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ORIGINAL ARTICLE

Efficacy of Esomeprazole in NSAIDs Induced Gastric Ulcer: A Meta-Analysis

Nimra Mujeeb[1,#], Muhammad Liaquat Raza[2,#,*], Ale Zehra[3]

[1] Department of Pharmacology, Faculty of Pharmacy, Hamdard University, Karachi, Pakistan

[2] Department of Clinical Sciences, Biomedical Centre – BMC, Lund University Hospital, Lund, Sweden

[3] Dow College of Pharmacy, DUHS Ojha Campus, Karachi, Pakistan

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1 Data Collection, Data Analysis, Drafting.
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#Contributed equally.

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****Address of Correspondence Author:***
liaquathej@yahoo.com

ABSTRACT

Background: Gastric ulcers are painful sores with discontinuity in the entire thickness of stomach lining. Proton pump inhibitors (PPIs) are among the major classes of drugs used in treatment of gastric ulcers by inhibiting H^+/K^+ATPase pump thus reducing acid secretion. The prototype of PPIs is omeprazole, one of its new derivatives, esomeprazole is known to have superior activity against NSAIDs induced gastric ulcer. We aimed to meta-analyzed various clinical studies on esomeprazole and tried to draw a conclusion that may suggest refined clinical efficacy.

Methods: Utilizing databases of FDA listed clinical trials and PubMed. We shortlisted randomized controlled trials that were only related to esomeprazole's efficacy in NSAIDs induced gastric ulcer. Additionally, comparison was also evaluated in regard to adverse events of esomeprazole. Data extraction and assessment of study validity was performed independently.

Results: After critically analyzing four major important related clinical trials (n=3837), it was found that at 24 weeks, patients maintained on esomeprazole 20 mg OD (167/173) were gastric ulcer free, in comparison to placebo group (112/168). Similar results were obtained with 26 weeks treatment of esomeprazole at doses of 20 mg, 40 mg (808/818), and (798/804), respectively. While, outcome of another trial at the same dose, for the duration of 52 weeks, 125 out of 130 patients showed recovery from gastric ulcer, compared to 40/799 in placebo group. Similarly, in the other trial, patients who were given esomeprazole in combination with naproxen (500 mg), displayed positive effect in 166 out of 218 patients. Adverse events were observed only in 5/218 and 6/216, respectively.

Discussion and Conclusion: Esomeprazole therapy showed efficacious results, both when it was given for the period of 24 weeks and over 50 weeks without producing serious adverse effects. Reduction in the NSAIDs induced gastric ulcer by esomeprazole was achieved effectively in chosen clinical trial, suggesting esomeprazole, a preferable choice for reducing the gastric ulcers.

Keywords: Ulcer, NSAIDs, proton pump inhibitor, acid release, ATPase.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs. NSAIDs are employed in various pain and inflammatory conditions such as rheumatoid arthritis, osteoarthritis, lumbago, low back pain, gout, ankolysing spondylitis. However, like many other drugs, it also produces adverse effect specifically on gastrointestinal (GI) tract. Notably, the major GI issues with the long term use of NSAIDs includes gastric and duodenal lesion, aggravation of stress-induced gastric ulcer and impairment in healing of gastric ulcers [1-4].

It is said that NSAIDs induced gastric damage occurs due to deficiency of prostaglandins (PGs) because of continuous use of NSAIDs. Yet it involves multiple expected elements including hyper-motility, neutrophils and free radicals. It is believed that deficiency of PGs by NSAIDs occurs chiefly due to inhibition of enzyme that affects the cyclooxygenase (COX) pathway. COX system comprises of two types of isozyme COX-1 AND COX-2. Majorly, COX-1 involves in housekeeping of the human body [5]. Primarily, reduction in gastric blood flow after administration of NSAIDs occurs by the inhibition of COX-1. It is believed that it increases with selective use of COX-1 inhibitor. Another reported factor is adherence of neutrophils with vascular endothelium of post capillary venules. Because of localized irritant effect of NSAIDs following above mentioned mechanisms lead to the gastric mucosal injury [6].

Esomeprazole, a well-known proton pump inhibitors (PPI), is an optical *S*-isomer of omeprazole used as acid suppressive therapy. Esomeprazole improves the gastrointestinal symptoms in various ulcerative conditions such as gastric and duodenal ulcers [7]. After the administration, in the human system it is converted to sulfonamide derivative by the action of gastric acid, which act on the H^+/K^+ATPase pump and inhibits the pump in gastric parietal cells, thus acid production suppresses [8].

In this meta-analysis we have reviewed safety and efficacy of esomeprazole in reducing gastric ulcers induced by the continuous administration of NSAIDs. Focusing patients with rheumatoid arthritis, osteoarthritis, ankolysing spondylitis, lumbago, *etc*.

MATERIALS AND METHODS

Types of Study, Participants and Interventions

Those studies were included in which patients have received NSAIDs for treatments of chronic illnesses either due to arthritic conditions, back pain, lumbago. Only those trials were included in which comparative efficacy of esomeprazole with placebo drugs were studied in reducing gastric ulcers induced by NSAIDs. Similarly, studies with patients receiving esomeprazole for reducing NSAIDs induced ulcer were considered.

Patients included in this meta-analysis were those having histories of peptic ulcer disease. In addition, these patients were also diagnosed with chronic condition (rheumatoid arthritis, osteoarthritis, lumbago) that requires daily intake of NSAIDs. Following types of patient were excluded from analysis, who have ulcer in active state or in healing stages, having history of gastric or duodenal surgery, having chronic renal or liver disease problems. The outcome reviewed in this study was “reduction of gastric ulcer in patients after taking esomeprazole”.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

An extensive search on data about esomeprazole efficacy and safety studies was performed, randomized clinical trials till December 2016 were reviewed. The selection of studies based on the criteria described above, subsequently data extraction was performed independently. Completed and published clinical trials were selected from FDA clinical trial web site and PubMed.

METHOD OF REVIEW

Studies Selection

Studies that clearly stated the information about number of patients treated with esomeprazole and the number of patients found without gastric ulcers were selected during and after the completion of clinical trial.

DATA EXTRACTION AND ASSESSMENT

Results of published trials were reviewed from previously mentioned data resources. The quality of trials was assessed by using parameters giving by oxford quality scoring system which includes trials in which randomization, double blinding and dropout and withdrawal pattern were observed.

Data extraction was performed by the extraction of following predefined values as shown in Table **1**.

Table 1. Reduction in NSAIDs induced gastric ulcers by esomeprazole.

Disease Type	Esomeprazole	Duration	Reduction in Ulcer	Reference
GUD	20 mg, OD	52 weeks	125/130	Sugano *et al*. [9]
GUD	20 mg, OD	24 weeks	167/173	Sugano *et al*. [10]
GUD	20 mg, OD 40 mg, OD	26 weeks	796/804 806/817	Scheiman *et al*. [11]

Table 2. Characteristics of selected clinical studies.

Publication Type	Methods	Gender and Age Route of Administration	Number of Patients Treated *vs*. Enrolled	Reference
Article	Non-randomized, Open label, Phase 3 study	Both, 20 years and older Oral	130/395	Sugano *et al*. [9]
Article	Randomized, Double blind, Phase 3 study	Both, 18 years and older Oral	173/343	Sugano *et al*. [10]
Article	Randomized, Double blind, Phase 3 study	Both, 18 years and older Oral	1621/2426	Scheiman *et al*. [11]

DATA SYNTHESIS

Primary Outcome

The outcome in this analysis, was reduction in ulcer with concomitant use of NSAIDs. The overall calculated values observed for reduction in ulcers with esomeprazole at dose of 20 mg was 1088/1107 and at 40 mg was 806/817, respectively.

Secondary Outcome

Another outcome in data synthesis, was the reported adverse effects during esomeprazole treatment. Total number of adverse effects observed in included trials were found at 20 mg and 40 mg (n=443/1916). Esomeprazole showed good safety profile and tolerance in Japanese NSAID users as well as cardiovascular patients with a history of peptic ulcer disease.

RESULTS AND DISCUSSION

Description of Studies and Efficacy of Esomeprazole in Eradication of Ulcer

Studies on esomeprazole efficacy in NSAIDs induced ulcer are shown in Table **1** [9-11]. Since overall reduction in ulcer was found to be 98% at the dose of esomeprazole 20 mg and 40 mg, OD. The characteristic of studies which we included in this meta-analysis are shown in Table **2** [9-11]. Three studies fulfilled the inclusion and exclusion criteria and were likewise selected for the analysis of outcomes. Overall patients treated with esomeprazole at 20 mg and 40 mg were 1924, out of which 1894 patients found without gastric ulcer at the end of study. The main results of meta-analysis are shown in the following Figures **1-4**.

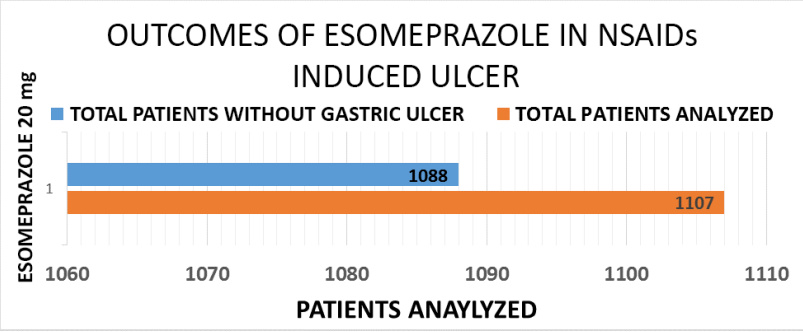

Figure 1. Outcomes observed after giving esomeprazole 20 mg in NSAIDs induced gastric ulcer patients.

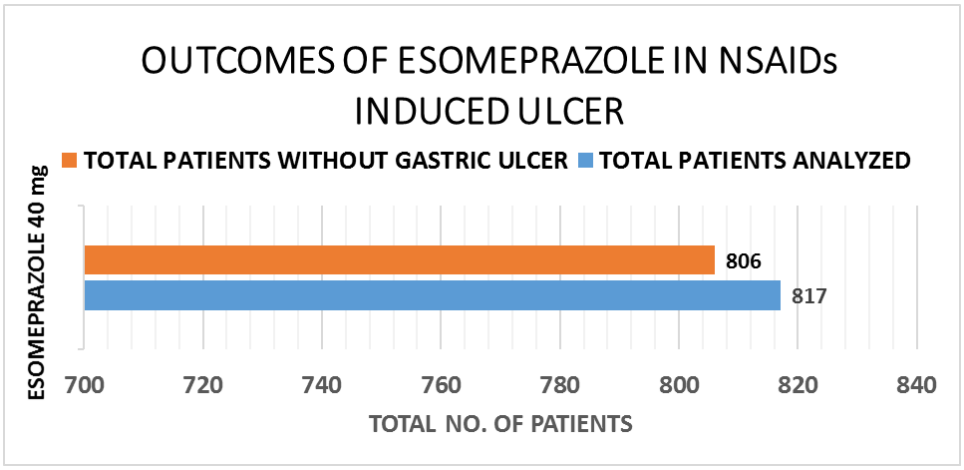

Figure 2. Outcomes observed after taken esomeprazole (40 mg) in NSAIDs induced gastric ulcer patients.

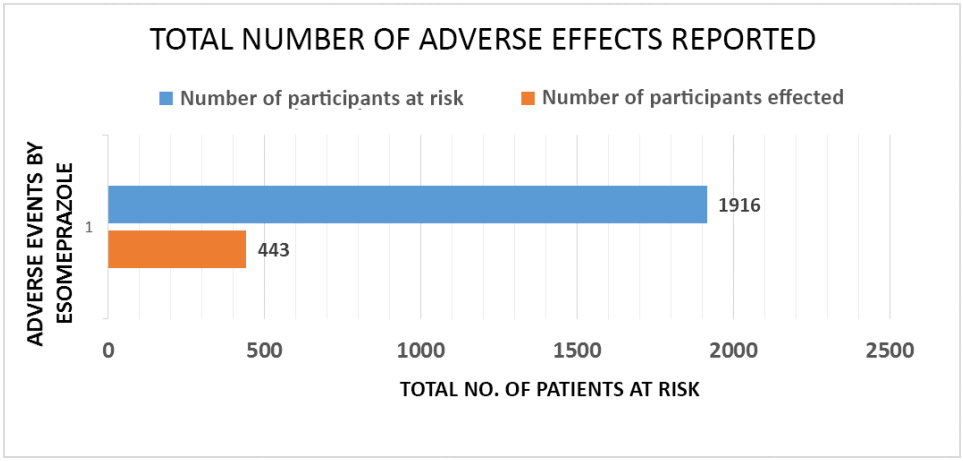

Figure 3. Total number of adverse events reported in NSAIDs induced gastric ulcer patients, in patients received esomeprazole 20-40 mg along with NSAIDs.

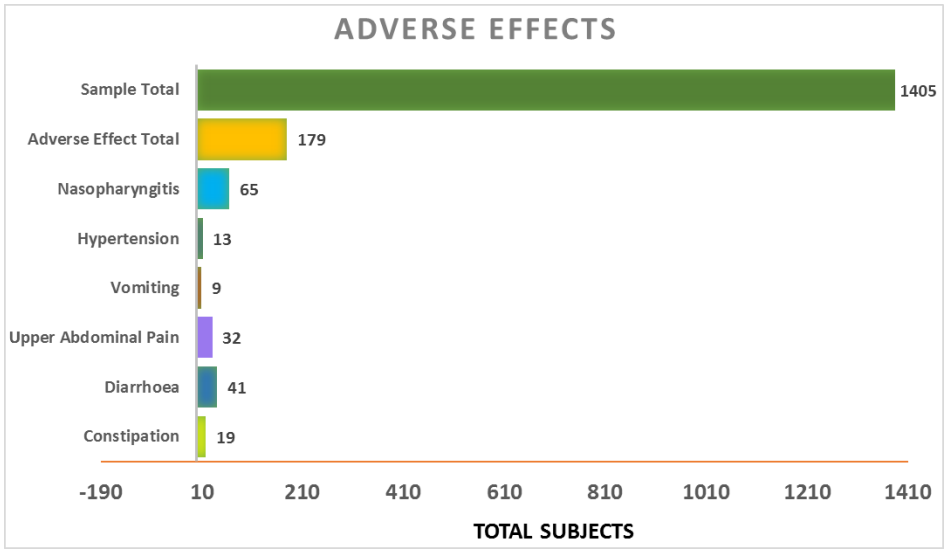

Figure 4. Adverse events reported in patients received esomeprazole 20 mg along with NSAIDs in NSAIDs induced gastric ulcer patients.

After selected related clinical trials and careful analysis about outcome on efficacy of esomeprazole, we found that the overall, treatment with esomeprazole was well tolerated and prevented peptic ulcer recurrence in patients. It is clear from the analysis that the gastro-protective effect was apparent after week 4 onwards. These results add to experience with other PPIs in Japanese NSAID users [12].

Diagnosis of NSAIDs induced ulcer was based on urea breath test and by the endoscopic examinations. Nature and frequency of adverse events observed was not too profound, only small proportion of patients experienced drug related adverse events. The most common adverse events reported were nasopharyngitis, aggravation of underlying rheumatoid arthritis and upper abdominal pain.

The analyzed trials' data revealed that those patients who received esomeprazole at doses of 20 and 40 mg from 4 weeks till 1 year, showed favorable safety profile. It was found tolerant in NSAIDs users, also in those cardiovascular patients who were maintained on low dose of acetylsalicylic acid [12]. Furthermore, these results were found consistent with lansoprazole (15 mg, OD) in a study [13]. Although, in a study - esomeprazole improved healing as compare to omeprazole at 20 and 40 mg, OD dosing. Importantly, estimated healing rate with esomeprazole was found to be 94.1% and 89.9% in reflux esophagitis patients [14].

As esomeprazole provide better intragastric pH control as supported by various published studies, when they compared it with other PPIs [15-17]. It was observed that it reduces the gastric ulcer induced by the continuous use of NSAIDs. Esomeprazole as compare to other PPI provides pH control >4 till 24 h, but other PPIs provided acid suppression only for 10 h [18]. The findings are consistent with studies of esomeprazole for prevention of NSAID-related peptic ulcers in Western populations as well as Japanese population [9-12].

Verification of Esomeprazole for NSAID Ulcers and Symptoms (VENUS) and Prevention of Latent Ulceration Treatment Options (PLUTO) studies were conducted in those patients who were at increased GI risk. It was noticed that peptic ulcer development was present only 5.2% in patients receiving esomeprazole 20 mg OD, whereas, the placebo group found to have 17.0% ulcer incidence (P<0.001), in 6-months' time period [19].

CONCLUSION

We may conclusively say that related the chosen clinical trials in this analysis reveals that esomeprazole provides better pH control and reduction in gastric ulcer, if it is used concomitantly with the NSAIDs users in ulcer and non-ulcerated patients as prophylactically. As it also reduces gastric symptoms in NSAIDs user patients. Further, with addition of esomeprazole one can improve the quality of life in NSAIDs users, esomeprazole would be helpful in patients having different gastric acid problems issues.

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