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Format for ANSWERING REVIEWERS

Sept 7, 2017

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Revision NO: **35607** doc).

Title: First Week Clinical Response of Dexlansoprazole 60 mg and Esomeprazole 40 mg in Treating Gastroesophageal Reflux Disease Grade A and B

Chih-Ming Liang, Ming-Te Kuo, Pin-I Hsu, Chao-Hung Kuo, Wei-Chen Tai, Shih-Cheng Yang , Keng-Liang Wu, Hsing-Ming Wang, Chih-Chien Yao, Cheng-En Tsai, Yao-Kuang Wang, Jiunn-Wei Wang,Chih-Fang Huang, Deng-Chyang Wu, Seng-Kee Chuah

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 35607

The manuscript has been improved according to the suggestions of the reviewers:

1 The format has been updated.

2 Revisions were made based on the suggestions of the reviewers.

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Answers to reviewers

Reviewer 1:

You have prepared an article devoted to the urgent problem of clinical medicine. The material is presented logically and correctly. Selected methods are adequate to the research problems and the aim.

Reply:

Thank you very much for your recommendation.

Reviewer 2:

This interesting study is focused on the comparative, short time, clinical effect of the novel PPI dexlansoprazole 60 mg versus esomeprazole 40 mg in GERD patients. Indeed, although percentage of time with pH>4 as well as average of mean pH have been shown to be greater following dexlansoprazole than esomeprazole, their symptomatic response, particularly on the short term, has not been comparatively investigated yet. In order to evaluate the symptomatic response at 1, 3 and 7 days following randomization with the two drugs, approximately 170 patients affected by grade A or B esophagitis underwent GERDQ questionnaire following a proper washout from PPIs or H2-antagonists. The Authors found similar symptom resolution rates between the two groups at day 1 and 7, being only in female patients a higher symptom resolution observed at day 3. Comments: The aims and findings of this investigation are very interesting. The study has been well conducted. My only comment refers to the tables, too many; some of them can be deleted, restricted or merged.

Reply:

Thank you very much for your recommendation.

We deleted the table 3 and 5 for the splitting data by age and weight.

Reviewer 3:

I think that the authors should submit the final results of the study and not only the results of the first week (long term efficacy of the drug). Anyway, the presented findings are not significant.

Reply:

Thank you very much for your recommendation. Indeed, the aims of our comparative studies of clinical effect ofdexlansoprazole 60 mg versus esomeprazole 40 mg in GERD patients focus on two stages: the short term (one week) and long term (24 weeks) effects. The first study has been completed and the second one is going until the last patient enrolled complete the F/U of 24 weeks.

PPIs represent the mainstay of treatment both for healing erosive esophagitis and for symptom relief as well as for preventing complications. **Rapid onset of proton-pump inhibitors for fast symptom release is an unmet need in treating gastroesophageal reflux disease(GERD). There was no report on the short-term clinical effects comparing dexlansoprazole 60 mg to esomeprazole 40 mg.**

This is the first study which compare the first week immediate response of the two PPIs. An interesting

finding in the short term data that feedback from patients. We needed to figure out why the female had poor response than male when taking PPIs.

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Editorial revisions:

(1) The title must be informative, specific, and brief (Title should be no more than 10~12 words/60 bytes. Please revise it). Words should be chosen carefully for retrieval purposes. All nonfunctional words should be deleted, such as 'the', 'studies on', 'observations of', and 'roles of', *etc.*

Answer: The title has been revised

(2) Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed research; Wang CL, Zou CC, Hong F and Wu XM performed research; Xue Jz and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed data; and Wang CL, Liang L and Fu JF wrote the paper.

Answer:

Liang CM and Kuo MT contributed equally to this work; Chuah SK designed research, critical revision of the manuscript for important intellectual content and finally approved the paper; Hsu PI, Kuo CH, Tai WC, Yang SC , Wu KL, Wang HM, Yao CC, Tsai CE, Wang YK[3], Wang JW, Huang CF, Wu DC, Chuah SK performed research; Liang CM, Kuo MT analyzed data and wrote the paper.

(3) Please add ORCID number of every authors, i.e., Michał Bulc (0000-0002-1402-5423); Katarzyna Palus (0000-0002-7593-9552)

Answer: They are all provided

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(4) A copy of the full approved grant application form(s), consisting of the information section and body section, should be provided to the BPG in PDF format.

Answer: It is uploaded

(5) Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email.

Please provide your professional email address issued by your institution (Xiyuan Hospital of China Academy of Chinese Medical Science), we do not accept personal Email address (*i.e.* @163, @ sina, @hotmail, @yahoo, @gmail) for corresponding author.

Thank you!

Answer: The correspondence is **Seng-Kee Chuah**

professional email address: chuahsk@cgmh.org.tw

(6) AIM (no more than 20 words): The purpose of the study should be stated clearly and with no or minimal background information, following the format of: "To investigate/study/determine…"

Answer:

It has been revised

To compare the one-week clinical effects of single dose of the two drugs for grade A and B erosive esophagitis.

(7) Please read the core tip then provide the audio core tip: **Acceptable file formats:** .mp3, .wav, or .aiff **Maximum file size:** 10 MB

To achieve the best quality, don't allow to have the noise.

Answer: It has been uploaded

(8) The format should be like this, please revise others.

Answer: It has been revised throughout the paper.

(9) Full Text Guide

1 Research Background

The background, present status and significance of the study should be described in detail.

GERD is a common gastrointestinal disorder worldwide and continues to increase in incidence with an aging population and the presence of an obesity epidemic. Although PPIs represent the mainstay of treatment for healing erosive esophagitis and for symptom relief, as well as for preventing complications, several studies have shown that up to 40% of GERD patients reported either a partial or a complete lack of response to their symptoms after taking a standard once daily PPI dose. Rapid onset of proton-pump inhibitors for fast symptom release is an unmet need in treating GERD. Thus far, there are no reports on the short-term clinical effects and timing to symptom relief of GERD between dexlansoprazoleat 60 mg and esomeprazole at 40 mg. This is the first randomized, controlled, open-label study to compare the 7-day clinical effects of single doses of dexlansoprazole at 60 mg and esomeprazole at 40 mg for Los Angeles (LA) Grades A and B erosive esophagitis.

2 Research motivation

The main topics, the key problems to be solved and the significance of solving these problems for future research in this field should be described in detail.

A study comparing the pharmacokinetic effects of different PPIs 12–24 hours postdose showed that the mean percentage of time with a pH >4 and the average of the pH mean were greater for dexlansoprazole than for esomeprazole (60% vs. 42%, $p < 0.001$ and 4.5 vs. 3.5 pH, $p < 0.001$). However, this study did not report the clinical effect after tablets were used. Therefore, the significance of solving these problems for future research in this field should be based on more large scale head-to-head comparison of these PPIs on the immediate symptom relief for GERD to fulfill the unmet need in the real world treatment.

3 Research objectives

The main objectives, the objectives that were realized, and the significance of realizing these objectives for future research in this field should be described in detail.

The main objectives, the objectives that were realized in this study provoked us to conduct this randomized, controlled, open-label study in order to compare the 7-day clinical effects of single doses of dexlansoprazole at 60 mg and esomeprazole at 40 mg for LA grades A and B erosive esophagitis.

4 Research methods

The research methods (*e.g.*, experiments, data analysis, surveys and clinical trials) adopted to realize the objectives as well as the characteristics and novelty of these research methods should be described in detail.

This study was funded by the Research Foundation of the Chang Gung Memorial Hospital, Taiwan (CMRPG8D1441) and has been registered in a publicly accessible registry (ClinicalTrials.gov number: NCT03128736).

We enrolled 175 adult GERD subjects, randomized them in a 1:1 ratio to two sequence groups, and defined the order in which they received single doses of dexlansoprazole (n=88) and esomeprazole (n=87) for an ITT. Written informed consent was obtained from each patient. Patients were requested to complete a Chinese GERDQ upon recruitment. Blood sampling for testing for fasting blood sugar, serum cholesterol, and triglyceride levels was carried out. In addition, a BMI was checked. A complete medical history and demographic data were obtained from each patient. Primary end points were complete CSR at days 1, 3, and 7. CSR was defined as no reflux symptoms sufficient to impair quality of life before the end of the initial treatment phase. The main outcome measures were the rates

of CSR at days 1, 3 and 7 of the initial treatment period. All patients starting esomeprazole or dexlansoprazole in the initial treatment were included in the ITT analysis. If patients had poor drug compliance, they were excluded from the PP analysis.

Research results

The research findings, their contributions to the research in this field, and the problems that remain to be solved should be described in detail.

Thirteen patients were lost during the follow up period, leaving 81 patients in each group for the per-protocol (PP) analysis. The CSRs for both groups were similar at days 1, 3 and 7. In subgroup analysis, female patients achieved higher CSRs in the dexlansoprazole group than in the esomeprazole group at day 3 (38.3% vs. 18.4%, $p = 0.046$). An increasing trend was observed at day 7 (55.3% vs. 36.8%, $p = 0.09$). In the esomeprazole group, being female was a negative predictive factor for CSR in postdose day 1 (OR: -1.249±0.543; 95% CI: 0.287 (0.099-0.832), $p = 0.022$) and day3 (OR: -1.254±0.519; 95% CI: 0.285 (0.103-0.789), $p = 0.016$). Patients with spicy food eating habits achieved lower CSRs on day 1 (37.3% versus 21.4%, OR: -0.969±0.438; 95% CI: 0.380 (0.161-0.896), $p = 0.027$).

6 Research conclusions

The following questions should be briefly answered:

What are the new findings of this study?

What are the new theories this study proposes?

What are the appropriate summarizations of current knowledge that this study provides?

What are the original insights into the current knowledge that this study offers?

What are the new hypotheses this study proposed?

What are the new methods this study used?

What are the new phenomena that were found through experiments in this study?

What are the hypotheses that were confirmed through experiments in this study?

What are the implications of this study for clinical practice in the future?

The conclusion of this study was that the overall CSR rate for GERD was similar at day 1 through day 7 for both the dexlansoprazole and the esomeprazole groups, although a higher incidence was observed at day 3 in female patients who received a single dose of dexlansoprazole. **These are the new findings of this study** that since there are by far no report on the short-term clinical effects

comparing dexlansoprazole 60 mg to esomeprazole 40 mg which is the unmet need in treating GERD in real world clinical practice. The findings in this study could be important implications for clinical practice in the future in treating grades A and B GERD patients. Furthermore, this study observed that female was a negative predictive factor for CSR in post dose day 1 and day 3 in the esomeprazole group. These findings implied that esomeprazole at 40 mg required more time (3 days) than dexlansoprazole at 60 mg to attain CSR in females. **The new theories proposed for the new observations** could be due to different in the pharmacokinetics report of esomeprazole and dexlansoprazole. Esomeprazole is time and dose dependent especially at day 1 and day 5. In dexlansoprazole, there is no accumulation of dexlansoprazole occurring after multiple once daily doses of 60 mg. We can assume this by calculating the Cmax of dexlansoprazole, which was 16 μmole*h/L on day 1 and 17.67 μmole*h/L on day 5. As a result, dexlansoprazole could almost achieve the target concentration on day 1. In addition, there was ample evidence that showed that estrogen and progestogen could enhance the relaxing of lower esophageal sphincters and inducing GERD symptoms, especially in post-menopausal women who take hormone replacement therapy. These hypotheses could explain why female patients who took esomeprazole needed at least 3 more days to accumulate enough plasma concentration to achieve plateau levels in order to achieve desirable clinical effects.

7. Research perspectives

The important message of this study was the rapid onset of PPIs for fast symptom release remained an unmet need in treating GERD and there was no report on the short-term clinical effects comparing dexlansoprazole 60 mg to esomeprazole 40 mg, this was a novel finding of this pilot study. It could be an important implication of this study for clinical practice in the future in treating grades A and B GERD patients. This pilot study was hampered by the small sample size, and we believe that large-scale randomized controlled trials are necessary to further fulfill the future perspectives.

(10) For the figures, the fonts and lines can be edited or moved. It can be made by ppt.

Answer: all the above has been revised and uploaded in PPT file