In the case of famotidine, the products are fewer, only five products containing this substance are on the pharmaceutical market in Romania and the production costs are higher, which justify the low percentage of the recorded sales.

The case of cimetidine is a particular one: cimetidine was withdrawn from the market for a period of about two years, but at the completion date of the study, it was reauthorized by the National Agency for Medicines and Medical Devices [10, 11]. Therefore, sales were almost non-existent.

Although authorized in Romania, nizatidine was not present in the 15 pharmacies throughout the study, so that it did not influence the results.

By analysing the results presented in Figure 2, regarding the sales of the substances from PPIs class, it was found that the differences between representatives of the class were significant. Thus, from the total of 40895 units sold, the highest percentage is represented by the sales of products containing omeprazole, 50.46% (20634 units), followed by pantoprazole, 23.88% (9767 units) and esomeprazole, 18.99% (7768 units). Ranked last in the PPIs sales is lansoprazole, 6.67% (2726 units), while rabeprazole and dexlansoprazole, although authorized in Romania, have not been released in none of the pharmacies studied. Proton pump inhibitors class is the sales leader, through the four representatives of the six authorized on the market, but especially through omeprazole, which is in top.

We found that the substances whose production costs are reduced will have priority in customers' preferences that choose the products after multiple criteria, including costs, the short time of getting the product and sometimes the manufacturing company. In the case of PPIs, with numerous generic products, patients can benefit from a variety of products containing the same medicinal substance, from which they can choose the product that meets both the desired therapeutic purpose and the financial criteria.

Quantitative sales of the active substances of both classes of antiulcer drugs in the 15 analysed pharmacies

This part of the research focused on the quantitative selling of drugs, dependent on external factors influencing the retail of products from a pharmacy, taking into account: the schedule of each pharmacy, the location of pharmacies, their position (central or peripheral), the presence or the absence of hospitals, specialty medical offices or family physicians' offices situated in the vicinity of pharmacies. The results were influenced by these factors and are presented below.

H2 antagonists - centralized results

The results were centralized in order to analyse and discuss overall about the quantitative sales, taking into account each pharmacy in part, out of the 15 analysed. In Figure 3 there were inserted the three substances present in pharmacies within the class of H2 antagonists: famotidine, ranitidine and cimetidine.

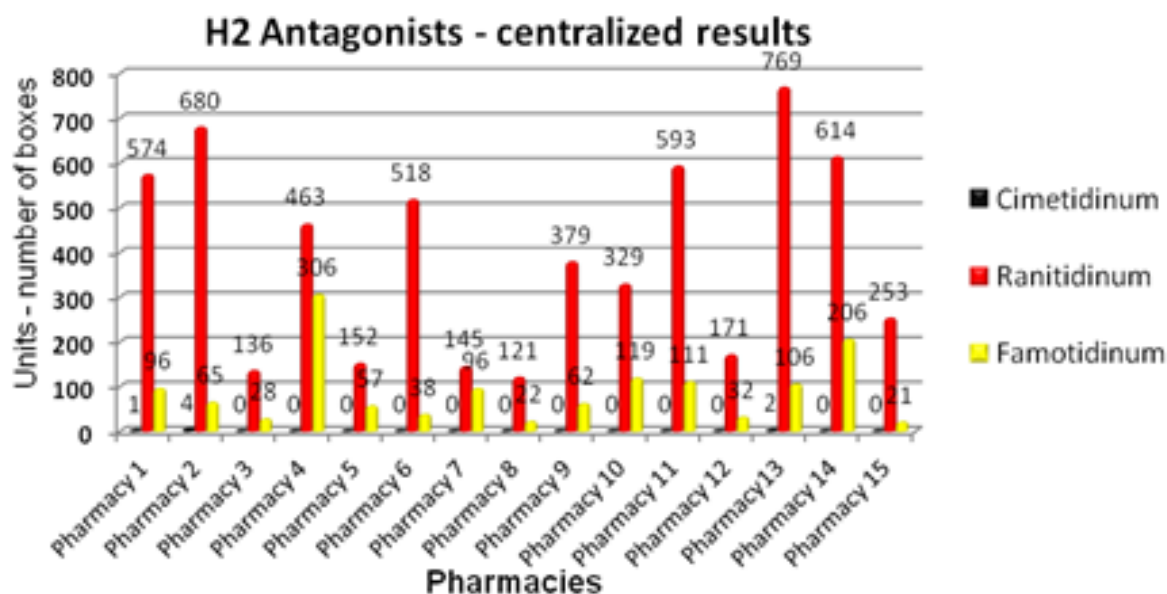


Figure 3.

Quantitative sales of H2 Antagonists in the 15 pharmacies analysed

By centralizing the data on sales of medicinal products containing substances of H2 antagonists class (Figure 3), we found that in the case of the

medicines containing the active substance ranitidine, the sales leader is Pharmacy 13. In case of sales of products containing famotidine, Pharmacy 4

accumulated almost threefold sales of Pharmacy 13, but the leader of cumulative sales of H2 blockers drugs is Pharmacy 13. Therefore, the highest cumulative sales of H2 antihistamines were recorded in Pharmacies 13, 4 and 2, while the lowest sales were recorded in Pharmacies 3, 8 and 12.

The results obtained show that these three pharmacies: 13, 4 and 2 are preferred by patients, irrespective of the choice made regarding the medicinal substance they need to purchase it.

Considerations concerning sales of each INN of the H2-antagonists class in the analysed pharmacies are further discussed.

Regarding the sales of famotidine in the 15 pharmacies, the leader is the Pharmacy 4 which is located on the outskirts of the city, close to two medical family physicians' offices, which influenced the results obtained, due to prescribing of this substance by the respective doctors. This pharmacy, being located on the outskirts, unlike the pharmacies centrally located, there are no other pharmacies nearby this one, so the options of the patients in the respective area are more limited concerning the choice of a pharmacy, besides they are loyal customers of this pharmacy.

Of the total of 1365 units of famotidine released in the 15 pharmacies, 306 units were sold within the Pharmacy 4, followed by Pharmacy 14 (206 units) and Pharmacy 10 (119 units). The lowest sales of famotidine were recorded in: Pharmacy 3 (28 units), Pharmacy 8 (22 units) and Pharmacy 15 (21 units). Although Pharmacy 15 is placed within a shopping complex and the program is extended (until 21:00 on weekdays and until 19:00 on Saturdays), patients that attend this pharmacy did not receive medical prescriptions for this drug, ranking this pharmacy on the last position regarding famotidine sales.

For ranitidine sales, Pharmacy 13 had the highest number of units sold (769 units) of the total 5897 units, but Pharmacies 2 and 14 followed closely with 680 or 614 units, the differences between pharmacies being lower than for famotidine. Although, Pharmacy 13 is positioned near a shopping centre, without medical offices or hospitals nearby, it is the pharmacy with the highest number of units sold of ranitidine. This fact is paradoxical considering the case of Pharmacy 2 which is located near a hospital and positioned centrally and where the physicians might prescribe this medicinal substance, but it is comparable with the case of Pharmacy 14 located within a shopping centre and having an expanded schedule, each day from 8:00 to 22:00. The pharmacies with the fewest units sold of ranitidine are the Pharmacies 12, 3 and 8 with 171, 136 respectively 121 units. Pharmacy 8 with only 121 units sold out of the total number of 5897 has expanded schedule during the week, from 8:00

to 22:00 including weekends schedule until 19:00 on Saturdays and until 17:00 on Sundays. Both in terms of functioning hours and the positioning, this pharmacy is accessible to patients, being available to their needs with operating hours every day and is near the means of public transport and it facilitates the access of patients, but however, it is ranked last in ranitidine sales.

Due to its withdrawal from the market, during the period of the study, cimetidine was present only in Pharmacies 1, 2 and 13, in an extremely reduced number, 1 unit in Pharmacy 1, 4 units in Pharmacy 2 and 2 units in Pharmacy 13. Cimetidine was re-authorized on the pharmaceutical market in Romania in a single dose 200 mg, under the patent of a single manufacturer, Arena [11].

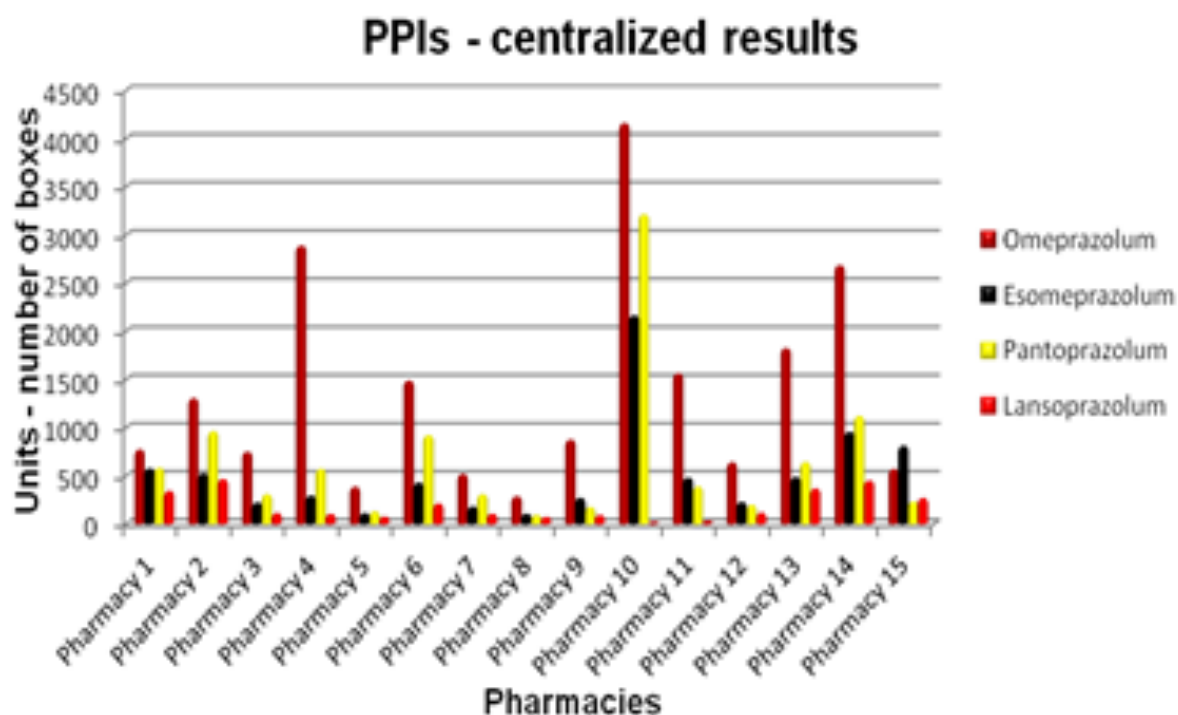
PPIs - centralized results

The results on the sales of drugs from the class of proton pump inhibitors were centralized for the pharmacies analysed, based on the four medicinal substances released. The graphical representation of centralized results is illustrated in Figure 4.

By synthesizing the results of the study in Figure 4, it can be stated with certainty that overall, for the PPIs, the leader is Pharmacy 10 with sales of 9521 units out of 40895 units, accounting for 23.28%, i.e. approximately a quarter of the total sales. The lowest values in sales of medicines containing PPIs were identified for Pharmacy 8, it recorded 531 units sold, i.e. 1.29%.

The results were influenced by a range of factors, such as: the localization of pharmacies, the placement of pharmacies (central or on the periphery of the city), the presence or the absence of hospitals and medical offices in the vicinity of pharmacies.

Other decisive factors that led to these results were: *the existence* of the multitude of products for some medicinal substances (as in the case of omeprazole, pantoprazole and esomeprazole) and the existence of less than 10 products in other case (lansoprazole); *the presence* of generics in the case of some substances, some of them being produced in Romania, which results in more affordable prices for patients, the costs representing a criterion which may influence the choice of medication, especially for long term; *the requirement* of a medical prescription for omeprazole or lansoprazole, but for various reasons, patients often prefer to choose a medicine recommended by the pharmacist, without consulting their doctor each time they need treatment; *the absence* from pharmacies of medicines containing dexlansoprazol or rabeprazole, although authorized on the pharmaceutical market in Romania; this issue highlights the preference of patients for the other three substances: omeprazole, esomeprazole, pantoprazole, substances which have been identified in significant quantities in the 15 pharmacies analysed.

**Figure 4.**

Quantitative sales of PPIs in the 15 pharmacies analysed

The class of proton pump inhibitors remains the sales leader in the antiulcer drug profile also at present as in the past. Studies showed that the leader of class was omeprazole [6]; the situation is similar today, as reflects the present research, the best-selling INN remaining omeprazole. Pharmacy 10 is ranked first in the hierarchy of drug sales having as an active ingredient omeprazole, with sales of 4155 units from total of 20634 units, i.e. 20.13% of the sales of the 15 pharmacies. The obtained results can be justified also by the schedule of the pharmacy, which is prolonged on weekdays and on weekends, but contributes also the fact that is located in a central, historical area, highly populated.

Pharmacy 10 is the leader of sales even for the medicines containing esomeprazole. From the total of 7768 units sold, 2159 units belong to Pharmacy 10 (27.79%), followed by Pharmacy 14 (950 units) and Pharmacy 15 (807 units). The location and the hours of operation of pharmacies certainly influence the sale of products containing esomeprazole, as in the case of omeprazole. The lowest values for esomeprazole were recorded for Pharmacies 7, 5 and 8, the last two pharmacies referred being found at the end of the ranking even in the case of products containing omeprazole. In the case of Pharmacy 8, the number of units issued was 100, a quantity which represents barely 1.28% of the total units sold from this product.

The sales of medicines containing pantoprazole totalled 9767 units, being the second substance regarding the sales of the proton pump inhibitors class. Also in this case, Pharmacy 10 remains the sales leader, with 3207 units, accounting for 32.83% of the total sales, followed by Pharmacy 14 with 1115 units (14.41%) and Pharmacy 2 with 958 units (9.8%). Pharmacy 14 was again ranked in the top three pharmacies within the hierarchy of sales. Placed in a commercial centre and functioning after a prolonged schedule which also includes the weekend, it is sought by patients for dispensing antiulcer drugs.

It should be noted also that pantoprazole is an OTC, so that patients do not require a medical prescription and its purchase can be made unconditionally by a prescription. Pharmacies 9, 5 and 8 recorded the lowest number of pantoprazole units sold, namely: 170 units, 126 units and 85 units respectively. Once again, Pharmacy 8 is the last in the descending order of sales, the number of units sold for this substance being very small, covering only 0.87% of total sales. Pharmacy 5 is a neighbour-hood pharmacy, but although it has this relative inconvenience compared to Pharmacy 8 which is centrally located, it recorded a double number of sold units of drugs containing the INN pantoprazole.

The sales of medicines containing as an active ingredient lansoprazole were compiled and from the results obtained in the 15 pharmacies studied

emerges that the leaders of sales of this INN are: Pharmacy 2 with 462 units, which is located close to a hospital, fact which justifies the sales, lansoprazole being released just on the base of a medical prescription, followed by Pharmacy 14 with 445 units and Pharmacy 13 with 363 units sold. Even though in the case of other substances, Pharmacy 10 was the sales leader, in case of products with lansoprazolum, it is positioned on the bottom of the ranking, not recording a single unit sold.

This aspect emphasizes that from this pharmacy were released only medicines containing the three active ingredients previously presented: omeprazole, esomeprazole and pantoprazole. In this case, Pharmacy 10 is accompanied on the bottom of the ranking of sales of lansoprazole by Pharmacy 11 with 19 units sold and by Pharmacy 8 with 63 units. One reason for these results could be the existence on the market of only six products containing this active substance, all of which are released only on the base of the medical prescription.

Conclusions

The two pharmacological classes of antiulcer drugs H2 antagonists and PPIs (out of which some are released from pharmacies based on medical prescription, others being OTCs) are well sold nationwide but also worldwide, as shown in the statistics. The data presented in the statistics highlights that antiulcer drugs have an important place in medicines' sales globally. Moreover, it is noted that the drug ranked the 9th in the global statistics belongs to the PPIs class. The importance of the representatives of this class is obvious and it is due to the increasingly higher demand due the complexity of the mechanism of action.

The results of the present market study, conducted during two years, showed that the active substances from the class of proton pump inhibitors are sales leaders, cumulating overall 84.91% of the total of 48164 units sold. Of this class, the best-selling active ingredient is omeprazole, drugs containing this substance representing 50.46% of sales, and the substance sold in the lowest percentage (6.67%) is lansoprazolum.

H2 antagonists accounted for only a percentage of 15.09% of total sales, the best-selling substance of this class being ranitidine, while cimetidine recorded a very low percentage, 0.10% due to its withdrawal from the market during the study.

The centralized results showed that in the case of PPIs, Pharmacy 10 is the sales' leader, cumulating 23.28% of the total sales of antiulcer drugs belonging to this class. Its success is supported by the central area where the pharmacy is located, but also by the prolonged working hours including also

the weekend. Pharmacy 8 recorded the lowest sales of PPIs (1.29%), with a total of 531 units released, although it is located close to public transportation stations and has a schedule which includes the weekends.

In the case of H2 antagonists, the leader of cumulative sales is Pharmacy 13 with 877 sold units of a total of 7269 units (12.06%). This pharmacy is located near a commercial centre and the schedule is prolonged during weekdays and it is available to patients also on Saturday. The lowest quantities of H2 antihistamines (143 units released, representing 1.96%) were recorded in the case of Pharmacy 8, the same as in the case of the proton pump inhibitors, although this pharmacy is located in an accessible area and the working hours include the weekends.

The market of antiulcer drugs is constantly growing, the products containing active pharmaceutical ingredients of these pharmacological classes are multiple, and their demand is becoming increasingly higher due to the condition addressed which is increasingly more widespread within the population.

References

1. Achimaş Cadariu A., Medical scientific research methodology, "Iuliu Haţieganu" University Medical Publishing House, Cluj-Napoca, 1999; 9, 14, 23, 43, (available in Romanian).
2. Bénazeth S., Boniface M., Demerquilly C., Lasserre V., Lemdani M., Nicolis I., Biomathematics. Analysis, algebra probabilities, statistics, Masson, Paris, 2001; 293-304, (available in French).
3. Boboia A., Polinicencu C., Applying Pareto analysis to the research of quantities of preparations in community pharmacies from Cluj-Napoca. *Clujul Medical*, 2010; 83(4): 620-624, (available in Romanian).
4. Crişan O., Good pharmacy practice in the context of crossborder healthcare. *Farmacia*, 2017; 65(2): 310-316.
5. College of Pharmacists in Romania - Cluj branch. Schedule of pharmacies in Cluj-Napoca. Available in Romanian; <http://www.colegfarmcluj.ro>.
6. Dubois P., Lasio L., Identifying Industry Margins with Unobserved Price Constraints: Structural Estimation on Pharmaceuticals. *Working Papers*, 2014; 823: 9-10.
7. IMS Health MIDAS, Top 20 Global Products 2014; www.imshealth.com.
8. IMS Health MIDAS, Top 20 Global Therapy Areas 2014; www.imshealth.com.
9. Mandache R.C., Boboia A., Research on the pharmaceutical market in Europe and Romania. *Rev. Int. Comp. Manag.*, 2015; 16(4): 528-539.
10. National Agency for Medicines and Medical Devices, List of Medicines from the Index of medicinal products for human use; www.anm.ro.
11. National Agency for Medicines and Medical Devices, List of Medicines from the Index of medicinal products for human use, Cimetidinum; www.anm.ro.

12. Rais C., Taerel A.E., Stănescu E., Brumărel M., Safta V., Adauji S., Priscu V., Soroceanu V., Epidemiological aspects of tuberculosis in adults in Romania *versus* the Republic of Moldova. *Farmacia*, 2016; 64(4): 643-650.
13. Trâmbițaș R., Statistical methods, Cluj University Press, Cluj-Napoca, 2000; 132-134, 137-141, 173-194, 218-222, (available in Romanian).