Turk J Gastroenterol *2014; 25 (Suppl.-1): 86-91*

Effect of 3-aminobenzamide on perforation an experimental colitis model

Ebru Menekse[1], Sezai Aydın[2], Aylin Sepici Dinçel[3], Abdullah Eroğlu[1], Mete Dolapçı[4], Osman Yıldırım[1], Ömer Cengiz[1]
[1]Department of General Surgery, Adana Numune Training and Research Hospital, Adana, Turkey
[2]Department of General Surgery, Güven Hospital, Ankara, Turkey
[3]Department of Medical Biochemistry, Gazi University Faculty of Medicine, Ankara, Turkey
[4]Department of General Surgery, Hitit University Faculty of Medicine, Çorum, Turkey

Original Article

ABSTRACT

Background/Aims: The anti-inflammatory activity of 3-aminobenzamide (3-AB) has been shown via histopathology and immunohistochemistry in various colitis models. We aimed to study the effects of 3-AB on tissue mechanical endurance and, associatively, preventing perforation in colitis.

Materials and Methods: Thirty male Wistar albino rats were randomly divided into three groups. Rectal saline was administered to Group 1 (sham + saline). Rectal trinitrobenzensulphonic acid was applied to induce colitis in Group 2 (colitis + saline) and Group 3 (colitis + 3-AB). Groups 1 and 2 were treated intraperitoneally with saline (1 ml every 12 hours) and Group 3 was treated with 3-AB (10 mg/kg every 12 hours). After seven days, rats were sacrificed and colon lipid peroxidation levels, the serum tumor necrosis factor alpha (TNF-α) level, bowel bursting pressures, and bowel wall tensions were measured.

Results: Bowel bursting pressure in Group 2 was significantly lower than in Groups 1 and 3 ($p<0.001$ for both groups). Bowel wall tension in Group 2 was significantly lower than in Groups 1 and 3 ($p<0.001$ for both groups). There were no significant differences between groups for serum TNF-α levels. For lipid peroxidation, malondialdehyde (MDA) levels were increased in Groups 2 and 3 compared to Group 1.

Conclusion: 3-AB may aid prevention of perforations that develop in inflammatory bowel disease, requiring surgical treatment.

Keywords: Poly (ADP-ribose) polymerase/synthetase inhibitor, 3-aminobenzamide, colitis, inflammatory bowel disease

INTRODUCTION

The etiology of inflammatory bowel disease (IBD) is not fully known (1). The aim of current IBD treatment is to initiate and maintain disease remission and to promote recovery from secondary effects rather than healing underlying pathogenic mechanisms (2). IBD therapies attempt to achieve remission without steroids, to prevent complications, to reduce surgeries required after complications arise, and to prevent disease recurrence (3,4).

Spontaneous perforations are one complication arising from IBD that, though rare, may be fatal. The incidence of perforations in patients with IBD is approximately 2% (5,6).

Anti-inflammatory pharmacological agents are frequently used in the treatment of IBD. The anti-inflammatory activity of 3-aminobenzamide (3-AB), a poly (ADP-ribose) polymerase-1 (PARP-1) enzyme inhibitor, has been shown but the agent has not been utilized to treat IBD (7). Phase 1 and 2 clinical trials continue for various PARP inhibitor agents to treat solid tumors, cancers, and cardiovascular diseases (8).

The 3-AB agent is used in laboratory research as a PARP-1 inhibitor but has a low action potential and is nonspecific (7,9). PARP-1 is a nuclear protein that functions in DNA-repair. At the same time, it is caused in transcription of pro-inflammatory genes. Therefore; it consumes cellular energy, resulting in cell dysfunction and tissue necrosis. PARP-1 inhibition therefore has the potential to increase cytotoxicity of DNA damage-inducing anti-

Address for Correspondence: Ebru Menekşe, Department of General Surgery, Adana Numune Training and Research Hospital, Adana, Turkey
E-mail: drebrumenekse@gmail.com
Received: September 27, 2012 **Accepted:** February 25, 2013

cancer medications by blocking DNA repair, to reduce necrosis that factors into stroke or myocardial infarction, and to down-regulate many pathways of inflammation and tissue injury that cause conditions such as colitis and diabetic complications (8).

The effects of PARP inhibitors on colitis models were demonstrated histopathologically and immunohistochemically (10-13). However, considering that IBD etiology is not completely known and that PARP inhibitors have complicated mechanisms of action, the impacts of PARP inhibitors on clinical disease treatment remain unknown.

In our study, 3-AB was used as a therapeutic in a rat model of colitis induced by trinitrobenzensulphonic acid (TNBS). Bowel wall tension (BWT) and bursting pressure (BP) were evaluated to show the therapeutic and protective impact of 3-AB against perforations, which are a complication of IBD.

MATERIALS AND METHODS

This study was approved by the Ankara Training and Research Hospital Education, Planning, Coordination, and Ethic Committee and performed in accordance with the National Institutes of Health guidelines for the care and handling of animals.

Stabilization period for animals

Thirty male Wistar albino rats weighing between 250 and 300 grams were obtained from the Ankara Training and Research Hospital (Ankara, Turkey) for this study. Rats were divided into 3 groups of 10 animals each and held in 3 separate cages throughout the study with 12-hour light/dark cycles. Daily standard cage cleanings were performed. Rats in all groups were fed with standard fodder. Fodder was stopped and rats were given only water 24 hours before TNBS or saline were rectally administered.

Induction of colitis

An 80 mg dose of ketamine (Ketalar R, Flakon 50 mg/mL, Pfizer; Turkey) and 4 mg/kg of 2% xylazine (Rompun R, injection solution 23.32 mg/mL, Bayer; Turkey) were intramuscularly administered as a general anesthesia. Colitis was induced with 0.8 ml of 5% (40 mg) TNBS (Sigma Chemical Co; St. Louis, MO, USA) mixed with 0.4 ml of pure ethanol (GATA Biochemistry Laboratory, Ankara; Turkey) administered rectally (14).

The TNBS-ethanol mixture was slowly administered using a 0.7 mm diameter polyethylene catheter inserted 8 cm into the anus. Rats were held vertically for 30 seconds to allow the substance to spread on the colon surface (14).

Study design and protocol

Group 1 sham + saline (n=10), (1 mL saline injected intraperitoneally [i.p.] every 12 hours, 1.2 ml of saline rectally).

Group 2 colitis + saline (n=10), (1 mL saline, i.p. every 12 hours, 1.2 ml of TNBS-ethanol rectally).

Group 3 colitis + 3-AB (Sigma; St. Louis, MO, USA) (n=10), (10 mg/kg 3-AB, i.p. every 12 hours, 1.2 ml of TNBS ethanol rectally).

A dose of 10 mg/mL of 3-AB (Sigma; St.Louis, MO, USA) was procured in order to give to treatment group and protected at +4 ºC until the experiment.

Treatments were initiated 24 hours before induction of colitis (15) and continued for 7 days. Intraperitoneal injections were performed slowly with an insulin injector into the right, lower peritoneum.

Measurement of BP and BWT

General anesthesia was applied before euthanizing the animals by cervical dislocation at the end of the 7th day of the study. Laparotomy was conducted on each animal in the supine position with a median incision.

The colitis segment plus the healthy colon 2 cm proximal and distal to the colitis segment were removed from subjects in Groups 2 and 3 and a 6 cm rectal segment was removed from subjects in Group 1. Colitis was defined as colon segments with macroscopically visible mucosal focal hyperemia, ulceration, or thickened colon wall (16). The fecal content was removed both mechanically and with serum physiologic solution. Two catheters were inserted toward the lumen from the proximal and distal ends of the resected colon and the lumen was bound with a 0.0 silk suture over the catheter. Serum physiologic solution was introduced into the lumen from the proximal catheter at 2 ml/min using an infusion pump and a cannula with a one-way valve. A standard infusion pump was used to form intracolonic pressure, which was increased at a fixed speed. The pressure was monitored via a one-way valve placed distally. BP was measured using a monitor system (PETAŞ, KMA R 900 Ankara; Turkey).

The colon bursting moment was defined as the moment of a sudden pressure drop. The highest pressure at that moment was recorded as the colon bursting pressure. The bowel was then longitudinally opened, the colon wall circumference was measured from the region where the perforation developed, and the colon diameter was calculated. BWT was calculated according to Laplace's law.

BWT (dyn/cm)=K (1.33 x 10^3 dyn/cm^2/mmHg) x BP (mmHg) x diameter (cm) (14).

Biochemical analysis

Tissue malondialdehyde (MDA) levels as a marker of lipid peroxidation, which is related to colitis disease severity, were analyzed using the thiobarbituric acid reactive substances (TBARS) assay and the novel radical formation analysis method of Mihara and Uchiyama (17). Colon tissues were homogenized with cold 1.5% potassium chloride to make a 10% homogenate for MDA analyses. Three ml of 1% phosphoric acid and 1 ml of 0.6% thio-

barbituric acid (TBA) aqueous solution were added to 0.5 mL of 10% homogenate. The mixture was heated for 45 min and, after cooling, 4 mL of n-butanol was added and mixed. Absorbance was measured at 535 and 520 nm. The difference of the two measurements defined the level of MDA (nmoL/g tissue).

Tumor necrosis factor alpha (TNF-α) levels were also analyzed from serum samples by enzyme-linked immunosorbent assay (Rat TNF-α ELISA, Biosource) as a marker of inflammation.

Statistical analysis

Data analysis was performed using the SPSS 11.5 statistical software package (SPSS, Chicago, IL, USA). Descriptive statistics were given as mean±standard deviation. Significance of the average differences between groups was assessed using one-way Analysis of Variance (ANOVA) and the Mann Whitney U test. When one-way ANOVA was determined to be significant, Tukey's range test from post-hoc tests was used to identify the group causing the difference. Results where $p<0.05$ were considered statistically significant.

RESULTS

Colitis was observed in an approximately 2 cm area of the colon maximally 10 cm proximal to the rectum in Groups 2 and 3.

For all experimental groups, BP as well as colon circumference and diameter were recorded and BWT was calculated according to Laplace's law.

BP at the moment of perforation in Group 2 (mean 87.1±9.46 mmHg) was significantly lower than that in Groups 1 and 3 (143.1±19.85 mmHg and 138.3±29.26, respectively) ($p<0.001$ for both groups). No significant difference was found between Groups 1 and 3 ($p=0.889$) (Table 1, Figure 1).

BWT at the moment of perforation in Group 2 (mean 0.36±0.038 dyn/cm.10^{-5}) was significantly lower than Groups 1 and 3 (mean 0.66±0.070 dyn/cm.10^{-5} and 0.66±0.17 dyn/cm.10^{-5}, respectively) ($p<0.001$ for both groups). No significant difference was found between Groups 1 and 3 ($p=0.994$) (Table 1, Figure 2).

A significant correlation between BP and BWT was found in all groups. It can therefore be inferred that diameter values were comparable between groups.

MDA levels were significantly increased in Group 2 (1.00±0.23 nmol/g tissue) and Group 3 (1.20±0.34 nmol/g tissue) compared to Group 1 (0.76±0.13 nmol/g tissue) (=0.006 and =0.003, respectively) (Figure 3). No significant differences were observed between Group 1 (36.51±6.89 pg/mL), Group 2 (36.52±7.14 pg/mL), and Group 3 (34.86±5.89 pg/mL) for serum TNF-a levels.

DISCUSSION

IBD is a heterogeneous disease with multiple etiologies (18). It is currently thought that the destructive activity of reactive oxygen and nitrogen radicals and overproduction of pro-

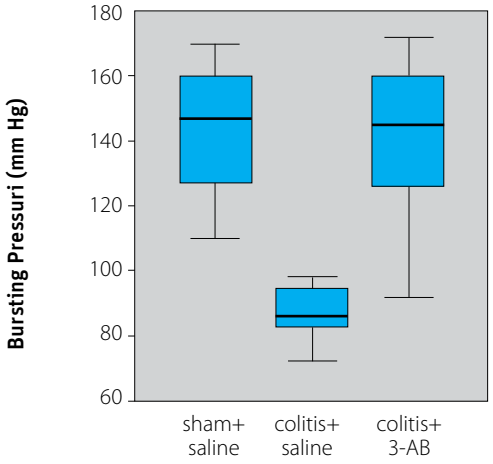

Figure 1. Bursting pressure differences between groups

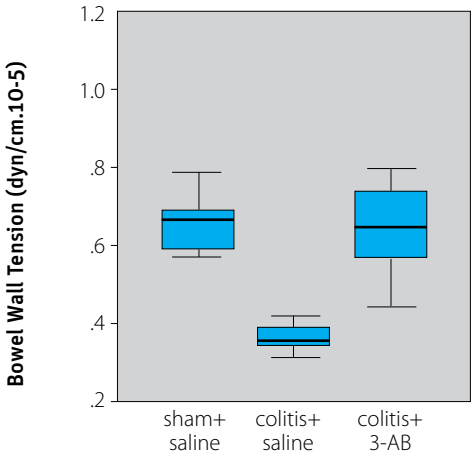

Figure 2. Bowel wall tension differences between groups

Table 1. Colon bursting pressure and bowel wall tension

	Group 1 (Sham + Saline)	Group 2 (Colitis + Saline)	Group 3 (Colitis + 3-AB)
Bursting Pressure (mmHg)	143.1±19.85†	87.1±9.46	138.3±29.26†,‡
Bowel Wall Tension (dyn/cm.10^{-5})	0.66±0.070†	0.36±0.038	0.66±0.171†,‡

3-AB, 3-aminobenzamide
†Statistically significant difference between Group 2 and other groups ($p<0.001$).
‡No significant difference between Group 1 and 3 ($p\geq0.05$).

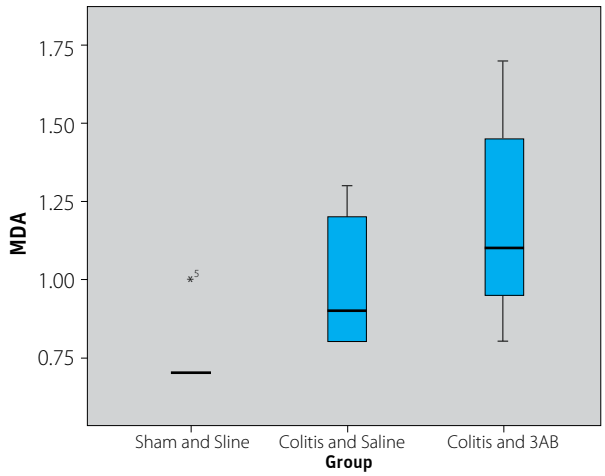

Figure 3. Differences in malondialdehyde (MDA) levels between groups

inflammatory mediators cause the disease (10,19-21). Accumulation of activated neutrophils results in production of large amounts of reactive oxygen species (ROSs) such as superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hypochlorous acid and release of the enzyme myeloperoxidase (MPO) (22,23). A growing body of evidence indicates that increased production of oxidants due to neutrophil accumulation in the colonic mucosa may be the underlying cause of mucosal ulcerations in IBD (24). Excessive production of oxidants has been well described in the plasma, colonic mucosa, and peripheral blood leukocytes of IBD patients (24,25). In addition, oxidant activity was found to be correlated with IBD activity (24). In our study, we also observed an increase in lipid peroxidation products (MDA levels) in both colitis groups. We expected to find decreased MDA levels in the 3-AB treatment group but measured the same levels as the untreated colitis group. A different study evaluated the systemic effect of oxidative stress in experimental colitis, reporting that increased MDA and decreased glutathione (GSH) levels are present in pancreatic tissue as well as colonic mucosa (26). It has also been shown that activated inflammatory cells in the colon are capable of producing a number of circulating cytokines including interleukin 1, interleukin 6, and TNF-α, which can regulate endothelial cell adhesion molecules and increase neutrophil accumulation (27). Although we did not observe statistically significant differences between the TNF-α levels in the groups, there was a slight decrease in TNF-α in Group 3 compared to Group 2. PARP inhibitors have been shown to have anti-inflammatory activities and the lack of observed anti-inflammatory effects in our study could be due to the dose and treatment duration.

IBD can induce various complications, including perforations, which can require emergency surgical treatment. Bowel perforation occurs where transmural involvement is present, as in Crohn's disease, or from inflamed and dilated areas, as in ulcerative colitis. Treatment of the acute phase of the disease and disease remission will reduce these and similar complications. Crohn's disease is characterized by a transmural intestinal inflammatory process where deep ulcers are found accompanied by abscesses and fistulae. Adhesion to intestinal and non-intestinal structures is also frequently observed (6). In Crohn's disease, histopathological findings showed that perforations are the result of increases in intraluminal pressure because of impaired circulation to mucosa and strictures (28). In ulcerative colitis, perforations usually occur as a result of toxic dilatation (5). In ulcerative colitis, inflammation is limited to the mucosa. Sometimes active inflammation progresses into the submucosa and acute ischemic changes cause development of toxic megacolon (29).

Studies using TNBS colitis models have demonstrated the anti-inflammatory activity of PARP inhibitors in the bowel macroscopically, pathologically, and immunohistochemically (7). TNBS nearly always induces transmural colitis (15). This full-thickness intestinal involvement allows induction of perforations similar to those found in Crohn's disease. However, this is not a true model of ulcerative colitis.

In a study by Rabau et al. (14), BP and BWT measurements were compared in a rat model of TNBS-induced colitis with groups with and without anastomosis. BP and BWT values were found to be significantly lower in animals with colitis without anastomosis compared to animals with normal colons without anastomosis. Thus, it was determined to be suitable to measure differences in BP and BWT in animals with colitis compared to those without, as in our study.

Cochrane et al. (30) studied the relationship between formation time of various cytotoxic free radicals and the time of PARP activation. They showed that cell death can be prevented by PARP activity reduction when catalase is added into the environment in the first 30 minutes of H_2O_2 inducing cell death. In our study, therefore, 3-AB treatment was initiated prior to inducing colitis.

The effect of 3-AB on normalizing BP and BWT may depend on its anti-inflammatory activity, its effect preventing oxidative injury in epithelium cells, and its effect strengthening the intestinal mucosal barrier contributing to increased resistance of the colon wall (7,13). Reducing perforation can also protect against abscesses and internal fistulae, which develop secondary to perforation.

Zingarelli et al. (10) showed that treatment with 10 mg/kg 3-AB i.p. twice daily for a week in a rat colitis model resulted in a statistically significant regression of colon injury as detected both macroscopically and histopathologically compared to untreated animals with colitis. Tissue MPO levels decreased, and nuclear localization of the two main transcription factors for inflammation signal production, Nuclear Factor kappa B (NF-KB) and activator protein-1 (AP-1), was reduced. Mabley et al. (12) showed pronounced protective effects of PJ34, a specific PARP inhibitor, against colon injury, lipid peroxidation, neutrophil infiltration, and mortality in a colitis model induced by dextran

sulphate solution.

PARP inhibitors prevent oxidative injury and apoptosis in intestinal epithelial cells. Giannone et al. showed that the PARP inhibitor nicotinamide reduced apoptosis and intestinal injury in a newborn rat model of necrotizing enterocolitis (13). Virag and Szabo showed that PARP inhibition could return cellular functions before inflammation in intestinal epithelial cells resulted in necrosis (31).

The effect of PARP on intestinal epithelial barrier functions is an active process and highly dependent on cellular ATP concentrations (32). PARP-dependent epithelial dysfunction causes intestinal hyperpermeability and bacterial translocation through the bowel increases (33). In an acute necrotizing pancreatitis model, 3-AB treatment reduced intestinal bacterial translocation along with oxidative stress parameters (34). This effect of PARP inhibitors on intestinal epithelium can also prevent perforations developing secondary to abscesses and fistulae on the intestinal wall during the course of disease progression.

Even though the therapeutic effect of PARP inhibitors was shown in experimental colitis models, further study is needed to understand the molecular mechanisms of this class of medications (10,35).

This study is a mechanical crosscheck of positive effects of 3-AB against colitis demonstrated in other studies via immunohistochemistry. In a rat model of colitis initiated by TNBS, 3-AB significantly increased BP and BWT. Though the mechanism of action is complicated, increased BP and BWT is a practical indicator of the therapeutic activity of PARP inhibitors on colitis and the preventative activity on perforations.

Future studies are needed to address whether 3-AB provides advantages over other treatments for prevention of colon perforation and in what stages of the disease treatment is successful. Since there are multiple mechanisms of action of PARP inhibitors and the etiology of IBD is not completely understood, further studies are needed to bring this class of drugs to clinical use.

Conflict of Interest: No conflict of interest was declared by the authors.

REFERENCES

1. Danese S, Fiocchi C. Etiopathogenesis of inflammatory bowel diseases. World J Gastroenterol 2006; 12: 4807-12.
2. Pithadia AB, Jain S. Treatment of inflammatory bowel disease (IBD). Pharmacol Rep 2011; 63: 629-42.
3. Meier J, Sturm A. Current treatment of ulcerative colitis. World J Gastroenterol 2011; 17: 3204-12.
4. Targan SR. Current limitations of IBD treatment: where do we go from here? Ann N Y Acad Sci 2006; 1072: 1-8.
5. Berg DF, Bahadursingh AM, Kaminski DL, Longo WE. Acute surgical emergencies in inflammatory bowel disease. Am J Surg 2002; 184: 45-51.
6. Freeman HJ. Spontaneous free perforation of the small intestine in Crohn's disease. Can J Gastroenterol 2002; 16: 23-7.
7. Virág L, Szabó C. The therapeutic potential of poly (ADP-ribose) polymerase inhibitors. Pharmacol Rev 2002; 54: 375-429.
8. Sodhi RK, Singh N, Jaggi AS. Poly (ADP-ribose) polymerase-1(PARP-1) and its therapeutic implications. Vascul Pharmacol 2010; 53: 77-87.
9. Szabó C. Potential role of the peroxynitrate-poly (ADP-ribose) synthetase pathway in a rat model of severe hemorrhagic shock. Shock 1998; 9: 341-4.
10. Zingarelli B, O'Connor M, Hake PW. Inhibitors of poly (ADP-ribose) polymerase modulate signal transduction pathways in colitis. Eur J Pharmacol 2003; 469: 183-94.
11. Sánchez-Fidalgo S, Villeges I, Martin A, Sánchez-Hidalgo M, Alarcon de la Lastra C. PARP inhibition reduces acute colonic inflammation in rats. Eur J Pharmacol 2007; 563: 216-23.
12. Mabley JG, Jagtap P, Perretti M, et al. Anti-inflammatory effects of a novel, potent inhibitor of poly (ADP-ribose) polymerase. Inflamm Res 2001; 50: 561-9.
13. Giannone PJ, Alcamo AA, Schanbacher BL, Nankervis CA, Besner GE, Bauer JA. Poly(ADP-ribose) polymerase-1: a novel therapeutic target in necrotizing enterocolitis. Pediatr Res 2011; 70: 67-71.
14. Rabau M, Eyal A, Kluger Y, Dayan D. Bursting pressure in anastomotic healing in experimentally induced colitis in rats. Dis Colon Rectum 1998; 41: 468-72.
15. Elson CO, Sartor RB, Tennyson GS, Riddell RH. Experimental models of inflammatory bowel disease. Gastroenterology 1995; 109: 1344-67.
16. Wallace JL, Le T, Carter L, Appleyard CB, Beck PL. Hapten-induced chronic colitis in the rat: Alternatives to trinitrobenzene sulfonic acid. J Pharmacol Toxicol Methods 1995; 33: 237-9.
17. Mihara M, Uchiyama M. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. Anal Biochem 1978; 86: 271-8.
18. Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. Gastroenterology 1998; 115: 182-205.
19. Zingarelli B, Salzman AL, Szabó C. Genetic disruption of poly (ADP-ribose) synthetase inhibits the expression of P-selectin and intercellular adhesion molecule-1 in myocardial ischemia/reperfusion injury. Circ Res 1998; 83: 85-94.
20. Zingarelli B, Szabó C, Salzman AL. Blockade of Poly(ADP-ribose) synthetase inhibits neutrophil recruitment, oxidant generation, and mucosal injury in murine colitis. Gastroenterology 1999; 116: 335-45.
21. Wright JP, Mee AS, Parfitt A, et al. Vitamin A therapy in patients with Crohn's disease. Gastroenterology 1985; 88: 512-4.
22. Kruidenier L, Verspaget HW. Review article: oxidative stress as a pathogenic factor in inflammatory bowel disease--radicals or ridiculous? Aliment Pharmacol Ther 2002; 16: 1997-2015.
23. Malle E, Furtmüller PG, Sattler W, Obinger C. Myeloperoxidase: a target of new drug development? Br J Pharmacol 2007; 152: 838-54.
24. Krudeinier L, Kuiper I, Lamers C, Verspaget HW. Intestinal oxidative damage in inflammatory bowel disease: semi-quandamageification, localization and association with mucosal antioxidants. J Pathol 2003; 201: 28-36.
25. Baskol M, Baskol G, Kocer D, Ozbakir O, Yucesoy M. Advanced oxidation protein products. A novel marker of oxidative stress in ulcerative colitis. J Clin Gastroenterol 2008; 42: 687-91.

26. Deger C, Erbil Y, Giris M, et al. The effect of glutamine on pancreatic damage in TNBS-induced colitis. Dig Dis Sci 2006; 51: 1841-6.
27. Geerling BJ, Badart-Smook A, van Deursen C, et al. Nutritional supplementation with N-3 fatty acids and antioxidants in patients with Chrohn's Disease in remission: effect on antioxidant status and fatty acid profile. Inflamm Bowel Dis 2000; 6: 77-84.
28. Hattori Y, Kobavashi K, Katsumata T, Saigenji K, Watanabe M, Okayasu I. Clinicopathologic features of Crohn's disease with free intestinal perforation. Hepatogastroenterology 2007; 54: 135-9.
29. Ajioka Y, Nishikura K, Watanabe G. Pathomorphology of ulcerative colitis. Nihon Rinsho 2005; 63: 763-9.
30. Schraufstätter I, Hyslop PA, Jackson JH, Cochrane CG. Oxidant-induced DNA damage of target cells. J Clin Invest 1988; 82: 1040-50.
31. Szabó C, Lim LH, Cuzzocrea S, et al. Inhibition of poly (ADP-ribose) synthetase attenuates neutrophil recruitment and exerts antiinflammatory effects. J Exp Med 1997; 186: 1041-9.
32. Kennedy M, Denenberg AG, Szabó C, Salzman AL. Poly(ADP-ribose) synthetase activation mediates increased permeability induced by peroxynitrite in Caco-2BBe cells. Gastroenterology 1998; 114: 510-8.
33. Taner AS, Cinel I, Ozer L, Onde U, Taner D, Koksoy C. Poli (adp-ribose) synthetase inhibition reduces bacterial translocation in rats after endotoxin challenge. Shock 2001; 16: 159-62.
34. Aydin S, Işik AT, Cinar E, et al. Does the 3-aminobenzamide effect on bacterial translocation affect experimental acute necrotizing pancreatitis? Turk J Gastroenterol 2009; 20: 20-6.
35. Jijon HB, Churchill T, Malfair D, et al. Inhibition of poly(ADP-ribose) polymerase attenuates inflammation in a model of chronic colitis. Am J Physiol Gastrointest Liver Physiol 2000; 279: G741-51.