Mesalazine and Coenzyme Q10: Effects on Disease Activity Index in Ulcerative Colitis

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Abstract

Objective: To imply the coloprotective role of Coenzyme Q10 and its activity when combined with an already established therapeutic agent; mesalazine in a rat model of dextran sulfate sodium-induced ulcerative colitis. Effects on the ulcerative colitis activity index, a derived parameter from the percentage of weight loss during the disease course, stool consistency, and blood in stool (either occult or gross), were observed in this study.

Material and Methods: This animal experimental study was conducted in the Department of Pharmacology, KEMU and UVAS (University of Veterinary and Animal Sciences), Lahore. Six groups of 8 rats each were kept in separate cages according to the animal ethical rules. The disease was induced by giving 4% w/v Dextran Sulfate Sodium solution for drinking in rats of disease control and experimental groups. Rats were treated with mesalazine and Coenzyme Q10 according to the assigned groups i.e., mesalazine at a dose of 50mg/kg/day in group E, and 100mg/kg/day in groups C and F, and Coenzyme Q10 at a dose of 30mg/kg/day in groups D and F. The body weight of each rat, and its stool consistency were observed, and its stool was examined for gross and occult blood daily. From these values, the ulcerative colitis activity index was also calculated daily throughout the study.

Results: After statistical analysis, the p-value came out to be significant. So, we can say that the study confirmed that combining mesalazine and CoQ10 has synergistic effects in reducing the Ulcerative Colitis Activity Index.

Conclusion: In conclusion, mesalazine and CoQ10 alone and in combination have been shown to have antioxidant and anti-inflammatory effects in UC. The combination of mesalazine and CoQ10 has been shown to have synergistic effects in reducing the severity of UC in animal studies. Further clinical trials are necessary to investigate the exact mechanism of CoQ10 in IBD and its potential as an agent for the therapy of UC

Keywords: ulcerative colitis, mesalazine, coenzyme-Q10, dextran sulfate sodium, body weight, stool consistency, blood in stool, ulcerative colitis activity index, disease activity index.

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Introduction

Ulcerative colitis (UC) is a phenotype of chronic inflammatory bowel disease (IBD) characterized by recurrent inflammation of the colonic mucosa, causing symptoms such as diarrhea, abdominal pain, low-grade fever, rectal bleeding, and anemia.[1] The prevalence of UC has been increasing globally, and it is associated with a significant decrease in the quality of life of affected individuals.[2,3] The etiology of UC is still not fully clear but it is believed to be a complex interplay between genetic, environmental, and immunological factors.[4,5] The current treatment options for UC include amino-salicylates, corticosteroids, immunomodulators, and biologic agents.[6] All of these agents help in curbing the progress of the disease and preventing relapses. These

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long-term therapies are associated with various adverse effects. Therefore, there is a need for alternative treatment options for UC.

Mesalazine or 5-aminosalicylic acid (5-ASA) is a first-line therapy for UC, and it works by reducing inflammation in the colonic mucosa.[7] Mesalazine is effective in reducing the severity of UC in both human and animal studies. Mesalazine significantly reduces colonic inflammation and histological damage in UC.[8] Similarly, a recent study found that mesalazine significantly reduced the disease activity index (DAI) and myeloperoxidase (MPO) activity in a mouse model of UC.[9] However, its efficacy is limited, and it is associated with significant side effects such as headache, nausea, diarrhea, blood dyscrasias, pneumonitis, and liver damage.[10]

Coenzyme Q10 (CoQ10) is a well-known intracellular antioxidant that may reduce oxidative stress and inflammation in UC.[11] CoQ10 has also been shown to have anti-inflammatory and antioxidant effects in UC. A recent study showed coloprotective properties of CoQ10 where it significantly reduced the colonic inflammation and oxidative stress related to UC in rat models.[12]

However, its efficacy as a monotherapy or combined with mesalazine in UC has not been well studied. Therefore, this study reviewed the effects of mesalazine and CoQ10 alone and in combination on the ulcerative colitis activity index in dextran sulfate sodium-induced ulcerative colitis in rat model.

Material and Methods

This animal experimental study was conducted in the Department of Pharmacology, KEMU and UVAS (University of Veterinary and Animal Sciences), Lahore. After the approval from IRB Committee Ref No. 789/RC/EMU dated:13-05-2024. Male, healthy Sprague-Dawley rats, weighing 180g to 220g were taken. Forty-eight rats were divided into six groups by lottery method and kept in the animal house of UVAS, Lahore. Throughout the experiment, the rats experienced natural day and night cycles within a room maintained at a temperature of 22±2°C and a humidity level of 50 ±5%. They were provided with unlimited access to rat chow and water. A seven-day acclimatization period was implemented before the commencement of the experiment to ensure their adjustment to the environment. Forty-eight rats were randomly assigned to six groups, each consisting of 8 rats. These groups were labeled as A, B, C, D, E, and F. Group A served as the normal control, while Group B acted as the disease control. Groups C, D, E, and F were designated as treatment groups. Throughout the study, all rats were fed a standard rat diet. The disease control group (Group B) and all treatment groups (Groups C, D, E, and F) received a 4% w/v solution of DSS instead of regular water. Mesalazine was prepared in 4% methocel and administered orally to groups C, E, and F (at a dose of 100mg/kg/day to rats in Groups C and F and at a dose of 50mg/kg/day to rats in Group E) CoQ10 was prepared in 0.5% carboxymethylcellulose and administered orally to rats in groups D and F at a dose of 30mg/kg/day. The stock solutions were prepared from the already calculated doses for individual rats i.e., 100mg/kg/day of Mesalazine was weighed and prepared in 4% methocel solution 13, and 30mg/kg/day of CoQ10 was weighed and prepared in 0.5% carboxymethylcellulose[12] A 4% w/v solution of DSS was made by adding DSS (molecular weight 40-50kDa) in water and rats of disease control and experimental groups were given this solution to drink throughout the study.[14]

a) Body Weight:

Body weight was measured in grams(g) daily till the end of the study and each rat was scored according to the %age weight loss.

- 0 for no weight loss.
- 1 for 1-5% loss.
- 2 for 5-10% loss.
- 3 for 10-20% loss.
- 4 for >20% loss.15

b) Stool consistency:

Stool consistency in terms of normal, loose stool, and diarrhea were noted and scored daily.

- 0 for Normal stool (well-formed pellets).
- 2 for Loose stool which is pasty and semi-formed (which does not stick to the anus).
- 4 for Diarrhea or liquid stool (that stick to the anus). 15

c) Blood in stool:

Blood in stool either gross or occult (evaluated by SBio Occult Blood Test kit) was noted daily and was scored accordingly.

- 0 for no blood.
- 2 for hemoccult- positive.
- 4 for gross bleeding. 15

Clinical assessment of UC (UC or disease Activity Index) was done by adding the weight loss scores, stool consistency, and bleeding and then dividing by 3. Disease was thought to be produced if any of the three parameters were present. So, a UCAI of 0.33 or above was considered to be significant.[15]

Data was analyzed by using SPSS software for Windows (version 23.0) and GraphPad Prism (version 8). Changes in body weight, stool consistency, and presence or absence of blood were scored as numbers and expressed as percentages of changes in groups. ANOVA and Chi-square test were used for evaluation. A P-value of <0.05 was regarded as significant.

Results

The body weight was similar in all groups at the start of the study. As the study went on, the mean weight of rats in Group A, increased significantly (192.00 ± 12.11 at the start vs 239.63 ±10.74 at the end). Whereas the weight of rats drastically decreased in group B (199.75 ± 14.92 at the start vs 147.63±17.49 in the end of the study). Animals in the group treated with mesalazine alone (group C) recouped body weight to an extent but the loss was still significant (201± 14.25 at the start vs 189.75±15.13 at the end). Similarly, rats in the group treated with Co-Q10 only (Group D) regained weight but the gain was not complete (203.00 ± 9.96 at the start vs 196.50±9.74 at the end). The rats in the group treated with a half dose of mesalazine alongwith Co Q10 (Group E), regained weight almost completely (197.00 ± 11.45 at the start vs 192±10.24 in the end). Similarly, rats in group treated with mesalazine and Co-Q10 (Group F) regained weight (201.38 ± 13.28 at the start vs 195.25 ± 10.54 in the end). On day 8, the mean weight of rats in Group B as compared to control group (Group A) was significantly low (147.63±17.49 vs 239.63 ±10.74) that shows DSS induced the disease that resulted in weight loss of rats. Animals in the group treated with mesalazine alone (group C) recouped body weight and at the end of the study, the mean body weight of rats of group C was 189.75±15.13. Similarly, the mean weight of rats in the group treated with Co-Q10 alone (group D) also went up (196.50±9.74). The rats in groups treated with combined therapy (group E and group F) also regained weight. (192±10.24 and 195.25 ± 10.54 respectively). On day-8 the highest mean weight of rat was seen on Group-A (239.63±10.74) followed by in Group-D (196.50±9.74) and Group-F (195.25±10.54) respectively.

Weight loss was scored by assigning score 0 for no weight loss, 1 for 1-5% loss, 2 for 5-10% loss, 3 for 10-20% loss and 4 for >20% loss.[15] At the end of the study, 100% (08 rats) in Group B had a score of 2(5-10% weight loss). 100% (08 rats) in Group C recouped the weight and none had a score of 1, 2 or 3. Similarly, in Group C, all the rats (100%) regained weight and had a score of 0 and none had score 1, 2 or 3. Similar result was seen in group D, where 100% rats had a score 0 and none had a score of 1, 2 or 3. While in Group E, 88% (07 rats) had a score 0 while 13% (01 rat) had a score 1 and none had score 2 or 3. In Group F, 100% (08 rats) had a score 0 and none had a score of 1, 2 or 3. When ANOVA was applied, the difference was significant with a p-value of <0.001.

Following table describes the stool consistency in all treatment groups at day 1,2,3,4,5,6,7 and 8 respectively. Stool consistency was assessed by assigning scores of 0 for normal stool which were well-formed pellets, 2 for loose paste like and semi-formed stool, which did not stick to the anus, and 4 for diarrhea like stool that sticked to the anus.[15] On the 8th day, the stool consistency score was highest (in 100% rats) in Group B (disease group) which shows that rats in group B developed the disease. On 8th day, in the treatment group C, 50% of animals (4 rats) had score 0. While 38% (3 rats) had a score of 2 and 13% (1 rat) had a score 4. While in treatment group D, 38% (3 rats) had a score of 0; 63% (5 rats) had a score of 2 and no rats had score 4. In treatment group E, 25% (2 rats) had score 0, 75% (6 rats) had score 2, and 0% had score 4. Similarly, in treatment group F, 50% (4 rats) had score 0, and 50% (4 rats) had score 2, and none had score 4. When ANOVA was applied, the difference was significant with a p-value of <0.001. These results show that the rats receiving CoQ-10 along with mesalazine had best prevention of the disease.

Following table describes the blood in stool in all treatment groups at day 1,2,3,4,5,6,7 and 8 respectively. Criteria for blood in stool scoring is that the score 0 is for no blood (gross or occult) in stool, 2 for presence of occult blood in the stool, and 4 for gross bleeding.[15] On 8th day, the blood in stool score was highest (100% rats) in Group B (disease group) that shows that rats in group B developed the disease. On 8th day, in the treatment group C, 38% of animals (3 rats) had score 0. While 38% (3 rats) had score 2 and 25% (2 rats) had score 4. While in treatment group D, 100% (8 rats) had score 0 and no rats had score 2 or 4. In treatment group E, 75% (6 rats) had score 0, 25% (2 rats) had score 2, and none

had score 4. Similarly, in treatment group F, 100% (8 rats) had score 0 and none had score 2 or 4. When ANOVA was applied, difference among the groups was significant with a p-value of of <0.001. These results show that in the rats receiving CoQ-10 along with mesalazine had best prevention of the disease.

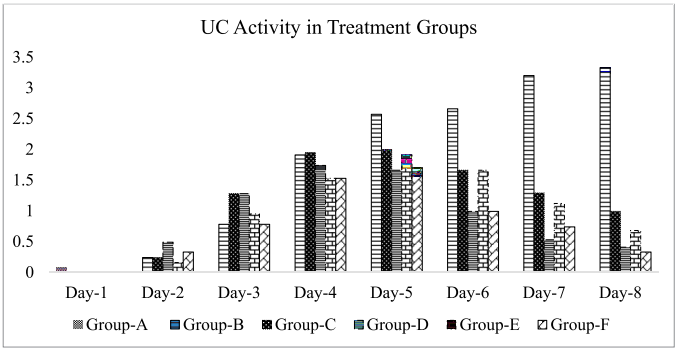

Figure 1: *Graphical representation of the effect of CoQ-10 on UC Activity in Treatment Groups. On day 8, the highest score can be seen in Group B and the lowest score can be observed in Group A followed by Group F.*

Group A = Normal Control Group, Group B = Disease Group, Group C = Mesalazine, Group D = Co-Q10, Group E=1/2Mesalazine+Co-Q10, Group F= Mesalazine + Co-Q10

Note: Clinical assessment of the disease (UC Activity Index) was done by adding the weight loss scores, stool consistency, and bleeding and then dividing by 3.

Discussion

In this research study, there was a significant increase in disease activity in group B (disease control group) as compared to group A (normal control) with a p-value of <0.001. In group C, in which rats were treated with mesalazine, significantly reduced disease activity was observed when compared with group B with a p-value of <0.001. Similarly, in group D, in which rats were treated with Co-Q10, reduced disease activity was observed when compared with group B with a p-value of <0.001. Likewise, in group E and group F in which a combination of Co-Q10 and mesalazine in different doses was used, a significant decrease in disease activity was observed when compared with group B with a p-value of <0.001 and <0.001 respectively. A number of unconventional therapy options have given similar results as shown by various previous studies. The findings of this study correlate with the effects of Qingchang Wenzhong Decoction (a traditional Chinese medicine)[16] and the water extract of Raphanus sativus L. (RSL) seeds (a traditional Korean medicine) that ameliorate colonic inflammation in rats that had shown a significant reduction in disease activity in DSS-induced colonic inflammation.[17] Likewise, Chelerythrine produced similar effects on UCAI in acetic acid-induced UC in rats.[18]

Conclusion

In conclusion, mesalazine and CoQ10 alone and in combination have been shown to have antioxidant and anti-inflammatory effects in UC. The combination of mesalazine and CoQ10 has been shown to have synergistic effects in reducing the severity of UC in animal studies. Further clinical trials are necessary to investigate the exact mechanism of CoQ10 in IBD and its potential as an agent for the therapy of UC.

Conflict of Interest: None

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Authors Contribution

HP: Conceptualization of Project
RR: Data Collection
NI: Literature Search
MM: Statistical Analysis
SZT: Drafting, Revision
HF: Writing of Manuscript