# The Effects of PPI Use on Clostridium Difficile Serum Antigen Levels

## PPI Kullanımının Clostridium Difficile Serum Antijen Değerlerine Olan Etkisi

PPI ile Clostridium Difficile Antijen İlişkisi / PPI Use and Clostridium Difficile Serum Antigen Levels

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**Özet**

Amaç: Larengofarengeal Reflü (LFR) hastalığının tedavisi amacıyla Proton pompa inhibitörü (PPİ) kullanan hastalarda tedavi öncesi ve üç aylık tedavinin sonunda serum Clostridium Difficile antijen miktarı ölçülerek PPİ kullanımının serum Clostridium Difficile serum antijen miktarı üzerindeki etkisinin değerlendirilmesi. Gereç ve Yöntem: Çalışmaya LFR hatalığı tespit edilen 32 hasta ( 24 ( % 80)'ü kadın, 8 (% 20)'i erkek) dahil edildi. Hastaların yaş ortalaması 34.13 ± 11.59 idi. Çalışmaya dahil edilen tüm hastalara tedavi için günde iki kez yemeklerden önce alınacak şekilde lansoprazol 30 mg tablet peroral olarak başlandı. Tedavi öncesinde ve üç aylık tedavinin sonunda hastaların LFR şiddeti Reflü Semptom İndeksi ( RSI) ve RBS ( Reflü Bulgu Skoru) kullanılarak değerlendirildi. Ayrıca hastalardan tedavi öncesi ve üç aylık tedavinin sonunda alınan kan serum örneklerinde beyaz küre, CRP, sedimantasyon ve serum Clostridium Difficile toxin A, B ölçümleri yapılarak karşılaştırmalı olarak değerlendirildi. Bulgular: Tedavi öncesi RSI ve RBS ortalamaları sırasıyla 20.81±4.05 ve 13.31±3.30 iken, üç aylık tedavi sonrasında bu ortalamalar sırasıyla 3.41±2.37 ve 1.50±1.88 olarak tespit edildi ( p< 0,05). Tedavi öncesi serum Clostridium Difficilie Ag değerlerinin ortalaması 140.56±11.74 iken üç aylık tedavi sonrasında bu ortalamanın 114.56±10.70 olduğu görüldü ( p< 0,05). Ancak diğer parametrelerde tedavi öncesi ve sonrasında istatiksel olarak anlamlı bir değişim saptanmadı ( p> 0,05). Tartışma: Elde ettiğimiz sonuçlara göre, proton pompa inhibitörü kullanan hastaların Clostridium difficilie toxin A, B serum antijen düzeylerinde istatistiksel olarak anlamlı bir düşüş olduğunu görüldü.

**Anahtar Kelimeler**

Proton Pompa İnhibitörleri; Serum Clostridium Difficile Antijeni; Larengofarengeal Reflü

**Abstract**

Aim: To evaluate the effects of proton-pump inhibitor (PPI) use on distrubtion of intestinal flora by measuring serum Clostridium Difficile antigen levels before and at the end of a three-months treatment in patients with Laryngopharyngeal reflux (LFR) treatment. Material and Method: The study covers 32 patients with LFR, out of which 24 were female (75%) and 8 were male (25%). The mean age of the patients was 34.13 ± 11.59. All patients included in the study were administered Lansoprazole 30 mg tablets perorally before meals and twice a day for treatment. Reflux Symptom Index (RSI), Reflux Finding Score (RFS), white blood cell count, CRP and serum Clostridium Difficile toxin A, B measurement results were comparatively evaluated through the blood serum samples drawn from the patients before and at the end of the three-months treatment. Results: While the mean values of pre-treatment RSI and RFI were 20.81±4.05 and 13.31±3.30 respectively, the mean values were measured to be 3.41±2.37 and 1.50±1.88 respectively following the three-months treatment (p< 0.05). The pre-treatment mean value of serum Clostridium Difficile Ag was 140.56±11.74, while it was seen that the same value became 114.94±10.70 after the three-months treatment (p< 0.05). There was, however, no statistically significant change in the other parameters. Discussion: According to the results obtained, it was seen that the treatment with PPI was not cause to increase Clostridium difficile toxin A, B serum antigen levels. So these drugs could be used in long time therapies confidently.

**Keywords**

Proton Pump Inhibitors; Serum Clostridium Difficile Antigen; Laryngopharyngeal Reflux

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## Introduction

Laryngopharyngeal reflux (LFR) was first described by J. Cherry [1] and Malcomson [2] in 1968 as one of the extraesophageal manifestations of gastroesophageal reflux (GER). LFR is an atypical form of gastroesophageal reflux and it is described as the retrograde flow of gastric content over the upper esophageal sphincter without any retching or vomiting. In relation to the fact that the larynx is the closest adjacent organ to the digestive tract located on the upper esophageal sphincter, the contact of the acid and pepsis in the gastric content with the larynx mucosa causes non-specific irritation and symptoms and mucosal lesions based on this irritation [2].

Studies demonstrated that the retrograde flow of the gastric acid into the larynx was associated with clinical conditions such as chronic laryngitis, contact ulcer and the granuloma of the larynx, vocal cord nodules, Reinke's edema, subglottic stenosis, laryngotracheal stenosis, larynx and hypopharynx cancer, paroxysmal larynx spasm, chronic cough, and globus pharyngeus [3].

The diagnosis of Laryngopharyngeal reflux patients is carried out with symptom and clinical finding indices with proven validity and safety [4].

Proton-pump inhibitors (PPI) are used in the treatment of the disease in order to reduce the amount of acid empirically in all patients together with different therapeutic approaches based on the patients' clinical conditions [5]. PPIs inhibit acid secretion by irreversibly blocking the H +, K +-ATPaz enzyme in the acid secreting parietal cell canaliculi [6].

It was demonstrated that there became differences in the amount of acid and pepsin in the gastrointestinal system that changed because of the use of proton-pump inhibitors and that it transformed the Clostridium Difficile spores in the GIS flora secondarily to these changes and sometimes caused disease [7].

On the other hand, the patients with elevated serum Clostridium Difficile antigenes induced by the PPI use and related complications are immunosuppressive. The patients most of whom have systemic infections, use different medications that might affect gastrointestinal flora, and are open to nosocomial infections [8; 9]. In such situations it is very hard to decisively establish whether the complications based on Clostridium Difficile were related to PPI or not.

Further, the diagnosis of Clostridium Difficile related infections is generally established by the analysis of stool samples. It is seen that the several difficulties in taking stool samples and its preparation also complicate the route to obtaining right results [10].

Taking all the above mentioned points into account, this study was designed to examine the relations between PPI use and the complications that might arise from the Clostridium Difficile in a more objective manner.

To this end, the study was carried out through serum Clostridium Difficile toxin A, B antigen measurement, which is hypothesed that the more reliable method with less procedure in sample taking and with less risk of contamination, of the young adult patients using PPI for LFR treatment with no other additional health problems.

## Material and Method

The consent of the Ufuk University Medical School's Board of Ethics for Clinical Trials was obtained for the study.

The study covered 32 patients who presented to the Ear, Nose and Throat Clinic with complaints of reflux and who were diagnosed with Laryngopharyngeal reflux following examination. Among those patients who presented to the clinic, the ones with systemic diseases and who were on constant medication were excluded from the study. Patients older than 55 years old were also excluded from the study for this purpose.

A total of 32 patients, 24 female (75%) and 8 male (25%), who had these characteristics were included in the study. The mean age of the patients was 34.13 ± 11.59.

For the standardization of the taking of serum samples, the fasting samples were taken from the patients in the morning and the samples were frozen at -80 degrees after centrifuged within an hour. All the samples were melted simultaneously and were studied.

### *The selection of patients*

The patients, who presented to the Ear, Nose and Throat Outpatient Clinic with complaints of LFR and whose RSI and RFS scores were over 13 and 7 respectively, were evaluated. An informed consent form was taken from each patient.

Utmost attention was paid to the fact that these patients did not have any systemic diseases (diabetes mellitus, hypertension, and asthma), any acute or chronic infective inflammatory diseases, and any history of constant medication use (theophylline, nitrate, anticholinergics, calcium channel blockers, oral contraceptives, etc). Patients suggested to have malignity were also excluded from the study.

### *PPI treatment*

All the patients included in the study were administered Lansoprazole 30 mg tablets perorally before the meals and twice a day for treatment. Each patient was examined twice before and after the three-month treatment. The patients were asked to complete the 9-item RSI questionnaire before each examination (Table 1). In order to calculate the Laryngeal Finding Scores, the indirect laryngoscopy images were recorded with a 90º rigid 5.8 mm Hopkins Telescope (Carl Storz Germany). The indirect laryngoscopy was performed by a single physician in order to obtain standardization. An otolaryngologist evaluated the indirect laryngoscopy images without knowing the process

Table 1. The Reflux Symptom Index ( RSI).

| Within the last month, how did the following problems affect you? | 0: No problem; 5: Severe problem. | | | | | |
|---|---|---|---|---|---|---|
| Hoarseness or a problem with your voice | 0 | 1 | 2 | 3 | 4 | 5 |
| The need to clear your throat | 0 | 1 | 2 | 3 | 4 | 5 |
| Excess throat mucus or postnasal drip | 0 | 1 | 2 | 3 | 4 | 5 |
| Difficulty swallowing food, liquids, or pills | 0 | 1 | 2 | 3 | 4 | 5 |
| Coughing after you ate or after lying down | 0 | 1 | 2 | 3 | 4 | 5 |
| Breathing difficulties or choking episodes | 0 | 1 | 2 | 3 | 4 | 5 |
| Troublesome or annoying cough | 0 | 1 | 2 | 3 | 4 | 5 |
| Sensations of something sticking in your throat or a lump in your throat | 0 | 1 | 2 | 3 | 4 | 5 |
| Heartburn, chest pain, or stomach acid coming up | 0 | 1 | 2 | 3 | 4 | 5 |

of diagnosis and treatment, and the endoscopic findings were scored (Table 2).

Table 2. The Reflux Finding Score (RFS).

| Reflux Finding Score | |
|---|---|
| Pseudosulcus ( Infraglottic edema) | 0 Absent |
| | 2 Present |
| Ventricular Obliteration | 0 Absent |
| | 2 Partial |
| | 4 Complete |
| Erythema-Hyperemia | 0 Absent |
| | 2 Aritenoids only |
| | 4 Diffuse |
| VC Edema | 0 Absent |
| | 1 Mild |
| | 2 Moderate |
| | 3 Severe |
| | 4 Polypoid |
| Diffuse Laryngeal Edema | 0 Absent |
| | 1 Mild |
| | 2 Moderate |
| | 3 Severe |
| | 4 Obstructing |
| Posterior Commissure Hypertrophy | 0 Absent |
| | 1 Mild |
| | 2 Moderate |
| | 3 Severe |
| | 4 Obstructing |
| Granulation | 0 Absent |
| | 2 Present |
| Thick Endolaryngeal Mucus | 0 Absent |
| | 2 Present |
| Total | |

*The evaluation of serum samples*

The white blood cell count, CRP, and sedimentation results of all the patients were evaluated by obtaining the fasting serum samples of all patients included in the study before the PPI treatment and at the end of the three-months treatment. The serum Clostridium Difficile toxin A, B measurement was carried out in the serum sample with the GA Generic Assays GmbH kit (Dahlewitz, Germany) that works with the ELISA (enzyme-linked immunosorbent assay) principle. The kit was adapted to the Dynex equipment (DSX 5.18 ELISA-USA) for the serum Clostridium Difficile toxin A, B measurements.

*Statistics*

All the collected data were transferred to the PASW (Predictive Analytics Software) Statistics 18.0 program. The Kolmogorov-Smirnov Normality Test was used to evaluate whether the data were distributed normally. The Pearson correlation coefficient was used to determine the intergroup relationship level. The Paired Samples T analysis was used for the comparison of results obtained before and after three-month of treatment for the data covering two groups.

**Results**

The Pearson correlation coefficients were calculated for the pre and post-treatment RSI (r=0.46) and RFS (r=0.67) values and it was seen that there was a statistically significant positive correlation among the data (p<0.05). The pre-treatment RSI values were minimum 14.00, maximum 29.00, and the mean value was 20.81±4.05, while post-treatment values were minimum 0.00, maximum 8.00, the mean value was 3.41±2.37. The pre-treatment RFS values were minimum 8.00, maximum 21.00, and the mean value was 13.31±3.30, while the post-treatment values were minimum 0.00, maximum 8.00, and the mean value was 1.50±1.88 (Table 3).

The Kolmogorov-Smirnov Test showed that the RSI and RFS data had a normal distribution. The Paired Samples T Test was conducted in order to determine whether there was a difference between the pre and post-test scores since the data had normal distribution. Consequently, it was seen that there was a significant difference between the scores (p<0.05) (Table 3).

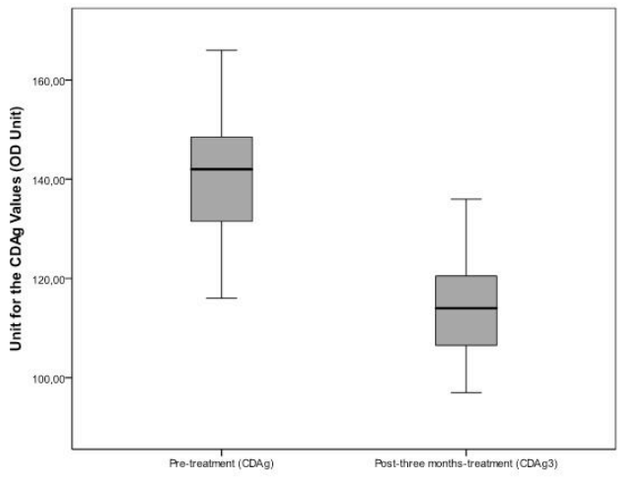
Table 3. Values of RSI, RFS, WBC, CRP and CDAg before treatment and after three month of treatment. (RSI: Pre-treatment Reflux Symptom Index, RSI3: Reflux Symptom Index after the three-month treatment, RFS: Pre-treatment Reflux Finding Score, RBS3: Reflux Finding Score after the three-month treatment, WBC: Pre-treatment serum white blood cell count, WBC3: Serum white blood cell count after the three-month treatment, CRP: Pre-treatment serum CRP value, CRP3: Serum CRP value after the three-month treatment, CDAg: Pre-treatment serum Clostridium Difficile antigen value, CDAg3: Serum Clostridium Difficile antigen value after the three-month treatment).

| | N | Minimum | Maximum | Mean±SS | p value |
|---|---|---|---|---|---|
| RSI | 32 | 14.00 | 29.00 | 20.81±4.05 | 0.000 |
| RSI3 | 32 | 0.00 | 8.00 | 3.41±2.37 | |
| RFS | 32 | 8.00 | 21.00 | 13.31±3.30 | 0.000 |
| RFS3 | 32 | 0.00 | 8.00 | 1.50±1.88 | |
| WBC | 32 | 4.60 | 10.70 | 7.62±1.66 | 0.012 |
| WBC3 | 32 | 5.00 | 11.00 | 8.06±1.48 | |
| CRP | 32 | 0.80 | 4.00 | 2.25±0.78 | 0.000 |
| CRP3 | 32 | 1.00 | 5.70 | 3.42±1.26 | |
| CDAg | 32 | 116.00 | 166.00 | 140.56±11.74 | 0.000 |
| CDAg3 | 32 | 97.00 | 136.00 | 114.94±10.70 | |

The Kolmogorov-Smirnov Test also showed that data about the pre and post-treatment Clostridium Difficile Ag values had normal distribution. The Paired Samples T Test was conducted in order to determine whether there was a difference between the pre and post-test scores since the data had normal distribution. It was pointed out that the post-treatment values were significantly lower than the pre-treatment values (p<0.05) (Graphic 1). The pre-treatment and the after the three-month treatment Clostridium Difficile Ag, WBC and CRP values were seen in Table 3.

The Kolmogorov-Smirnov Test showed that the data about the pre and post-treatment values had normal distribution. The Paired Samples T Test was conducted in order to determine whether there was a difference between the pre and post-test scores since the data had normal distribution. There was no statistically significant difference between pre and post-treatment regarding both values (p>0.05).

Graphic 1. The pre-treatment (CDAg) and post-three-months (CDAg3) treatment values of Clostridium Difficile Ag (p<0.05) (The unit for the CDAg values is OD Unit).




## Discussion

In literature the methods that are used to investigate Clostridium Difficile infections in patients using PPI are generally microbiological methods based on the analysis of stool. It is clear that these methods have some possible disadvantages [11;12]. These possible disadvantages are listed as follows:

1.The difficulties that the patient may come across during stool collection; the inability to have stool samples whenever wanted, the proper selection of stool, the proper collection of stool without outside contamination, and the delay in transport.

2. The difficulties in the selection of the appropriate material because of structures like mucus, indigested food, and cellular remains that form the stool content, the difficulties in the process of the extraction of stool.

3. The possibility that the Clostridium difficile antigen in the stool may have cross reactions with the other flora in the gastrointestinal system or with the antigens belonging to the microorganisms that show pathogenity at that moment.

4. The fact that changes may take place in the normal antigenic content of the intestinal structure because of cancer, ulcer, inflammatory intestinal diseases, enteropathies, etc. and the fact that many similar antigenic structures may appear.

5. The possible formation of similar antigenic determinants by food and food additives.

The fact that stool pH may change according to the type of the food consumed and the fact that this may affect the results of the test.

The possibility that changes in the intestinal wall and content may take place because of food sensitivity which is seen to be on the rise in the society.

The listed error sources may further increase if the multiple diseases and the related increased number of medication for older patients is taken into consideration.

It is clear that the evaluations based on the stool antigen determination for patients treated with PPI may mislead physicians because of the above listed factors. This is the reason why we used serum Clostridium Difficile antigen determination which is a relatively independent evaluation method than the above mentioned factors.

Many studies in the literature reported Clostridium Difficile related complications in patients using PPI. On the other hand, it is known that in most of these studies the patients who had complications were elderly patients in poor health and that they also had systemic diseases thus were using multiple medications affecting the gastrointestinal bacterial flora including the antibiotics [13; 14]. The fact that our study covers healthy young adult patients with a mean age of 34.13 ± 11.59 and the fact that these patients had no additional systemic diseases, so there were not any additional medication that differentiate this study from many other studies.

Studies in the literature reported that the patients who were seen to have elevated antigen levels in stool samples and who had complications administered 20 to 60 mg doses of PPI [15]. In our study, the daily therapeutic dose of the patients with LFR was set at 60 mg in line with literature. None of our patients had symptoms like fever, nausea, vomiting, abdominal pain, and diarrhea which might have been signs of infection during our study. Moreover, there were no changes in the CRP and white blood cell counts.

It is also known that the conditions of patients who had elevated levels of antigen in stool and who had complications were also related to long-term PPI use [16]. In our study, the initial treatment period for LFR patients was set to 90 days in line with literature upon the diagnosis of the disease. According to our results, in order to understand whether the significant decrease obtained in the serum Clostridium Difficile antigen after a 3-month treatment period, which can be considered to be fairly short, will change or not with the prolongation of the treatment, the evaluations need to be repeated with longer periods of use.

As a result, it is hard to establish the appropriate conditions for the detection of Clostridium Difficile antigen in stool and this situation makes it hard to obtain healthy results. Evaluations done in serum, on the other hand, are independent of all these external factors. We believe that healthier results will be obtained when the blood samples taken in proper conditions are analyzed with standardized laboratory equipment in proper conditions.

Moreover, according to our results, patients using proton-pump inhibitors had statistically significant decreases in their Clostridium difficile toxin A, B serum ag levels. This result points out to a decrease in the serum toxin A and B ag level, or in other words signifies a decrease in the transition of the bacterium from its spore form to the germinative phase, in contrast to the studies which argued that the Clostridium spores show germination in relation to the decrease in acidity in the gastric environment [17-21]. Further, no GIS disease or infection was detected in the investigation of the patients using PPI following the medication and no laboratory finding (WBC, CRP, etc.) was obtained which showed this.

It should be pointed out here that all of the findings we obtained were based on the effects of treatment with Lansaprasol 30 mg x 2 /day. So it is necessary to evaluate the effects of other medications which belong in PPI on the serum levels of Clostridium difficile toxin A, B .

Recent studies have also made us suspicious of the view that the changes that took place in the gastrointestinal system based on proton-pump inhibitors activated Clostridium difficiles

and therefore the bacteria became infective causing many complications [22-24]. However, we could not achieved any related article which evaluated in this subject to compare our results. Additionally, in the literature there were not any report studied the effects of PPI drugs on Clostridium difficile toxin A, B in the healthy young adults. All of the results on the reports which claimed that PPI treatment caused to Clostridium difficile enfections were studied on the complicated patients such as immunsupressive or that in the intensive care unites and the measurements were made on the stool specimens. But the most brilliant result on our patients were the higher pretreatment values of the Clostridium difficile toxin A, B were significantly decreased in the posttreatment periot. So, we can say here that, Lansaprasol is not have a side affects on gastrointestinal flora at least in partly that related in Clostridium difficile.

We believe that more comprehensive studies investigating the relationship between PPI and Clostridium difficile infection through simultaneously analyzing the serum and stool samples collected from healthy and non-hospitalized patients are needed.

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