ANADOLU ÜNİVERSİTESİ BİLİM VE TEKNOLOJİ DERGİSİ –C
Yaşam Bilimleri ve Biyoteknoloji

ANADOLU UNIVERSITY JOURNAL OF SCIENCE AND TECHNOLOGY –C
Life Sciences and Biotechnology
Cilt/Vol.: 2-Sayı/No: 2 : 75-87 (2012)

ARAŞTIRMA MAKALESİ /**RESEARCH ARTICLE**

EFFECT OF PANTOPRAZOL A PROTON PUMP INHIBITOR ON SMALL INTESTINAL PANETH CELLS

Orhan ÖZATİK [1], Firdevs GÜRER [2], Eser VARDARELİ [3]

ABSTRACT

In previous studies of proton pump inhibitors may have effects on systems other than the stomach has not been investigated sufficiently. Especially in patients treated in intensive care conditions and the resulting use of the mucosal immune system may be very important complication of a defect or failure might be the result does not have any work was done. Therefore, in our study, the mucosal immune system, which is one of the components of the cells on primarily paneth, proton pump inhibitors was to investigate the possible effects. For this purpose, 42 Wistar Albino rats, separated into six different groups. In addition, each H2 receptor blocker and proton pump inhibitor groups, with antibiotics given; the existence of bacteria in the environment and between paneth cells release antimicrobial agent relationship has been planned to be exposed. As a result of the histological examination with light microscope, pantoprazol to be effective on the small bowel paneth cells and thus a component of the mucosal immune system, antibiotic peptides that block degranulation was found. This effect, the close enteroendocrine cells, mast cells and leukocytes of lamina propria of ileum also directly or indirectly affect.

Our findings generally common knowledge, pantoprazol outside gastric parietal cell proton pump containing cells was also thought to influence. In conclusion our study results show that paneth cell secretion activities in both groups were not needed are corroborative with the fact that mucosal immunity potential can only be induced by microbial environment.

Keywords: Pantoprazole, Mucosal immunity, Paneth cells, Enterochromaffin cells, Mast cells, Globule and polymorphous leukocyte.

[1,] Eskişehir Osmangazi University, Medical Faculty, Department of Gynecology and Obstetric.
E-mail: orhanozatik@yahoo.com
[2,] Eskişehir Osmangazi University, Medical Faculty, Department of Histology and Embryology.
E-mail: fgurer26@hotmail.com
[3,] Acıbadem Kozyatağı Hastanesi, İnönü Caddesi, Okur Sokak, Kozyatağı İstanbul.
E-mail: eservardareli@yahoo.com

Recieved: 31 October 2011; **Revised:** 15 February 2012; **Accepted:** 28 February 2012

BİR PROTON POMPASI İNHİBİTÖRÜ OLAN PANTOPRAZOLUN İNCE BARSAK PANETH HÜCRELERİ ÜZERİNE ETKİSİ

ÖZ

Mide hastalıklarının tedavisinde kullanımı en yaygınlarından proton pompası inhibitörlerinin, midedeki pariyetal hücreler üzerine oldukça spesifik olduğu ve diğer dokulardaki proton pompaları üzerine etkilerinin olmadığı ileri sürülmektedir. Özellikle yoğun bakım şartlarında tedavi edilen hastalarda kullanılması ile ortaya çıkan çok önemli komplikasyonların, mide pH sının yükselmesi ile sekonder gelişen bakteri kolonizasyonundaki artmaya bağlı olabileceği öne sürülmüştür. Ancak bu komplikasyonların mukozal immün sistemde olabilecek bir defekt veya yetmezlik sonucu olabileceğine dair yapılmış herhangi bir çalışma bulunmamaktadır. Bu nedenle çalışmamızda, mukozal immün sistemin komponentlerinden biri olan paneth hücreleri üzerine, proton pompası inhibitörlerinin olası etkilerinin araştırılması amaçlandı. Ayrıca, antibiyotik uygulamaları ile ortamda bakterilerin bulunması ve paneth hücrelerinden antimikrobiyal madde salınımı arasında ilişkinin ortaya konması planlandı. Bu amaçla 42 adet Wistar Albino sıçan, altı ayrı gruba ayrılarak; ayrı gruplarda H_2 reseptör blokeri, proton pompası inhibitörü ve bu gruplardan her birinde, antibiyotik ile birlikte verildi. Işık mikroskop ile yapılan histolojik incelemeler sonucunda, pantoprazolün ince barsak paneth hücreleri üzerine etkili olduğu ve böylece mukozal immün sistemin bir komponenti olan antibiyotik peptitlerin degranülasyonunu engellediği saptandı. Mukozal direnci düşürecek bu etkinin; yakın konumlu enterokromafin hücreler, mast hücreleri ve ileum lamina propriası lökositlerini de dolaylı veya doğrudan etkilediği bulundu.

Genel yaygın bilgiye karşın, pantoprazolün mide pariyetal hücreleri dışındaki proton pompası içeren hücrelere de etkiyebileceği düşünüldü. Paneth hücrelerinde gözlenen etkinin, gerek barsak ve diğer mukozal savunma sistemlerine olası etkilerinin gerekse sistemik etkilerinin incelenebilmesi yolunda ileri çalışmalara öncülük edebileceği öngörüldü.

Anahtar Kelimeler: Pantoprazol, Mukozal immünite, Paneth hücreleri, Enterokromafin hücreler, Mast hücreleri, Polimorf nükleer ve globül lökositler.

1. INTRODUCTION

Nowadays, the most common gastrointestinal diseases are the gastric pathology. The cause of pathology in stomach diseases occurring due to various factors are mostly associated with the increase in stomach acid secretion (Peterson W.L., 1995). Excessive acid secretion from the stomach causes the most important predisposing factor of diseases that occur in the stomach such as ulcer and gastritis (Peterson W.L., 1995). The acid secretion in the stomach is provided by a proton pump from the parietal cells (Sachs G., et al. 1995).

Proton pump inhibitors are known to be quite effective for the control of gastric acid hyper secretion (Tang SJ., et al. 2002). Proton pump inhibitors are claimed to specifically inhibit the secretion of acid from the parietal cells. However, side effects such as diarrhea, headache, dizziness, pruritis and skin eruption can also be encountered during the use of these medications (Fitton A, and Wiseman L. 1996). These systemic side effects have led to speculations on the specific ness of the medications.

The proton pumps are not only special to cells that are in the gastrointestinal system. Despite existing to a high degree in parietal cells in the stomach, this system exists in nearly all the cells in our body. When the side effects of the medication are examined, it is suggested that it can have effects on other systems (Blandizzi C,, et al. 2000, Bliesath H, 1994, Fitton A, and Wiseman L. 1996). There are many defense

mechanisms in our body. One of these defense mechanisms is mucosal immune system. The paneth cells residing in the small intestine are also a part of this mucosal immune system. The paneth cells are located in the small intestine cryptal. A recent hypothesis claims that the antibiotic peptides are one of the components of mucosal immunity (Ouellette A.J. 1999).

As is known in enteroendocrine intestinal cells, gastrin, somatostatin, secreted peptides such as enteroglucagon and generally includes Lieberkühn crypts (Özbek E,and Eşrefoğlu M. 1999). Enterochromaffin-like cell and enterochromaffin cells (EC cells) are also considered enteroendocrine cells. Enterochromaffin-like cells or ECL cells are a type of neuroendocrine cells found in the gastric glands. Embryologically, the EC cells are derived from the neural crest, a group of migratory cells derived from the ectoderm. Group of basal granular cells of the gut whose granules stain readily with silver and chromium salts. In the past, not stained with haematoxylin and eosin method of Lieberkühn crypts, but especially in the bottom section of paneth cells scattered among the individual, light-colored cytoplasm, large, rotund or oval-shaped cells that enteroendocrine cells were confirmed by silver stain, has been reported (Özbek E., and Eşrefoğlu M. 1999).

The cells secrete serotonin, substance p, and enkephalins. There are three types: gastric (antral mucosa), duodenal, and intestinal. Its location within glands at the base of intestinal crypts and its basal extensions projecting into adjacent glands attest to its local regulatory role. For example, Serotonin [5-hydroxytryptamine (5-HT)] is synthesized in the ileal EC cells (Kidd M., et al. 2006). The other cells responsible for mucosal immunity in the intestine are globule and polymorphonuclear leukocytes.

This study was planned to determine the possible effects of proton pump inhibitors on primarily to paneth cells, enterochromaffin cells (EC cells), mast cells, globule and polymorphous leukocyte.

MATERIALS AND METHODS

42 Wistar Albino rats were used in the study. The rats were divided into 6 separate groups and in each group 7 rats were included in the experiment. H2 receptor blocker and proton pump inhibitor was administered in separate groups to rats contained in the experiment groups. Sub-groups to which antibiotics were administered were also formed under each of these groups. The aim of administering the antibiotics was to determine the association between the existence of bacteria in the medium and secretion of antimicrobial substance from the paneth cells. The administration of H2 receptor blocker was due to the absence of any effect on sepsis related death incidence as a result of usage on intensive care patients and because it basic environment acidity. Moreover, comparison of it with proton pump inhibitors was aimed.

Only intra peritoneal normal saline was applied to the rats in the 1st group for duration of seven days and they were sacrificed by ether anesthesia at the end of the 7th day. Since there was a direct proportion between the bacterial agents present in the medium and the secretion from paneth cells, feces culture was obtained from all the rats in all of the groups as well as the control group.

5 mg/kg dose of H2 receptor blocker (Ulcuran®) was administered intra peritoneal for seven days to the rats in the 2nd group and their feces culture was obtained after they were sacrificed.

Proton pump inhibitor (Pantoprazol-Pantpas®) at a dose of 1 mg/kg was administered intra peritoneal for seven days to the rats in the 3rd group. Their feces culture was obtained after they were sacrificed.

Ciprofloxacin (Cipro®) at a dose of 30mg/kg administered intra peritoneal for seven days to the rats in the 4th group. The intestine flora was attempted to be eliminated through the administration of antibiotics. Their feces culture was obtained after they were sacrificed.

H2 receptor blocker (Ulcuran®) at a dose of 5 mg/kg and Ciprofloxacin (Cipro®) at a dose of 30mg/kg was administered intra peritoneal for seven days to the rats in the 5th group. Their feces culture was obtained after they were sacrificed.

Proton pump inhibitor (Pantoprazol-Pantpas®) at a dose of 1 mg/kg and Ciprofloxacin (CiproR) at a dose of 30mg/kg was administered intra peritoneal for seven days to the rats in the 6th group. Their feces culture was obtained after they were sacrificed. One centimeter away to ceacum from the distal ileum tissues was fix-

ating using 10% formalin solution. The 3µm paraffin sections were stained with Haematoxylin and Eosin, Grimelius silver staining, Masson Trichrome with Aniline blue, May Grunwald Giemsa and Gram staining techniques. Olympus BH 2 models light microscope was used for examinations and micrographs.

Control and experimental group and the applications are as outlined in Table 1.

Examining the morphological characteristics of cells of Paneth cells, consider whether, from base amount that they contain granules. They or their secretion granules have reduced the number of granules identified; irregular and short paneth cells were evaluated as degranulated. Completely filled with granular cytoplasm, uniform pyramidal shaped and basal nuclei were evaluated as granule cells paneth. Amount of paneth cells were determined contained a number in one crypt and rates were determined accordingly. Enterochromaffin cells counts and evaluation was defined, semi-quantitative number and content of enterochromaffin granule cells compared to control group as normal or increased/decreased in crypts. Polymorphonuclear and globule leukocyte increased in number or as a normal course were held to assess. Mast cells are granulated and the control group was evaluated according to the number semi-quantitative. Cocci and bacilli found in the crypt lumen, crypt lumens were evaluated according to the intensity.

RESULTS

Since the mucosal immune system has a fairly complex structure consisting of elements which operate in cooperation with each other, in our study in which EC cells, mast cells and polymorphonuclear and globule leukocyte as well as paneth cells were examined, histological significant differences were determined during the examination of histologic sections belonging to control group and experiment groups. This purpose the secretory cells of distal ileum glands of rat were compared, using Haematoxylin-Eosin and Aniline Blue, Masson Trichrome, May Grunwald Giemsa and Gram stain techniques staining techniques. Enterochromaffin cells (EC cells) were stained chromaffin-like in histologic sections, which are characterized by Grimelius silver staining. Feces cultures from all of the rats were obtained in addition to histological examinations and as a result of the performed cultures E.coli was determined not to reproduce in any of the groups to which antibiotics were administered. It was found that in all of the other groups 100% E.coli reproduced.

As a result of histological examinations carried out on the distal ileum of control group (Group 1) rats, it was observed that nearly all of the paneth cells were found completely full with granules (Figure 1). The ratio of granulated cells over total cells was around 75%. The degranulated cells were determined to be around 25%. The coccus and bacilluses observed in crypt lumen were determined as +. 100% E.Coli reproduced in cultures that were obtained from the feces (Table 2).

It was observed from the examination carried out on the histologic sections obtained from the rats included in the group to which H2 receptor blocker (Group 2) was administered that paneth cells discharged their granules significantly; even more, there was no granule left within the paneth cells in some crypts and those cells were completely degranulated (Figure 2). Morphological differences in accordance with secreting cell characteristics were also observed. In mast cells and polymorphonuclear leukocytes a different feature has not been determined as compared with the control group. However, the number of EC cells and globule leukocytes of increasing the number of granules was seen. Abundant globule leucocytes and extra cellular granules were also seen in addition to intracellular granules. The coccus and bacillus amount found in the crypt is more when compared to the control group. 100% E.coli reproduced in cultures obtained from the feces (Table 2).

Table 1. Control and experimental groups and the applications.

GROUPS	MEDICATION USED	STAIN APPLIED	FECES CULTURE
Group 1 control	Intra peritoneal normal saline	H&E, May Grunwald Giemsa, MT, Gram, Grimelius	Done
Group 2	Intra peritoneal H2 receptor blocker	H&E, May Grunwald Giemsa, MT, Gram, Grimelius	Done
Group 3	Intra peritoneal proton pump inhibitor	H&E, May Grunwald Giemsa, MT, Gram, Grimelius	Done
Group 4	Intra peritoneal ciprofloxacin	H&E, May Grunwald Giemsa, MT, Gram, Grimelius	Done
Group 5	Intra peritoneal H2 rec. bl.+ ciproflox	H&E, May Grunwald Giemsa, MT, Gram, Grimelius	Done
Group 6	Intra peritoneal PPI + ciprofloxacin	H&E, May Grunwald Giemsa, MT, Gram, Grimelius	Done

PPI: proton pump inhibitor H&E: Haematoxylin Eosin MT: Masson Trichrome

Table 2. Microbiological and histological findings according to the experimental group.

Experiment Group	**Paneth Characteristic**	**Feces Culture**	**Coccus and Bacillus**	**PMNL Characteristic**	**ECC Characteristic**	**Mast Cell Characteristic**
Group1: Control group	%75 Granulated	E. Coli	+	+	++	+
Group 2: H2Receptor Blocker	Degranulated	E. Coli	++	+	+++	+
Group 3: PPI	Granulated	E. Coli	+++	+	+++	+
Group4: Antibiotics	Granulated	No Reproduction	None	+	+	+
Group 5: PPI+ Antibiotics	Granulated	No Reproduction	None	++	+	+
Group 6: H2 Receptor Blocker +Antibiotics	Granulated	No Reproduction	None	+	+/++	+
+:low ++:average +++:high PPI:Proton Pump Inhibitor						

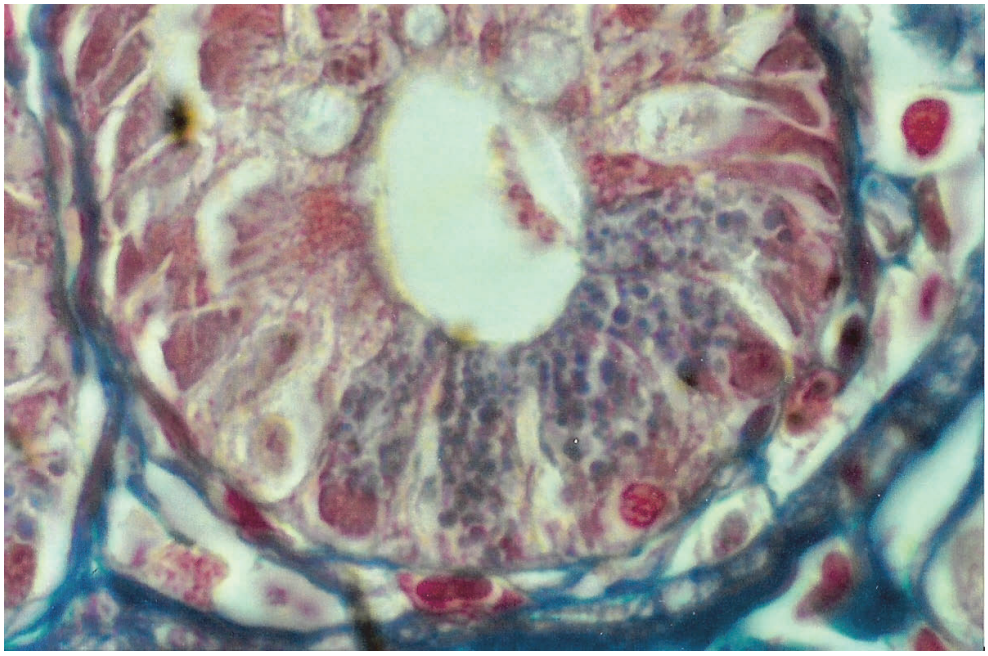

Figure 1. Light microscopic micrograph of control group showing the Paneth cells were stained a dark purple and nearly all granulated in this group. Masson Trichrome with Aniline blue staining. Original magnification X 500.

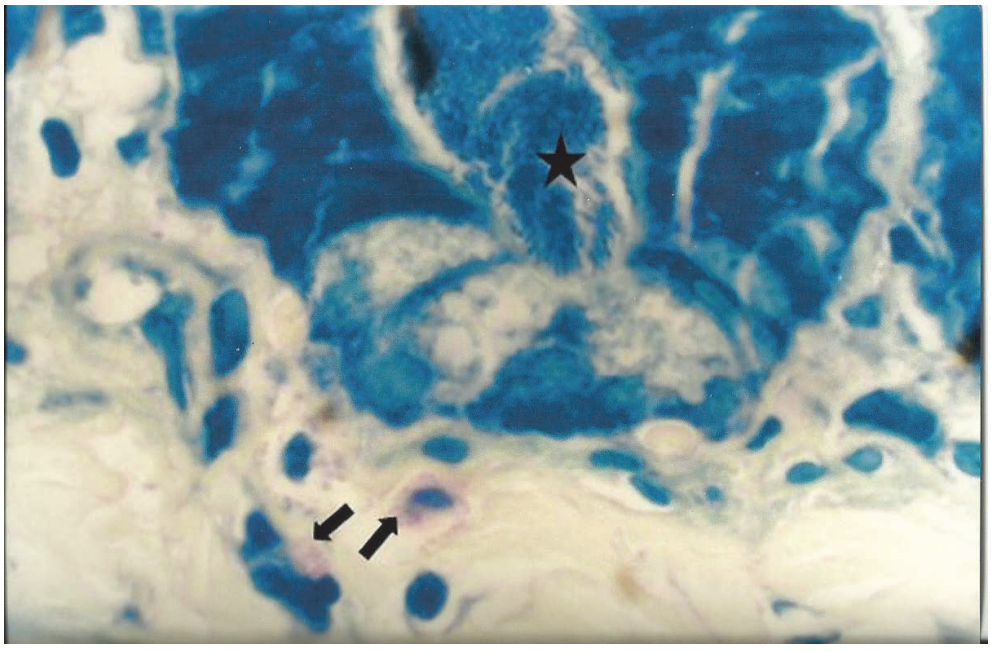

Figure 2. This light microscopic micrograph shows the Paneth cells release induced by H2 receptor blocker. The Paneth cells discharged their granules significantly; even more, there was no granule left within the paneth cells in some crypts and those cells were completely degranulated. Abundant globule leucocytes and extra cellular granules (arrows) were also seen in addition to intracellular granules. The coccus and bacillus amount found in the crypt (*) is more when compared to the control group. May Grunwald Giemsa. Original magnification X 500.

Nearly all of the paneth cells were determined to be full of granules (Figure 3) at the histological examination of histologic sections obtained from the rats included in the group to which proton pump inhibitor (Group 3) was administered. In the proton pump inhibitor group, globule leukocytes were found abundant than H2 receptor blocker group. The number of EC cells and granule content, and also extracelluler exocytose were found increased (Figure 4). The coccus and bacilluses observed in the crypt were considered to increase quite a lot when compared to the group to which H2 receptor blocker was administered (Figure 2 and 3). 100% E.coli reproduced in cultures obtained from the feces of the rats (Table 2).

When the histologic sections that were obtained from the rats in the group to which ciprofloxacin group antibiotics (Group 4) have been administered were examined, it was determined that paneth cells completely granulated. There was no coccus or bacillus in the crypt lumen (Figure 5). E.Coli did not reproduce in cultures obtained from the feces of the rats (Table 2).

As a result of examination of the histologic sections which were obtained from the rats in the group that proton pump inhibitor and antibiotics (Group 5) were administered to, it was determined that the morphological structure and granules of paneth cells carried nearly the same characteristics of those in the group that only proton pump inhibitor was given and in the group that only antibiotics were administered. Approximately 20% ratio of degranulated paneth cells were found only in the histologic sections which was obtained from the 2nd animal of this group. It was observed that paneth cells have been completely granulated in the histologic sections which were obtained from other animals. Coccus and bacillus images were not found in the crypts. E.coli did not reproduce in the feces cultures that were performed (Table 2).

As a result of the examination of the histologic sections which were obtained from the rats in the group that antibiotics were given in addition to H2 receptor blocker (Group 6), paneth cells was seen to have a granulated structure. Coccus or bacillus was not seen in the crypt. E. coli did not reproduce in the feces cultures that were tested (Table 2).

The similar numbers mast cells and granulated feature were found in PPI, H2 and antibiotic groups with control group (Figure 6a-b).

DISCUSSION

Proton pump inhibitors which are the one of the most important medicines that are used in the treatment of gastrointestinal diseases, have made a significant progress in the last 20 years and quite a lot of its different molecular forms have been released to the market. Its effect mechanism is based on the inhibition of the proton pumps on parietal cells in the stomach and prevention of acid secretion.

As it is known, most of the cells in body function and maintain their lives through the proton pumps on cell membranes. Many secretion functions are also performed by this way. There are defense systems in all creatures in order to protect body from pathogen factors that might come from outside. These defense systems consist of a lot of components. Mucosal immune system is the one of these important defense systems. Paneth cells residing in small intestine are important components of mucosal immunity as well.

In the treatment of gastric disease, the acid secretion from parietal cells revealed that the pathological problems that eliminate the use of the most common ones, are proton pump inhibitors. For this reason, proton pump inhibitor in the experimental group, which is one of three groups Pantoprazole, was used in our study. Control purposes in the Group two and Group six was working with the H2 receptor blocker. Our findings from control group had shown that paneth cells contribute to mucosal immunity by giving their granules into crypt. This is also in compliance with previous studies.

Paneth cells in the proton pump inhibitor group they are filled with granules were detected. Globule leukocytes were found abundant than H2 receptor blocker group. The number of EC cells and granule content, and also extracelluler exocytose were found increased.

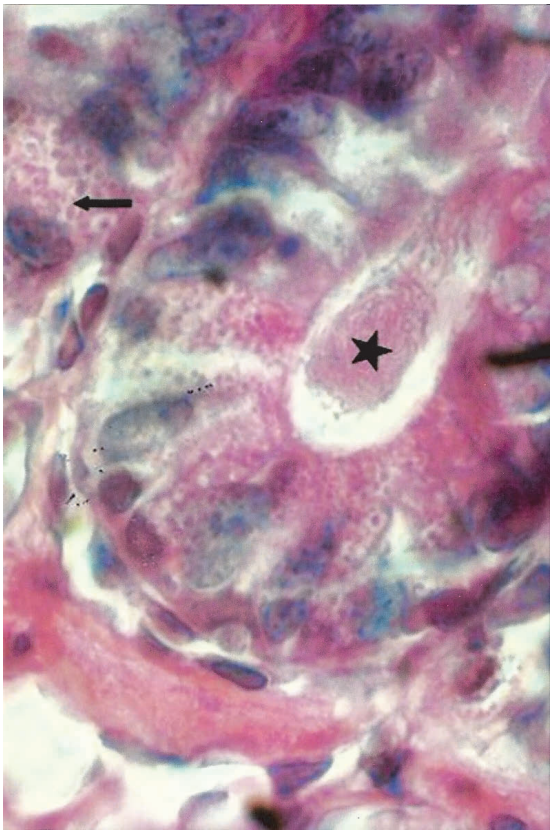

Figure 3. Light microscopic micrograph showing six Paneth cells and one globular leukocyte (arrow) in the proton pump inhibitor group. The Paneth cells were stained pink and nearly all granulated in this group were determined to be full of granules. The coccus and bacilluses observed in the crypt were considered to increase (*) quite a lot when compared to the group to which H2 receptor blocker. Haematoxylin and Eosin. Original magnification X 500.

Cocci and bacilli observed in the crypt of the control group and the H2 receptor blocker groups compared to the increased amounts were considered to be quite a lot. Received a 100% cultures of rat feces E. coli was produced.

In order for the paneth cells residing in small intestine releasing their granules to the environment, there must be a microbial stimulator. This information is verified by determining that the inside of the paneth cells are full of granules when an environment without flora is provided and intra peritoneal was applied as antibiotics in the study. Besides, no reproduction of E.coli in cultures that were performed shows the effectiveness of the process carried out. Our findings regarding no discharge of granules into crypt lumen by the paneth cells in the group that proton pump inhibitor was administered. The amount of coccus and bacillus in the crypt lumen was also observed to increase, support these data.

Observing no histological difference in the comparison of the group to which antibiotics in addition to H2 receptor blocker were administered to the group to which antibiotics in addition to proton pump inhibitors were given appears to be dependent on the elimination of the environment which would require the mucosal immune system to work more actively by the antibiotic which has been administered. The study results which show that paneth cell secretion activities in both groups were not needed are corroborative with the fact that mucosal immunity potential can only be induced by microbial environment.

In this work, the similar numbers mast cells and granulated feature were found in PPI, H2 and antibiotic groups with control group.

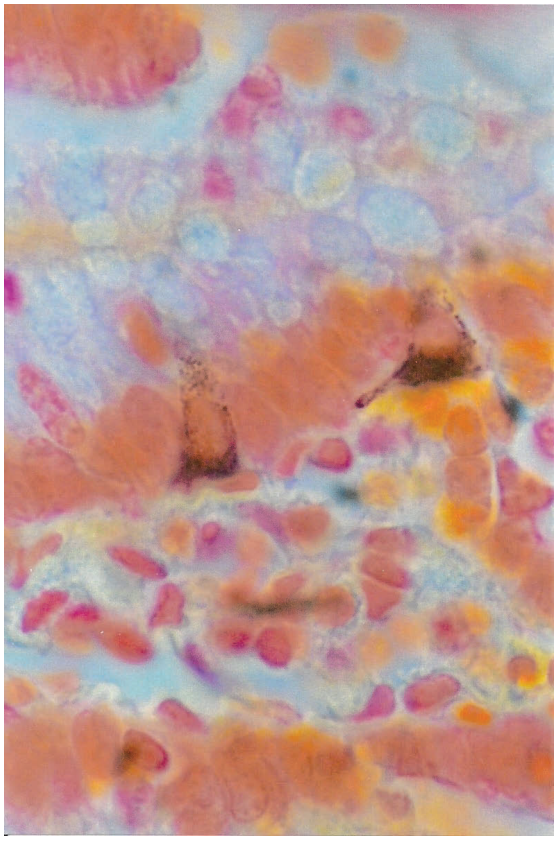

Figure 4. This silver stain micrograph demonstrates the effect of administrated Proton pump inhibitor on the enterochromaffin cells (EC cells) secretion (probably serotonin) which basal granules and apical exocytose granules stain readily with silver. EC cells which are located in the lower portions of ileal Lieberkühn crypts and have a broad base and a basal concentration of secretory granules. With sufficient resolution, these cells can sometimes be recognized in routine light microscopic preparations by their relatively pale cytoplasm with a broad base and a basal concentration of secretory vesicles. Grimelius silver staining. Original magnification X 500.

However, the ileal EC cells have increased the number and granule content, and also extracelluler exocytose made found in PPI group. At the same time the number of globule leukocytes has increased and the granule content is also an interesting in PPI group. On the one hand, recent data indicate that ileal enterochromaffin cells are the main source of serotonin (5-hydroxytryptamine) (Kidd M., et al. 2006, Schworer H., et al.1992). As is known that, serotonin secretion of the ileal EC cell is a key regulator of intestinal secretion and motility. Serotonin increases suggest that it may be of clinical relevance in a number of gastrointestinal problems including diarrhea, motility abnormalities, and irritable bowel syndrome (Kidd M. Et al. 2006).

On the other hand, visceral hypersensitivity in the gastrointestinal system, intestinal mucosa, and altered receptor sensitivity in plexus myentericus may occur through, with mucosal inflammation, enteric nerves near degranulation of mast cells or increased serotonin activity may be possible, and probably with of the environment or the change in bacterial infection with increases. (Drossman DA., 2006).

In our present study, we present that PPI treatment may increased the release of serotonin, indicating a spontaneous neuronal excitatory input to the enterochromaffin cells. It is possible that proton pump inhibitors cause side effects such as diarrhea etc. (Drossman DA.,2006, Fitton A,and Wiseman L. 1996).

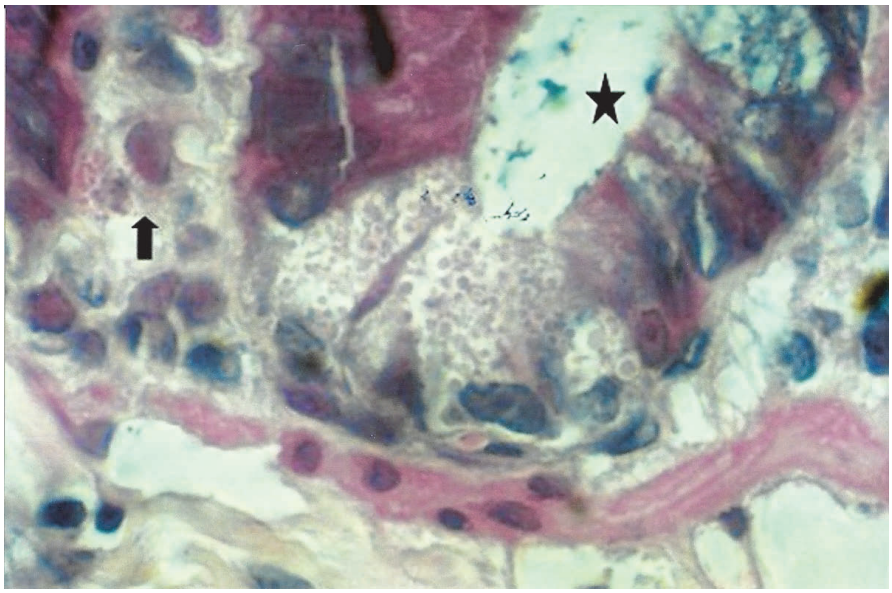

Figure 5. Light microscopic micrograph of the ileal Lieberkühn crypt from the rats in the ciprofloxacin group antibiotic showing four Paneth cells and one globular leukocyte (arrow). The Paneth cells completely granulated and located at the ends of ileal Lieberkühn crypt. There was no coccus or bacillus in the crypt lumen (*). Haematoxylin and Eosin. Original magnification X 500.

In addition, our results provide an opportunity to assess the potential role of the EC cells in diseases of unsolved mechanism well such as irritable bowel syndrome (Kidd M. Et al.2006).

Especially in patients treated in intensive care conditions and use of important complications may be the result might be a defect or failure in mucosal immune system which is possible effects of proton pump inhibitors also to all the other cells in the organism besides parietal cells, as it is seen in paneth cells and enterochromaffin cells. Since such compensations result from the paneth cell inhibitions, each factor which can affect the functions of paneth cells might constitute a predisposition for bad prognosis instances, primarily for endotoxic chocks. Proton pump inhibitors which we observed to inhibit paneth cell function would play a role in this predisposition. In addition, the serious complications which occur with the use of proton pump inhibitors in intensive care patients might not be only related to pH that increases in the gastroenterological system.

Consequently in this study which examines effects of proton pump inhibitors on small intestine paneth cells and other mucosal immune system cells, we have concluded that; paneth cells contribute mucosal immunity by giving their granules into the crypt and microbial stimulator is required for paneth cells to release their granules. On the other hand, the inhibitions in paneth cell defense system are compensated via stimulating other mucosal immunity elements which are EC cells, mast cells, globule and polymorphous leukocyte. Polymorphous nuclear leukocyte with antimicrobial peptide content and rat globule leukocyte that we believe to correspond to NK mononuclear leukocyte in humans as per the findings of our study function in small intestine lamina propria in this compensation.

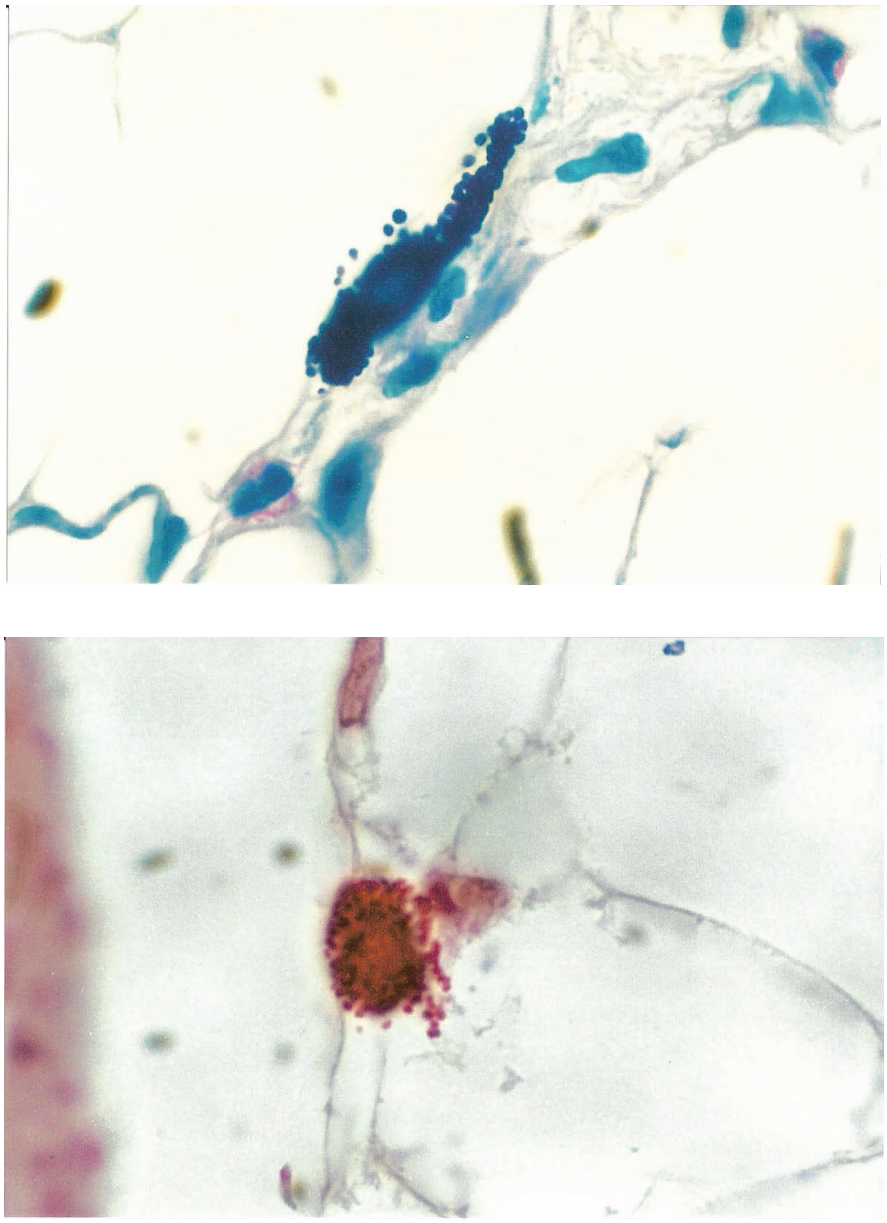

Figure 6 a-b. Light microscopic micrographs of mast cells with its typical granules. The similar numbers mast cells and granulated feature were found in all groups. a) May Grunwald Giemsa staining. Original magnification X 500. b) Gram staining. Original magnification X 500.

REFERENCES

Blandizzi, C., Natale, G. and Gherardi, G. (2000). Gastroprotective Effects of Pantoprazole Egaints Experimental Mucosal Damage. Fundamental Clinical Pharmacology 14, 89-99.

Bliesath, H., Huber, R. and Hartmann, M. (1994). Dose Linearity of The Pharmaco Kinetics of The New H/K ATPase Inhibitor Pantoprazole After Single Intravenous Administration. International Journal of Clinicial Pharmacology Ther.; 32(1), 44-50.

Drossman, D.A. (2006). Fonksiyonel Gastrointestinal Bozukluklar ve Roma III Süreci. *Gastroenterology Türkçe Baskı* 2, 135-51.

Fitton, A. and Wiseman, L. (1996). Pantoprazole Areview of its Pharmacological Properties and Therapeutic Use in Acid-Related Disorders. *Drugs* 51(3), 460-482.

Kidd, M., Modlin, I.M. and Eick, G.N. (2006). Isolation, functional characterization, and transcriptome of *Mastomys* ileal enterochromaffin cells. *American Journal of Physiology Gastrointestinal and Liver Physiology* 291(2), 778–91.

Özbek, E. and Eşrefoğlu, M. (1999). The structural and histochemical features of the glands within the duodenum of rabbit and the rat. *Turkish Journal of Gastroenterology* 10(2), 126-31.

Peterson, W.L. (1995). The Role of Acid in Upper Gastrointestinal Haemorrhage due to Ulcer and Stress-related Mucosal Damage. *Aliment Pharmacol Ther 9 Suppl* 1, 43-6.

Ouellette, A.J. (1999). Mucosal Immunity and Inflammation IV.Paneth Cell Antimicrobial Peptides and The Biology of The Mucosal Barrier. *American Journal of Physiology Gastrointestinal and Liver Physiology* 277(2), 257-261.

Sachs, G., Shin, J.M. and Briving, C. (1995). The Pharmacology of The Gastric Acid Pump: The H, K ATPase. *Annual Review Pharmacology and Toxicology* 35, 277-305.

Schworer, H., Katsoulis, S. and Racke, K. (1992). Histamine inhibits 5-hydroxytryptamine release from the porcine small intestine: Involvement of H3 receptors. *Gastroenterology* 102(6), 1906-12.

Tang, S.J., Nieto, J.M. and Jensen, D.M. (2002). The novel use of an intravenous Proton Pump Inhibitor in a patient with Short Bowel Syndrome. *Journal of Clinical Gastroenterol* 34(1), 62-3.