Original Article

The Effects of Sulfasalazine and Ezetimibe on Proinflammatory Cytokines in Male Rat with Induced Colitis: A Comparative Study

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Abstract

Background: Ulcerative colitis is a chronic debilitating disease. The existing treatment, including sulfasalazine, corticosteroids, azathioprine/6-mercaptopurine, cyclosporine, and antitumor necrosis factor therapy, frequently fails to cure the disease, necessitating the investigation of new drugs with less adverse effects. **Objectives:** The purpose of this study was to compare the anti-inflammatory effects of ezetimibe to those of sulfasalazine (salazosulfapyridine) in rats with experimentally induced colitis. **Materials and Methods:** A total of 40 adult males Albino-Wister rats were divided into four groups (each with 10 rats). Group I received no treatment and served as a negative control. Acetic acid4% (vol/vol) was used rectally to induce experimental colitis in the other three groups, where group II left without treatment. Sulfasalazine 100 mg/kg (group III) or ezetimibe 10 mg/kg (group IV) were used as a therapeutic dose orally for 1 week. The following parameter was estimated in the tissue homogenate of the colon: tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), nuclear factor kappa B-cell (NF-κB), and a histopathological score of the colonic tissue. **Results:** Both sulfasalazine and ezetimibe significantly reduced the level of TNF-α, IL-1β, and NF-κB compared with the induced colitis. Colon homogenate of TNF-α and IL-1β did not differ significantly between group III (197.25 ± 64.97 and 190.87 ± 36.86 pg/mL, respectively) and IV (223.72 ± 70.05 and 240.93 ± 61.56 pg/mL, respectively); however, ezetimibe-treated rats had significantly higher NF-κB than sulfasalazine-treated rats (3.35 ± 0.74 versus 2.11 ± 0.88 pg/mL). Both treatment modalities significantly ameliorated the histopathological score compared with induced colitis (3.0 ± 0.0), with the superiority of sulfasalazine over ezetimibe (0.57 ± 0.093 versus 1.39 ± 0.17). **Conclusions:** The results indicate that ezetimibe is an effective treatment (compared with sulfasalazine) for induced colitis by reducing the inflammatory response and ameliorating histopathological changes.

Keywords: Acetic acid, ezetimibe, inflammatory parameters, ulcerative colitis

Introduction

Ulcerative colitis (UC) is an inflammation that involves the mucosal layer of the colon, causing rectal bleeding and diarrhea, causing the epithelial barrier to be disrupted and epithelial ulceration to occur.[1,2] Among the most common symptoms of inflammatory bowel disease (IBD) are abdominal pain, chronic diarrhea, blood in the rectum, and mucus in the stools. Nothing is known about the disease's genesis. It is thought to be caused by an aberrant host response to endogenous or environmental antigens or microorganisms, resulting in early tissue harm followed by response amplification.[3,4] There is evidence of a strong local immunological response accompanied by transmural infiltration of lymphocytes, neutrophils, macrophages, and mast cells, resulting in mucosal rupture and ulceration.[5,6] As these invading cells are activated, they release a variety of proinflammatory mediators that play an important role in tissue damage and the spread of the inflammatory response. Proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α)

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and interleukin-1 (IL-1) were shown to be elevated in the colonic mucosa of UC patients.[7]

Despite significant progress in the treatment of UC, drug-induced toxicity over long treatment durations and a high relapse rate limit their use. As a result, new techniques for restoring the altered immune response are required.[8,9] Ezetimibe belongs to the class of drugs known as azetidinone cholesterol absorption inhibitors. In hypercholesterolaemia, it is used in conjunction with diet and statins.[10] It prevents cholesterol absorption from the duodenum by inhibiting a transport protein (NPC1L1) at the brush boundary. It also limits the excretion of cholesterol in bile[11,12] and has anti-inflammatory capabilities, as evidenced by the reduction of articular cartilage alterations caused by a decrease in levels.[13]

Sulfasalazine is a disease-modifying antirheumatic drug that was originally proposed as a treatment for rheumatoid arthritis because of its anti-inflammatory and antimicrobial activities. The exact mechanism of action remains to be elucidated; the main mechanism includes inhibition of cyclooxygenase and lipoxygenase, subsequently leading to reduced production of prostaglandins and leukotrienes, respectively. However, Sulfasalazine is associated with a wide range of adverse side effects that include agranulocytosis, nephrotoxicity, neurotoxicity, and pulmonary toxicity.[14,15]

The present study aimed to investigate the therapeutic effect of ezetimibe in experimentally induced colitis through the estimation of inflammatory and histopathological scores.

Materials and Methods

Experimental animals

Adult male Albino-Wister rats weighing 200–220 g were housed in polypropylene cages in a controlled room (temperature 24–25°C, humidity 35%–60%, 12-h light/dark cycle). Throughout the tests, rats had free access to tap water. To avoid coprophagy, rats were placed in cages with a large wire-mesh floor during hunger.[16] All ethical aspects of the animal research were carefully reviewed, and the experimental procedure was approved by the Institutional Review Board of Al-Nahrain University's College of Medicine (20210903 and November 21, 2021).

Induction of ulcerative colitis

Rats were fasted for at least 24 h before colitis induction to ensure adequate colitis induction by evacuation of feces from the colon, although they were allowed to drink tap water. The experimental colonic ulceration was performed in accordance with the approach proposed by Mousavizadeh *et al.*[17] with modifications. Under light ether anesthesia, rats were given a single intrarectal infusion of 4% acetic acid in a dose of 5 mL/kg solution (8 cm into the colon) using a flexible plastic tube (2 mm extrinsic diameter). To inhibit acetic acid discharge, rats were placed in a horizontal position for 2 min.

Experimental design

Rats were categorized into four groups (10 for each). Group I received no treatment and served as negative control (normal saline infusion rectally). Colitis was induced by rectal administration of 4% acetic acid (v/v) in the other three groups. Group II represents positive control and did not receive any treatment. Before administration, the sulfasalazine and ezetimibe were freshly prepared. Estimated medicines were made into suspensions in distilled water. Standard therapy consisted of 100 mg/kg sulfasalazine.[18] Sulfasalazine 100 mg/kg was given orally to Group III, whereas ezetimibe 10 mg/kg was given to Group IV. Based on a prior study on experimental colitis,[19] the therapy in both groups lasted 7 days.

Determination of colonic proinflammatory mediators

Rats were sacrificed by inhaling an excessive amount of diethyl ether at the end of the trial. During the dissection of the abdomen, the colon was quickly removed. The colon specimen was gently washed with normal saline after being opened lengthwise. The colon was stored in ice-cold phosphate buffer saline (0.02 mol/L, pH 7.2–7.4). The tissues were cut into small pieces and homogenized in a specific amount of phosphate buffer saline (PBS) (typically 1-g tissue to 9-mL PBS) using an ice-cold homogenizer. To further break down the cell membranes, the solution was frozen and thawed twice. The homogenate was then centrifuged for 15 min at 5000 rpm.[20]

Homogenate levels of TNF-α, IL-1β, and nuclear factor kappa B-cell (NF-kB) (inflammatory cytokines) in the homogenized colon tissue were measured using ready commercial enzyme-linked immunosorbent assay kits, according to the manufacturer's instructions (Elk Biotechnology, Wuhan, China).

Histopathologic scores

At room temperature, the colonic samples were fixed in 10% formalin. The material was dehydrated, paraffin-embedded, and deparaffinized. Each colonic sample was cut into 4 m thick sections and stained with hematoxylin and eosin. Prepared slides were examined for histopathological lesion by an experienced histopathologist. The results were evaluated based on a scoring system ranging from 0 to 3 (0: normal, 1: focal, 2: zonal, and 3: diffuse). These scores assess the extension of epithelial damage and/or glandular crypt dilation, inflammatory cell infiltration, loss of goblet cells, crypt abscesses, mucosal hemorrhage, edema, and dysplasia.[21]

Statistical analysis

To summarize, analyze, and present the data, the statistical package for the social science (SPSS), version 23

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software program (SPSS Inc., Chicago, Illinois, USA) was utilized. The mean and standard deviation of quantitative (numerical) variables were used. One-way analysis of variance (ANOVA) was used to investigate the difference in mean of quantitative variables across groups, followed by a post hoc least significant difference test to assess the mean difference within groups. The significance level was set at $P \leq 0.05$.

Results

Determination of colonic proinflammatory mediators

The multiple comparisons of proinflammatory cytokinesis are shown in Table 1. Treated groups with sulfasalazine and ezetimibe reduced significantly both TNF-α (197.25 ± 64.97 /mL and 223.72 ± 70.05 pg/mL, respectively) and IL-1β (190.87 ± 36.86 and 240.93 ± 61.56 pg/mL, respectively) compared with induced colitis group (434.5 ± 53.47 and 646.1 ± 58.65 pg/mL, respectively). Interestingly, there were no significant differences between sulfasalazine and ezetimibe in the homogenate level of these proinflammatory cytokines. Similarly, sulfasalazine- and ezetimibe-treated groups showed a significant reduction in tissue homogenate of NF-κB (2.11 ± 0.88 and 3.35 ± 0.74 pg/mL, respectively) compared with induced colitis (9.05 ± 0.74 pg/mL). However, sulfasalazine has a priority over ezetimibe in this regard.

Histopathologic scores assessment

The results of histoscore in different groups are shown in Table 2 and Figures 1–4. Sulfasalazine- and ezetimibe-treated animals had lower histoscore (0.57 ± 0.093 and 1.39 ± 0.17, respectively) than the induced colitis group (3.0 ± 0.0) with highly significant differences. However, ezetimibe had lower activity than sulfasalazine in this regard.

Discussion

UC is a disorder of the intestines characterized by chronic refractory inflammation and ulceration of the colon, and usually with a relapsing form. Several drugs have been developed to treat UC. However, there were inadequate responses and significant adverse effects. Therefore, novel and safer therapies with more curative efficacy are required.[22]

The current study revealed that ezetimibe administration resulted in a significant reduction in tissue homogenate of NF-κB, TNF-α, and IL-1β in colonic mucosa in experimentally induced colitis in rats when compared to the induced nontreated group. This data is consistent with prior research showing that ezetimibe dramatically decreases the level of the proinflammatory cytokine TNF-α.[23,24]

Recently, Weng *et al*.[25] investigated whether the ezetimibe could ameliorate ankylosing spondylitis in a mouse model through an anti-inflammatory effect. Ezetimibe treatment reduced IL-1-induced breakdown of the extracellular matrix, particularly aggrecan and collagen II. Ezetimibe also reduced IL-1-induced production of MMP3, MMP13, and ADAMTS5.

The complex mechanism of the anti-inflammatory activity of ezetimibe is attributed to the reduction in oxidative stress through the activation of the AMP-activated protein kinase (AMPK)/Nrf2 pathway in animal models.[26] In fact, nuclear factor-E2-related factor 2 (Nrf2) is a master transcription factor that

Table 1: Proinflammatory cytokines of tissue level homogenate in different groups

Variables	Healthy (n = 10)	Induced colitis (n = 10)	Sulfasalazine (n = 10)	Ezetimibe (n = 10)	P-value
Colonic TNF-α (pg/mL)	139.8 ± 76.57 A	434.5 ± 53.47 B	197.25 ± 64.97 C	223.72 ± 70.05 C	<0.001
Colonic IL-1β (pg/mL)	142.5 ± 42.09 A	646.1 ± 58.65 B	190.87 ± 36.86 C	240.93 ± 61.56 C	<0.001
Colonic NF-κB (pg/mL)	1.21 ± 0.75 A	9.05 ± 0.74 B	2.11 ± 0.88 C	3.35 ± 0.74 D	<0.001

TNF-α: tumor necrosis factor-alpha, IL-1β: interleukin-1-beta, NF-κB: nuclear factor κ B-cell, values were expressed as mean ± standard deviation (SD); different letters indicate significant differences, n = number of animals

Table 2: Histopathologic scores in control and study groups

Variables	Healthy control (n = 10)	Induced colitis (n = 10)	Sulfasalazine (n = 10)	Ezetimibe+ (n = 10)	P-value
Histo Score	0.00 ± 0.00 A	3.0 ± 0.0 B	0.57 ± 0.093 C	1.39 ± 0.17 D	<0.001

n: number of animals

Values were expressed as mean ± standard deviation (SD); different letters indicate significant differences

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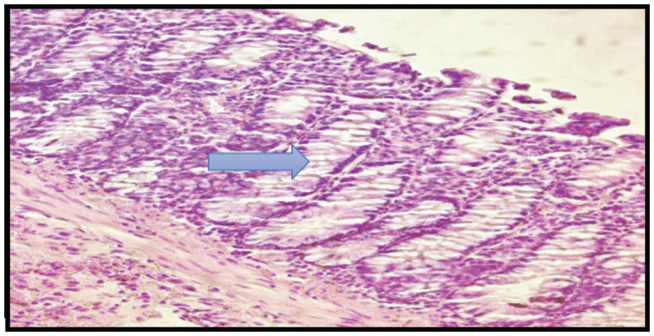

Figure 1: Histological section through the colonic wall of negative control (apparently healthy) group animal showing normal mucosal and submucosal pattern (with no evidence of inflammation and preservation of colonic gland with goblet cells in rat; (20× H&E) stain

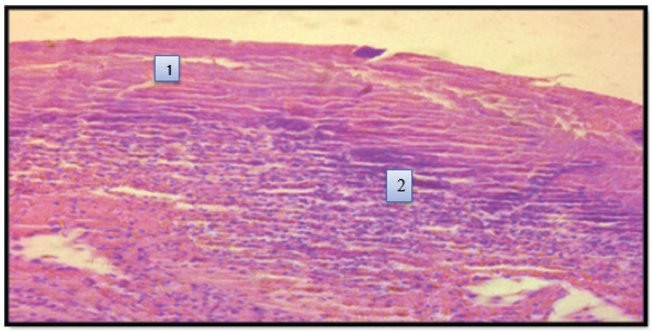

Figure 2: Histopathological section through colonic wall showing mucosal ulcerative and necrotic tissue (1) and sever mononuclear inflammatory infiltrate (2) in experimentally induced colitis in rat; (20× H&E) stain

targets genes coding for antioxidant proteins and detoxification enzymes.[27,28] It also controls the basal and induced expression of antioxidant response element-dependent genes, such as heme-oxygenase-1 and glutamate-cysteine ligase catalytic subunit, to regulate the physiological and pathophysiological outcomes of oxidant exposure.[29]

Another possible mechanism is that ezetimibe reduces the blood cholesterol level by preventing cholesterol absorption in the small intestine by blocking the intestinal cholesterol transporter Niemann-Pick C1-Like 1.[30,31] Oxidized low-density lipoprotein influences the Th17/Treg balance. A high serum concentration of oxidized low-density lipoprotein is negatively correlated with the number of Treg cells and positively correlated with the number of Th17 cells.[32] Therefore, it is expected that the reduction of blood lipid levels using ezetimibe would ameliorate inflammation by reducing the number of Th17 cells.[33]

In the present study, ezetimibe was associated with a significant amelioration of colitis lesions as indicated by histoscore. This effect could be attributed to the pharmacological properties of this drug as anti-inflammatory and immunomodulatory effect. It reduces

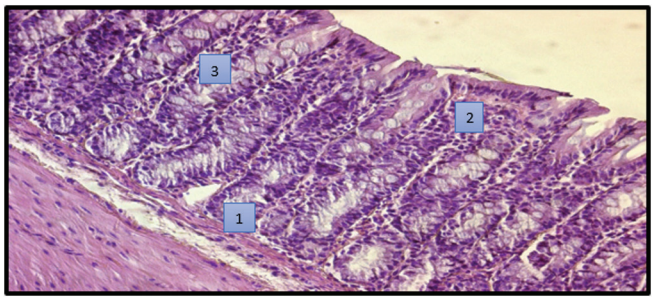

Figure 3: Section through the colonic wall in rat showing sulfasalazine effect after 7 days treatment in which there is evidence of mucosal regeneration and glandular formation (1), mild inflammation (2), and goblet cells regeneration (3); (20× H&E) stain

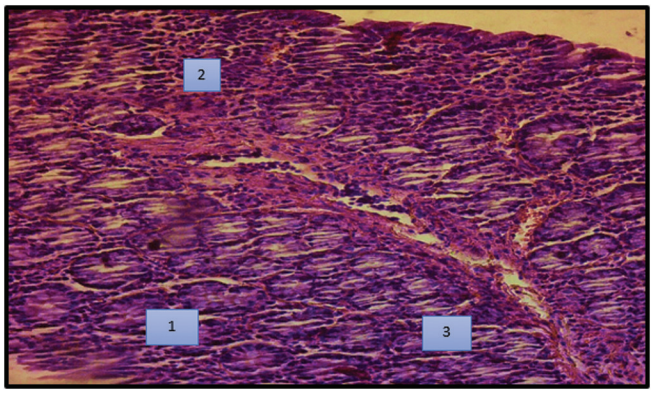

Figure 4: Section through the colonic wall in rat showing drug ezetimibe effect after 7 days of treatment in which there is evidence of mucosal regeneration and glandular formation (1), moderate inflammation (2), and mild goblet cell depletion (3); (20× H&E) stain

cytokine production, inhibits macrophage aggregation, and improves inflammatory response in colitis.[34]

Conclusions

Although ezetimibe is primarily used in the management of hypercholesterolemia, the present study illustrated its high effectiveness against induced colitis in rats. This effectivity was comparable to that of sulfasalazine with no or few side effects. This opens the door for a new era of UC treatment; however, clinical trials are required.

Ethical Approval

Not Applicable.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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