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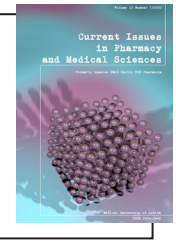

Comparative characteristics of proton pump inhibitor effectiveness in the treatment of gastric ulcer and duodenal ulcer

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ABSTRACT

Aim. The aim of this study is to evaluate the efficiency of proton pump inhibitors in the treatment of gastric and duodenal ulcers as based on literature.
Materials and methods: The materials of this research are the results of 86 original studies on the effectiveness of proton pump inhibitors analysis.
Methods. Descriptive, statistical, retrospective.
Results and Conclusion. According to the clinical random researches, Omeprazole preparations are not included in the list due to proven better effectiveness of Esomeprazole drugs. Moreover, lansoprazole drugs are not included according to proven short-acid inhibitory effect. In addition, the brand of mentioned above preparation does not exist on the pharmaceutical market of Ukraine. Furthermore, rabeprazole preparations are presented in the research by Pariet (brand) and by the effective generic Barol, while pantoprazole preparations are represented in the research by Kontrolok (brand) and by the generic Pultset, as well as by Nolpaza. Herein, the Pantosan effect was not significantly different from the effect of Pultset and Nolpaza, but the preparation is much more expensive. In terms of efficiency (%), 4 week repair of mucosal defects was carried out by way of the following treatment regimens: Barol + Amoxicillin + Clarythromycin (90.9±6.2), Pariet + Amoxicillin + Clarythromycin (83±2.6), Kontrolok + Amoxicillin + Clarythromycin (100±1.3), Pultset + Amoxicillin + Clarythromycin (88±4.1), Nolpaza + Amoxicillin + Clarythromycin (72±4.1), Ezolonh + Amoxicillin + Clarythromycin (87.7±3.8), Neksium + Amoxicillin + Clarythromycin (96.1±3.1).

INTRODUCTION

He who neglects all that justifies itself,
and wants to lead researches different to that of others,
deludes himself and deceives others.
Hippocrates

High morbidity, frequent relapses, long unserviceability of sick patients, significant economic losses – all of this allows the attribution of most urgent to the problem of stomach ulcer (SU) in modern medical practice. Herein, the inhibitors of proton pump (PPIs) show a high efficiency and safety in treating acid-dependent diseases (ADD). However, researches of efficiency in this area have not ceased. Hence, the purpose of this publication is a listing of data submission of comparative efficiency of PPIs in ADD treatment, based on the results of multicentre study.

About 30 years have passed since the beginning of research of medicaments which lower gastric secretion by blocking the H+/K+ AT phase. Due to this, anticholinergic drugs and H2 histamine antagonists, now practically entirely removed from pharmaceutical market, were substituted by such pills as Omeprazole, Lansoprazole, Pantoprazole, Esomeprazole, Rabeprazole, all of which are ascribed as being inhibitors of proton pump (PPIs).

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Stomach ulcer (SU) is a disease of important medical-social value. According to the data of the World Health Organization, 10-15% of all the world's adult population suffer from stomach ulcers[1,2]. Moreover, according to the data of the Centre for Health Statistics, the morbidity rate to stomach and duodenal intestine ulcer (SDIU) has increased by 38.4% for the last 10 years in Ukraine. Thus, today, of more than 8 151 283 individuals suffering from digestive system diseases, 12.47% have stomach ulcers and 23.30% suffer from duodenal ulcers (DU). This means 2239.8 and 4186.5 patients per 100 thousand of population in Ukraine.

Successful anti-Helicobacter therapy of Hp-positive ulcers promotes a total recovery in 80-85% of all cases, as a rule, the frequency of ulcer relapses does not exceed 6% and the frequency of complications is only around 2-4% [3]. Still, stomach ulcer is one of the leading reasons of productivity loss and development of disability [4].

According to data of the Centre for Statistics of the Ministry of Health of Ukraine, annually, almost 1 million of SU sick patients undergo follow-up care, each second patient passes treatment in the in-patient clinic, while more than a third of all sick patients use work incapacity certificates repeatedly. SU results in heavy complications (perforation, bleeding etc.) that are the reason for urgent surgical interferences in 25-30% of all cases [4].

The economical loss from SUDU almost to two times exceeds loss from cardiovascular pathology. Average annual charges to treatment of one SUDU patient in the USA amounts to $ 23819, in Southern Korea – from 959.60 to $ 2553.10. More than $ 750 million per year are spent in the USA for treatment of SU patients with bleeding complications. Unfortunately, the data for Ukraine is not available as yet. The above-mentioned points to the necessity of treatment cost optimization of the disease and application of clinical and economical approaches to choosing the pharmacotherapy for the patients with the given pathology.

MATERIAL AND METHODS

In this study, 86 literary sources with evidence base of efficacy of proton pump inhibitors in the treatment of stomach ulcer and duodenal ulcer were used. The work was based on Best Evidence. Abstract and full-text medical databases, Internet-sources were mined. The methods used include descriptive, statistical and retrospective. Herein, descriptive research is used to describe characteristics of a population or phenomenon being studied. The statistical methods applied are mathematical formulas, models and techniques that are used in the statistical analysis of raw research data. The statistical methods were applied to extract information from research data and provide diverse ways of assessing the robustness of research outputs. The retrospective analysis or retrospective study is a research method that is used when the outcome of an event is already known. A retrospective study looks backwards and examines exposures to suspected risk or protection factors in relation to an outcome that is established at the start of the study.

STUDY RESULTS AND DISCUSSION

Currently, there are 6 groups of PPIs that are active pharmaceutical ingredients for the treatment of stomach ulcer and duodenal ulcer: Omeprazole (Omeprazole, Omez, Gasek, Ozolm), Lansoprazole (Lansoprazole, Lancerol, Lanza, Lanzoptol), Dexlansoprazole (Dexlansoprazole, Deksilant), Rabeprazole (Rabeprazole, Pariet, Rabimak, Barol), Pantoprazole (Pantoprazole, Kontrolok, Nolpaza, Proksium) and Esomeprazole (Esomeprazole, Neksium, Ezolong, Emanera, Ezomealoks, Ezera) [5].

Proton-pump inhibitors (PPIs) are a group of drugs, the main action of which is a pronounced and long-lasting reduction of stomach acid production. Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H+/K+ ATPase, or, more commonly, the gastric proton pump) of the gastric parietal cells. The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion.

The evaluation of the pharmacotherapy of SU from clinical and economical positions has become a subject of intensive research [6-11]. With the help of the pharmaco-economic method of "minimization of charges" worked out by. Germanuk *et al*. [12], the following parameters were defined: the most economically profitable tablets for SUDU treatment; economically profitable alternate layouts of anti-helicobacter therapy (threefold therapy and fourfold therapy); and the number of sick patients who can be treated by the cheapest alternate layouts of threefold therapy and fourfold therapy comparatively to their more expensive variants[12].

In the work of Grushkovskaya [13], we can follow the results of comparative estimations of cost and curative efficiency of layouts of anti-helicobacter SUDU therapy. In his study, the author determined the optimum approach based on the criterion "expenditures-efficiency".

Using the pharmacoeconomic methods of "expenditures-efficiency" and "expenditures- utility" as proposed by Oisodlo *et al*. [10], we also determined the pharmacoeconomic advantages of new modes of anti-helicobacter therapy deemed sequential therapy and compared these to traditional layouts.

According to the results by Orlovsky *et al*. [14], "Barol" (Rabeprasol) as a part of anti-helicobacter therapy is faster and more effective than Omeprasolin and its use eliminates a clinical semiology of recrudescence of peptic ulcer of duodenal intestine, as well as congestion and oedema of the gastrointestinal mucosa. As a part of combined anti-helicobacter therapy, "Barol" (Rabeprasol) supplies high levels of *H. pylori* eradication (90.9%) relatively to the layout in which Omeprasol (83.3%) was used against a background of absence of clinically significant by-effects.

The prescription of Nolpaza (Pantoprasol) in the dose of 0.04 g two times per day positively affects all criteria of efficiency of ulcer suppressive therapy within anti-helicobacter treatment of patients with gastropathy. Furthermore, a seven-day layout of anti-helicobacter pharmacotherapy on the basis of Nolpaza 0.04 g two times per day, Claryth-romycin 0.5 g two times a day and Amoxicillin 1.0 g two

time/day can supply hyper-eradication in 96% of all patients with non-steroidal anti-inflammatory drugs gastropathy [13].

According to the data supplied by Scherbinina [15], the frequency of esophageal defects healing in four weeks was 14% in the placebo group, while the frequency of healing in four weeks administation of Nolpaza at a daily dose of 40 mg accounted for 72%. Moreover, the frequency of healing in 8 weeks was 88% [14].

In a study undertaken by Ilchenko *et al*. [16], of 50 patients with DU, the latent period, overall duration of drug effect, maximum time of drug effect, as well as the difference in intensity of anti-secretory action of the first taken dose of Ranitidin, Omeprasol, Rabeprasol were assessed. Accordingly, in 10 patients, the time of action of 20 mg of Rabeprasol was 15.5 hours [16]. In addition, in other comparative research of PPI efficiency in the treatment of DU, on the 1st day of treatment, 20 mg of Rabeprasol pH > 3 accounted for 60.1±3.5 of total effect. This was higher than that of the prescription drugs Ezomeprasol and Omeprasol [17].

Further research includes that of Wang Hand *et al*. [18] in which they compared the efficiency of Rabeprasol (10 mg two times/day) and Omeprasol (20 mg two times/day) on the first day of administration [18], and that of Babak, who carried out a comparative evaluation of clinical efficiency of Rabeprasol and other inhibitors of proton pump by applying meta-analysis. Herein, the taking of 10 mg of Rabeprasol on the 1st day of treatment resulted in epigastric burning disappearing in more than 28% of all studied patients, and when up to the end of the 4th and the 8th weeks of therapy – in 83,5 and 98.2% of all cases, respectively. The mentioned symptom control against a background of daily taking of 20 mg Ezomeprasol was noted only on the 5th day. Furthermore, after 8 weeks of Rabeprasol therapy, the total number of refluxes per day with pH<4 decreased from 19.1±2.7 to 1.4±0.5 ($p<0.05$), and in groups of Ezomeprasol therapy – from 19.0±0.6 to 3.0±0.01 ($p<0.05$) and from 19.2±0.6 to 1.8±0.02 ($p<0.05$) respectively.

The clinical efficiency of 20 mg Rabeprasol and 20 mg Omeprasolin treatment of active duodenal ulcer was also studied in a European randomized multi-institutional double-blind experiment in which 205 patients participated who were taking PPIs for 2 or 4 weeks. In the score of frequency and rate of pain attacks, Rabeprasol showed superiority over Omeprasol. In the study, statistically significant differences with regard to the given pain attacks was evident on the 4th week (there was no pain in 92% of all individuals for Rabeprasol, as compared to 83% for Omeprasol; $p=0.038$) [19].

Dashiyev *et al*. [20] carried out a comparative evaluation of the effect engendered by different inhibitors of proton pump (Omeprasol, Neksium and Kontrolok) in patients with SUDU. Herein, the evaluation of anti-helicobacter therapy efficiency was carried out as of 6-7 weeks post-treatment. Accordingly, frequency of by-effects development on the whole accounted for 40.2%, but the differences between groups were not reliable. The most frequent by-effects of the therapy were bowel disorders (diarrhea) – 20.1% of all those studied and headache – 8.1% of the total. On the whole, the rating of threefold therapy efficiency was at 77.2% (Omeprazol – 80 mg per day, Kontrolok – 80 mg per day, Ezomeprazol – 80 mg per day) [20].

Yastrebkova carried out a comparative clinical efficiency trial of Rabeprasol (Pariet) and Ezomeprazol (Neksium) in the treatment of acid-dependent diseases of the gastrointestinal tract. Accordingly, the duration of antisecretory action of Pariet on the 4th day of intake (18.3±1.3 hours) statistically exceeded such duration of Neksium (14.1±1.1 hours) ($p<0.05$). Moreover, percentage part of the day during which pH in the stomach remained was > 3 and > 5, in the group of sick patients who took Pariet (respectively, 83.2% and 56.3%). This exceeded similar ratings in the group of patients who took Neksium (62.7% and 36.2%). While taking Pariet at the dose of 20 mg, the frequency of by-effects (headache, vertigo, diarrhea, nausea, skin rashes) was 2% (in 7 patients out of 360), in contrast, that of 20 mg of Ezomeprazol (Neksium) was 15.3% (in 38 patients out of 250). What is more, compared to Omeprazol, the healing of gastric ulcers after 4 weeks of Pantoprasolin uptake was higher (88 against 77%). In addition, epigastric burning disappeared in patients of administered "Pulcet" (Group I) after 4.7±1.8 days, and in patients administered Omeprazol (Group II) after 5.0±1.9 days. Still, differences in speed of symptoms relief are doubtful ($P > 0.05$). However, over-night epigastric burning at the beginning of treatment was observed in 3 patients of Group I (9.7 5%±5.3%) and in 7 of Group II (22.5%±7.5%). In addition, reflux esophagitis disappeared, according to control gastroscopy data in 27 patients of Group I (87.1%±6.0%), and the regress of esophagitis from degree B to degree A was observed in 4 patients. In Group II, the healing of gastrointestinal mucosa was noted in 20 patients (64.5%±8.4%), in 7 – a regress from degree B to degree A, in 4 – catastasis was not improved. Differences in frequency of esophagitis healing between groups are reliable ($P<0.05$). Clinically significant by-effects are not registered [20].

The eradication level with Kontrolok, as stated in the original researches by Kliarytska, ranged from 74.4% up to 95.7%. Herein, the lowest percent of eradication was at PPIs – threefold modes which contain Metronidazole (Kontrolok + Amoxicillin + Metronidazole – eradication at 37%; Kontrolok + Metronidazole + Intetrics – eradication at 74.4%; Omeprasol + Amoxicillin + Metronidazole – eradication at 46.7%). The corresponding figures for quadruple therapy give an eradication level range of 93.75% to 95.7%; at PPIs – threefold mode – 93% [21].

The research undertaken by Vasilyev and Kasianenko of a test population of 19 patients that was based upon the quick urea test and 13C-urea breath test indicated that 4 weeks after the ending of a 7-day regimen of eradication therapy, total eradication HP was determined in all 19 patients (100%); and per histologic research in 18 out of 19 patients (94.7%) [22]. It should be noted that all by-effects were mild-to-moderate, nor was change of the regimen or cancellation of therapy needed.

CONCLUSIONS

In this study of current therapy, Omeprazol pills are not included because of proven greater efficiency of

Ezomeprazol pills; while Lansoprazol pills are not included because of proven short acid-inhibitory effect (and the product is not sold in Ukraine), Rabeprazol pills are presented in the research as 'Pariet' (brand), as well as by the effective generic 'Barol'; Pantoprazol pills are presented in the research as 'Kontrolok' (brand) and Pantosan (brand), as well as by generics 'Pulcet' and 'Nolpasa' (herein, the effect of Pantosan is not different from the effect of Pulcet and Nolpaza, however, it is far more expensive); finally, Ezomeprazol pills are presented by brand pills of 'Neksium' and the generic 'Ezolong'.

The author concludes this work by stating that it is necessary to continue further multisite randomized comparative researches of clinical efficiency of other PPIs, as well as the evaluation of results.

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