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The effects of ciprofloxacin and ursodeoxycholic acid on bacterial translocation in obstructive jaundice

Tıkanma sarılığında siprofloksasin ve ursodeoksikolik asidin bakteriyel translokasyon üzerine etkileri

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Background/aims: *We aimed to search the effects of two different drugs in bacterial translocation, both in combination and alone: ursodeoxycholic acid, the effectiveness of which was evidenced previously, and ciprofloxacin, which had not been used before, in an experimental obstructive jaundiced rat model.* ***Methods:*** *Fifty Wistar Albino rats were divided into five groups: sham group (A), control group (B), ciprofloxacin group (C), ursodeoxycholic acid group (D), and ciprofloxacin + ursodeoxycholic acid group (E). Except in Group A animals, the common bile ducts in all animals were ligated. Hematological, microbiological and histopathological changes were compared between the groups.* ***Results:*** *White blood cell counts were elevated in all common bile duct-ligated test subjects. The median white blood cell count in Group B was significantly higher than that in Group D and Group E (p=0.022 and p=0.037, respectively). There was no significant difference between the control group and the study groups in terms of biochemical changes. Blood cultures were negative in Group A and Group E. The positive blood culture rate in Group B was significantly higher than in Groups A and E (p<0.05). Positive mesenteric lymph node culture rate was significantly lower in Group E than in the control group (p=0.026). In the histopathological evaluation, there was no difference in the morphology of the terminal ileum between the groups, but Group E animals had significantly less inflammatory cells in the intestinal wall compared to Group C and D animals.* ***Conclusions:*** *Ciprofloxacin and ursodeoxycholic acid have a synergic effect on prevention of bacterial translocation in obstructive jaundice.*

Key words: Obstructive jaundice, bacterial translocation, ursodeoxycholic acid, ciprofloxacin

Amaç: *Tıkanma sarılığı oluşturulmuş rat modelinde, iki farklı ilacın, (etkinliği daha önce kanıtlanmış olan ursodeksikolik asit ve daha önce bu amaçla kullanılmamış olan siprofloksasinin) ayrı ayrı ve birlikte kullanımının bakteriyel translokasyon üzerine etkisini araştırmayı amaçladık.* ***Gereç ve Yöntem:*** *Elli adet Wistar albino rat beş gruba ayrıldı: Sham grubu (A), Kontrol grubu (B), siprofloksasin grubu (C), ursodeoksikolik asit grubu (D) ve siprofloksasin + ursodeoksikolik asit grubu (E). A grubu hariç tüm deneklerde ana safra kanalı bağlandı. Hematolojik, mikrobiyolojik ve histopatolojik değişiklikler gruplar arasında karşılaştırıldı.* ***Bulgular:*** *Kanda beyaz küre sayısı ana safra kanalı bağlanan tüm deneklerde yükseldi. Ortalama değer B grubunda, D ve E gruplarına göre anlamlı olarak yüksekti (p değeri sırası ile 0.022 ve 0.037). Biyokimyasal olarak kontrol grubu ile çalışma grupları arasında anlamlı fark yoktu. Kan kültürleri grup A ve grup E'de negatifti. Pozitif kan kültürü oranı B grubunda A ve E gruplarına göre anlamlı olarak yüksekti (p<0.05). Grup E'de pozitif mezenterik lenf nodu kültür oranı kontrol grubundan anlamlı olarak düşüktü (p=0.026). Histopatolojik değerlendirmede terminal ileum morfolojisi açısından gruplar arasında fark yoktu; ama intestinal duvardaki imflamatuvar hücre sayısı C ve D gruplarındaki hayvanlarda anlamlı olarak düşüktü.* ***Sonuç:*** *Siprofloksasin ve ursodeoksikolik asitin tıkanma sarılığında bakteriyel translokasyonu önlemede sinerjik etkisi vadır.*

Anahtar kelimeler: Tıkanma sarılığı, bakteriyel translokasyon, ursodeoksikolik asit, siprofloksasin

INTRODUCTION

Bacterial translocation is determined by the transition of living or dead bacteria and their toxic products through the liver, spleen, mesenteric lymph nodes, and systemic circulation after intestinal barrier function failure (1).

Cholestasis is the collection of bile in hepatic cells and bile trunks due to obstruction of bile flow through the intestine. Because of diminishing or ceasing bile flows to the intestine, the amount of the products eliminating via bile, increase in the blo-

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od. After obstruction in the bile tree, a series of pathologic changes occur in the organism. These are reticuloendothelial system function failure, immune system suppression, architectural and functional changes in intestinal mucosa, oxidative destruction on intestinal wall, diminishing of antibacterial and detergent function of bile salts due to failure of their enterohepatic circulation, bacteremia, and endotoxemia. After all of these changes, the intestinal barrier system corrupts and bacterial translocation occurs (2).

The bacterial balance in intestinal flora changes in favor of gram-negative bacterial overgrowth when bile salt deficiency occurs. Ursodeoxycholic acid (UDCA) has been shown to be effective in the prevention of bacterial translocation (3-6); however, the role of antibiotics in this issue has not been studied previously. Since ciprofloxacin is a very effective antibiotic on gram-negative bacteria, with a high oral bioavailability, we hypothesized that oral administration of this drug may reduce bacterial translocation in obstructive jaundice. We also aimed to compare the effects of ciprofloxacin and UDCA in bacterial translocation.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee and by the Scientific Research and Thesis Committee. Fifty Wistar Albino female rats weighing 240–280 g were divided into five groups (4 animals died during the study); all of the animals were fed by standard food and water for 10 days.

Group A (n=10): Sham Group: After laparotomy, the common bile duct (CBD) was found and dissected, and then the abdomen was closed. Animals were not given any additional drug. The sham group was composed to compare the anesthetic drug effects and possible contamination risks with the other groups and for standardization of the study.

Group B (n=9): Control Group: After laparotomy, the CBD was found and dissected and ligated using 4/0 silk, and then the abdomen was closed. Animals were not given any additional drug.

Group C (n=9): Ciprofloxacin Group: CBD ligations were carried out as with the control group. In this study group, 15 mg/kg/day oral ciprofloxacin (*Cipro®*, *Biofarma Ilac Sanayi ve Ticaret AS - Istanbul*) was given from the 4th to the 10th postoperative days.

Group D (n=9): UDCA Group: CBD-ligated rats were given 10 mg/kg/day oral UDCA (*Ursofalk®*, *Ali Raif Ilac Sanayi AS - Istanbul*) for 7 days (from the 4th to the 10th postoperative days).

Group E (n=9): UDCA+Ciprofloxacin Group: CBD-ligated rats were given 10 mg/kg/day oral UDCA and 15 mg/kg/day oral ciprofloxacin for 7 days (from the 4th to the 10th postoperative days).

All the animals were treated humanely according to the Declaration of Helsinki. After providing general anesthesia by administration of 50 mg/kg ketamine sodium (*Ketalar® Pfizer Ilac Sanayi Ltd. Sti. - Istanbul*) via intramuscular injection, hair covering the anterior abdominal wall was cut and sterilization of the surgical area was provided by povidone iodine solution. Median laparotomy was done. In the sham group, the CBD was found and dissected, the operation was terminated, and abdominal wall layers were closed with 4/0 silk sutures in anatomic plan. In the control and test groups, the CBD was ligated using 4/0 silk suture. After the operation, animals were put in a hot environment for recovering. Oral feeding began in the postoperative 6th hour.

Obstructive jaundice clinically began in the control group and test groups in a three-day period. UDCA 10 mg/kg/day and ciprofloxacin 15 mg/kg/day were weighted on a sensitive scale and were given in 2 mL serum physiologic via orogastric tube. On the 10th postoperative day, all animals were reoperated under general anesthesia: blood samples were collected from portal veins for blood culture; liver, spleen, and mesenteric lymph node samples were taken for bacteriologic studies; blood samples were collected from vena cava before sacrifice for biochemical and hematological measurements; and a terminal ileal segment was resected for histopathological evaluation.

Liver, spleen, and mesenteric lymph node samples were weighted on a sensitive scale and homogenized with 2 mL/g serum physiologic and then 0.01 mL were planted on blood agar and EMB agar cultures. For blood culture, 2 mL portal venous sample was put in Bactec® Plus (+) Aerobic/F (Becton, Dickinson and Company, Sparks, MD, USA) aerobic hemoculture bottle and then transported to Bactec 9050 Becton Dickinson® hemoculture system (Becton, Dickinson and Company, Sparks, MD, USA). All cultures were incubated in Heraeus® Function Line B6 incubator (Hanau, Germany) at 35-37°C for 24-48 h. In positive cultures, bacterial identification and gram specifications were obtained.

Beckman Coulter® Gen-S System (Beckman Coulter Diagnostic System Laboratories, Inc, Texas, USA) was used for hematological studies. For biochemical studies, the blood samples in siliconized tubes were centrifuged at 6500 rpm for 5 min and serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, and conjugated bilirubin levels were measured with Hitachi® P800 Automatic Analyzer system (Hitachi Co., Ltd., Tokyo, Japan) and UV photometric, colorimetric and enzymatic methods.

For histopathological examination, a 2 cm terminal ileal segment proximal to the ileocecal valve was resected. Terminal ileal samples were fixed in formol 10% solution tamponated for 3 h. After alcohol, acetone, xylene and paraffin procedures, they were blocked. Then 5 micron cuts were obtained from blocks and stained with hematoxylin-eosin. The preparations were evaluated under 40X and 10X optics in Olympus BX50® microscope (Olympus Optical Co., Ltd., Tokyo, Japan) and photographed with the microscopic camera. The number of villi in a 2 mm area was counted and the diameters (micron) of villi were measured. Inflammation (cell count in 10X enlarging optic), edema and mucosal necrosis were evaluated. The existence of intestinal edema was scored as the system described in the literature from 0 to 3 points: (No edema=0, mild edema=1, moderate edema=2, and severe edema=3) (7).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, USA). Whether the continuous variables were normally distributed or not was determined using Shapiro Wilk test. While continuous data were expressed as median (interquartile range [IQR]), nominal data were shown as frequency and (percentages). The differences among groups regarding continuous data were evaluated by Kruskal Wallis variance analysis. When the p-value from the Kruskal-Wallis test statistics was statistically significant, multiple comparison test was used to determine which groups differed from which others. Nominal data were analyzed by Pearson chi-square or Fisher's exact test, where applicable. A p value less than 0.05 was considered as statistically significant.

RESULTS

Hematological and Biochemical Analyses

The hematological and biochemical analyses are summarized in Table 1. The median white blood cell (WBC) count was significantly lower in Group A compared with the other groups (p=0.001). The median WBC count in Group B was significantly higher than those in Group D and Group E (p=0.022 and p=0.037, respectively). Total and

Table 1. Hematological and biochemical analyses

Variants	Group A	Group B	Group C	Group D	Group E	p
WBC (/mm³)	4950.0 (4225.0-6025.0)	17400.0† (10950.0-20050.0)	10400.0† (10000.0-13950.0)	7300.0†,‡ (6750.0-14500.0)	9000.0†,‡ (6450.0-17000.0)	<0.001[a]
Conjugated bilirubin (mg/dl)	0.02 (0.017-0.03)	4.2† (2.02-8.3)	6.7† (2.5-8.9)	6.7† (0.7-7.7)	2.3† (1.0-8.6)	<0.001[a]
Total bilirubin (mg/dl)	0.07 (0.06-0.09)	5.5† (3.2-9.7)	7.5† (3.8-10.6)	7.5† (1.3-9.3)	4.0† (2.1-10.7)	<0.001[a]
ALT (IU/L)	48.0 (43.0-57.0)	134.0† (119.0-137.5)	120.0† (88.0-189.0)	98.0† (82.0-162.0)	156.0† (93.5-205.0)	<0.001[a]
AST (IU/L)	125.5 (110.5-203.7)	587.0† (545.5-793.0)	537.0† (353.5-655.5)	497.0† (291.5-667.0)	648.0† (271.0-1052.5)	<0.001[a]
ALP (IU/L)	320.5 (221.0 -416.7)	796.0† (672.5-855.5)	982.0† (754.5-2435.0)	635.0† (564.0-843.5)	723.0† (648.5-1137.5)	<0.001[a]

Values are median (25-75 percentiles)
a Kruskal Wallis test
† The difference vs Group A is statistically significant (p<0.001)
‡ The difference vs Group B is statistically significant (p<0.05)

Table 2. Microbiologic analyses

Variants	Group A (n=10)	Group B (n=9)	Group C (n=9)	Group D (n=9)	Group E (n=9)	p[a]
Blood	0 (0%)	8 (88.9%)†,‡	5 (55.6%)†,‡	3 (33.3%)	0 (0%)	<0.001
Liver	0 (0%)	5 (55.6%)†	2 (22.2%)	4 (44.4%)†	1 (11.1%)	0.016
Spleen	0 (0%)	4 (44.4%)†	3 (33.3%)	3 (33.3%)	2 (22.2%)	0.092
MLN	0 (0%)	4 (44.4%)†,‡	1 (11.1%)	2 (22.2%)	0 (0%)	0.026

MLN: Mesenteric lymph node
a Pearson chi-square test
† The difference vs Group A is statistically significant (p<0.05)
‡ The difference vs Group E is statistically significant (p<0.05)

conjugated bilirubin, ALP, ALT and AST levels were elevated significantly in the test and control groups compared with the sham group (p=0.001).

Microbiologic Analyses

Results of microbiological analyses are shown in Table 2. Blood cultures were negative in Group A and Group E. Positive culture rates in Groups B, C and D were 88.9%, 55.6% and 33.3, respectively. *Escherichia coli* and *Enterococcus faecalis* were identified in Bactec® cultures at rates of 22.2% and 77.8%, respectively. The positive culture rate in Group B was significantly higher than those in Groups A and E (p<0.05). For Groups B, C, D and E, the microorganisms recovered from the liver, spleen and mesenteric lymph nodes were *E. coli* (31.4%), *E. faecalis* (60%), and other gram-negative enteric bacilli (*Klebsiella oxytoca, Enterobacter cloaca* and *Citrobacter freundii*) (8.6%). Positive rates of all tissue cultures of the control group were significantly higher compared with the Sham group (p<0.05). The only difference between test groups and the control group was noted in mesenteric lymph node cultures: positive culture rate was significantly lower in Group E compared with the control group (p=0.026).

Histopathological Analyses

Results of histopathological analyses are presented in Table 3. There was no significant difference between the groups with respect to the count and length of villi. For inflammatory cell count and edema scoring, the average of a randomly selected 20 areas on 10X augmentation was accepted for each preparation. Inflammatory cell count was significantly lower in the Sham group compared with Groups B, C and D (p=0.0106, p=0.0018 and p=0.0003, respectively). Group E animals had significantly less inflammatory cells compared with Group C and D animals (p<0.05). There was no difference between the groups regarding edema scoring.

DISCUSSION

Bacterial translocation is described as living or dead microorganisms and endotoxins passing over intestinal mucosal epithelium, then through the lamina propria and mesenteric lymph nodes and spreading to other tissues (1, 2, 8). It is believed that the disturbance of balance between intestinal microflora and the host defense mechanisms (mucosal barrier, immunologic defence, gastric acid, gastrointestinal motility) is the main factor affecting bacterial translocation (1, 3, 5, 8-12). Bile duct obstruction and cholestasis cause bacterial translocation via depression in intestinal barrier function, immune system deficiency and phagocytic mononuclear function damage (9, 11, 13-15). In an experimental study, Parks et al. (16) showed that there was elevation in bacterial translocation in blood, mesenteric lymph nodes, liver and spleen and also morphological changes in terminal ileum mucosa in test subjects one week after bile duct obstruction, when compared with the control group.

It has been shown that the cecal population of gram-negative bacteria is significantly increased in obstructive jaundice (14). Since this pathologic overgrowth is one of the factors responsible for bacterial translocation, in this study we used ciprofloxacin, which is an effective antibiotic against gram-negative bacteria, in order to decrease bacterial translocation. To compare their effects, we also gave animals UDCA, which has been shown to decrease cecal intraluminal bacterial content and bacterial translocation (4, 17), both in combination with ciprofloxacin and alone. In the groups in which we used ciprofloxacin or UDCA alone (Group C and Group D), the decreased bacterial translocation rate in blood cultures did not reach statistical significance. On the other hand, there was no growth in Group E, in which both were given in combination (p<0.001). Moreover, only in Group E, the positive mesenteric lymph node culture rate was significantly lower compared with

Table 3. Histopathological analyses

Variants	Group A	Group B	Group C	Group D	Group E	p[a]
Villus count	25 (19-28)	22 (19-25)	20 (18-27)	20 (17-24)	22 (19-30)	0.680
Villus length	540 (450-600)	420 (380-580)	480 (410-500)	440 (420-570)	500 (430-640)	0.468
Inflammatory cell count	60 (52-70)	70 (63-99)†	80 (69-91)†,‡	88 (71-110)†,‡	68 (45-80.5)	0.017
Edema	1 (1-2)	2 (1-2)	2 (1-3)	2 (1-3)	1 (1-2)	0.104

a Kruskal Wallis test
† The difference vs Group A is statistically significant ($p<0.05$)
‡ The difference vs Group E is statistically significant ($p<0.05$)

the control group. Furthermore, the decrease in the positive culture rates of the liver and spleen samples compared with the control group was more prominent in Group E compared with Groups C and D, although this decrease was not statistically significant. Therefore, we can say that ciprofloxacin and UDCA had a powerful additive effect on the prevention of bacterial translocation in obstructive jaundice.

In our study, the median WBC count was significantly higher in bile duct-ligated rats compared with the Sham group; it was significantly decreased in UDCA-given groups (Groups D and E) compared with the control group. Again, inflammatory cell count of the intestinal wall was found to be significantly decreased in Group E. Intestinal oxidative stress was claimed to be responsible for obstructive jaundice-induced gut barrier dysfunction (2). It has been shown that UDCA has antioxidative properties (18) and immunomodulatory effects by decreasing cytokine production (19). Ciprofloxacin, possibly by decreasing overgrowth of gram-negative bacilli, potentiated the antiinflammatory effect of UDCA in this study.

Kitani et al. (20) showed that after the administration of UDCA, severe regression occurred in microvesicular fatty changes of hepatocytes, and according to these changes, AST, ALT and gamma glutamyl transpeptidase (GGT) levels decreased in obstructive jaundice test groups. In our study, there were statistically significant elevations in AST, ALT, ALP, total bilirubin and conjugated bilirubin levels in obstructive jaundice test groups ($p<0.001$), but there was no difference in AST, ALT, GGT, ALP, total bilirubin and conjugated bilirubin levels between the test groups and the control group.

It is clear that bile has a trophic effect on intestinal mucosa and it induces the villus intensity and hypertrophy in the layers of the intestinal wall (2, 16). In in vitro studies, it was shown that bile salts start intestinal epithelial cell proliferation with a c-myc-dependent mechanism and protect intestinal mucosa against apoptotic cell death with NF-kappa ß activation (21). On the contrary, some studies found no effect of bile acids on histopathologic changes in the intestinal mucosa in obstructive jaundice (12, 17). The negative effects of obstructive jaundice on intestinal mucosal morphology (decrease in villus density and mucosal thickness) were shown in some former studies (2, 4, 16, 22). However, in our study, although villus counts and lengths were decreased in bile duct-ligated animals, and villus lengths were increased in the study groups compared to the control group, the differences did not reach significance, possibly due to the small sample size. Perhaps another shortcoming of this study was the caloric intakes of animals, which might have had effects on mucosal integrity and bacterial translocation; however, this was not monitored.

In conclusion, while ciprofloxacin and UDCA alone had no significant effect on bacterial translocation, when they were used in combination, bacterial translocation was significantly decreased in obstructive jaundiced rats. It can be proposed that while UDCA had a preventive effect on bacterial translocation from the intestinal lumen, ciprofloxacin targeted translocated bacteria and prevented the growth in secondary sites. However, to use them in clinical practice to decrease infective complications in obstructive jaundiced patients, further randomized clinical studies are needed.

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