

# Study The Overprescription Of Proton Pump Inhibitors And Their Relation With Recurrent Community Aquired Infections In Outpatient Refilled Prescriptions Of Chronic Diseases Patients

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doi: 10.19044/esj.2016.v12n6p116 [URL:http://dx.doi.org/10.19044/esj.2016.v12n6p116](http://dx.doi.org/10.19044/esj.2016.v12n6p116)

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## Abstract

**Background:** proton pump inhibitors are widely used worldwide and studies have demonstrated that the use of PPIs to be associated with various diseases such as several types of infection.

**Study objectives:** to explore the effect of using PPIs on patients through studying some inflammatory biomarkers including WBC, neutrophil count, ESR, CRP, and IL-6.

**Methods and subjects:** a retrospective study design was followed to collect data from study participants. The study included 62 patients receiving PPIs and 60 persons without being prescribed for PPIs. A working sheet was created for each patient and included the following information: age, WBC, neutrophil count, ESR, CRP, and IL-6. Data analysis was carried out using SPSS version 20. The relationship between variables was tested using independent T test. Significance was considered at alpha level  $\leq 0.05$ .

**Study findings:** age was not varied significantly between study group and control group. All inflammatory biomarkers under study were significantly elevated in study group compared with control group.

**Conclusions:** the findings of the present study showed that the use of PPIs was associated significantly with increased inflammatory biomarkers. We

think that health settings should pay much attention to the role of pharmacists and pharmacy doctors to increase the awareness about the use of PPIs.

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**Keywords:** PPIs, infection, IL-6, ESR, WBC, CRP

## **Introduction**

Proton pump inhibitors (PPIs) are prescribed to prevent the production of gastric parietal cell acid through the irreversible inhibition of the luminal H<sup>+</sup>/K<sup>+</sup> adenylypyrophosphatase (ATPase) (Lindberg et al., 2003). Reviewing literature showed the use of PPIs in various inflammatory conditions such as upper gastrointestinal tract infection, erosive esophagitis, gastric and duodenal ulcers (Vandenplas et al., 2009; Koletzko et al., 2011; Dellon et al., 2013).

PPIs have been reported to be highly prescribed due to their effectiveness and safety. Among PPIs is omeprazole which is one of the most popular drugs worldwide. It has been assumed that omeprazole is a potential drug for treating several diseases (García-Torres et al., 2016).

The study of García-Torres et al (2016) has shown that omeprazole has cytotoxic effects in *Giardia* and it can inactivate giardial triosephosphate isomerase (GITIM). The researchers thought that PPIs act through modifying the Cys 222 residue. Furthermore, significant changes on structural level, thermal stability of inactivated- GITIM was observed.

Yu et al (2015) conducted a study to assess the association between PPI use and spontaneous bacterial peritonitis (SBP) incidence and mortality using case control and cohort studies. Researchers analyzed 10 case-control and six cohort studies which included 8145 patients. Findings indicated that PPI use was associated with SBP (OR = 2.11, 95% CI: 1.46–3.06). Furthermore, no association was observed between PPI therapy and mortality during hospitalization or within 30days after SBP.

Landray et al (1998) reported that the use of omeprazole induced inflammatory reactions which were reflected through increased levels of erythrocyte sedimentation rate (ESR).

Simpson et al (2006) conducted a study to study the clinical parameters of 15 patients who had acute interstitial nephritis (AIN) and acute renal failure due to the prescription of PPI. Study findings showed that both ESR and CRP were increased during time of diagnosis. The mean of ESR was 85 mm/h, and that of CRP was 81 mg/L.

Sanduleanu et al (2003) conducted a study to examine hypothesis that serum cytokines may offer additional data to gastrin and pepsinogens in screening for atrophic body gastritis (ABG). Study findings showed that patients with ABG had significantly higher serum gastrin ( $P < 0.01$ ) than

those without ABG. furthermore, study findings showed that the levels of serum IL-6 were significantly higher in the subjects with ABG than in those without ABG ( $P < 0.0001$ ).

Gouraud et al (2010) conducted a study taking into account several considerations among which are PPIs are widely used with efficacy and well tolerance. Another consideration was that neutropenia and agranulocytosis are considered rarely adverse conditions to occur in association with treatment by PPI. According to authors, the use of omeprazole has been involved in previous works involving isolated neutropenia. The authors described a case of omeprazole induced neutropenia with further recurrence upon pantoprazole treatment. The treatment with omeprazole increased both white blood count and neutropenia. When the treatment with omeprazole discontinued, white blood count and neutrophil count returned to normal range.

### **Study objectives**

The main objective of the present study was to explore the effect of using PPIs on patients through studying some inflammatory biomarkers including WBC, neutrophil count, ESR, CRP, and IL-6.

### **Methods and subjects**

#### ***Study design and setting***

A retrospective study design was followed to collect data from study participants. The study was conducted at Royal Medical Services.

#### ***Study sample***

Study sample included 62 patients with prescribed PPIs and 60 subjects without PPIs as a control group.

#### ***Study procedure***

An ethical approval was obtained from the IRB committee from Jordanian Royal Medical Services. A working sheet was prepared for each patient which included the required information about patients including age, white blood cell count (WBC), Interleukin- 6 (IL-6), neutrophil count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Data was filled for each participant in an excel sheet to collect the raw data for each patient. In a further step, data was analyzed using SPSS version 20. Independent T test was used to investigate the relationship between study groups. Significance was considered at an alpha level  $<0.05$ .

## Results

As seen in table 1, the mean age of patients in study group was  $55.34 \pm 13.54$  years, and this was less than that of control group  $57.06 \pm 10.27$  years. No significant variations were observed between study and control groups ( $p=0.516$ ).

Study findings showed that all inflammatory markers under study were significantly higher in study group compared with control group. WBC mean in study group was  $8.23 \pm 1.52 \times 10^3$  which was significantly higher than that of control group  $6.34 \pm 1.58 \times 10^3$  ( $p=0.001$ ). The mean level of IL-6 was  $19956.86 \pm 2620.24$  and this was significantly ( $p=0.000$ ) higher than that of control group  $13318.85 \pm 8297.30$ . The neutrophil count in study group ( $8.13 \pm 1.66$ ) was significantly higher ( $p=0.000$ ) than that of control group ( $4.14 \pm 1.77$ ). The results also indicated that the mean level of ESR in study group was  $38.5 \pm 21.7$  mm/hr, and this was higher than that of control group  $20.1 \pm 10.76$  mm/hr. This variation was statistically significant ( $p=0.000$ ). The mean level of CRP in study group was  $36.80 \pm 26.80$ , while in control group, it was  $2.40 \pm 2.60$ . The variation was statistically significant ( $p=0.000$ ).

Tale 1: General characteristics of participants

Variable	Study group		Control group		P value
	Mean	SD	Mean	SD	
Age	55.34	13.54	57.06	10.27	0.516
WBC	8.23	1.52	6.34	1.58	0.001
IL-6	19956.86	2620.24	13318.85	8297.30	0.000
Neutrophils	8.13	1.66	4.14	1.77	0.000
ESR	38.5	21.7	20.1	10.76	0.000
CRP	36.80	26.8	2.40	2.60	0.000

## Discussion

The present study was conducted in view of the facts that PPIs are widely used in the local and global level. The purpose of this study was to explore the effect of PPIs on patients.

We studied the effects of PPIs on several inflammatory biomarkers including WBC, neutrophil count, ESR, and CRP.

We showed that the mean of WBC and neutrophil count in study groups were significantly higher than that in control group ( $p=0.000$ ). Our findings confirmed the findings of other studies such as the study of Gouraud et al (2010) who reported increased WBC and neutrophil levels to be associated with PPIs including the uses of omeprazole treatment.

The study findings showed that the levels of IL-6 was significantly increased in study group compared with control group ( $p=0.000$ ). Our findings agree with other reported studies including the study of Sanduleanu

et al (2003) who reported that all cytokines including IL-6 were significantly elevated in patients with ABG compared with persons without ABG.

Finally, our results showed that both ESR and CRP were significantly increased in patients who received PPIs compared with those in control group. We confirm previous results that showed the use of PPIs increased levels of both ESR and CRP (Landray et al., 1983; Simpson et al., 2006).

## **Conclusion**

The findings of the present study showed that the use of PPIs was associated significantly with increased inflammatory biomarkers. We think that health settings should pay much attention to the role of pharmacists and pharmacy doctors to increase the awareness about the use of PPIs.

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