Prophylactic Administration of Montelukast Ameliorates the Deleterious Effect of Dexamethasone on Stress-Induced Gastric Lesions in Rats

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Abstract

Objectives: The present study aimed to evaluate experimentally the impact of prophylactic administration of montelukast (MLK) on the ulcerogenic effect of exposure to cold-restraint stress with and without administration of dexamethasone (DXM) in rat model.

Material and Methods: The present study included 64 adult male Sprague Dawley rats divided into negative (Group I, n=8) and positive (Group II, n=8) control groups and MLK-pretreated group (Group III) included 24 rats that were pretreated with MLK and subdivided according to used MLK dose (3, 10 & 30 mg/kg p.o.), 30 minutes before the start of 3-hrs of acute cold-restraint stress. Group IV (DXM group): included 16 rats that received DXM in 2-variant doses (0.25 or 0.5 mg/kg orally), 30 minutes before the start of 3 hrs of acute cold-restraint stress and subdivided equally. Group V (MLK-pretreated DXM group): included 8 rats that received MLK (10mg/kg p.o.) concomitant with DXM (0.5mg/kg orally) 30 minutes before the start of 3 hrs of acute cold-restraint stress. Animals were immobilized in open wire restraint cages and placed at 4 ± 1ºC for 3 hours; then were sacrificed by decapitation, the stomach was excised, opened, and examined macroscopically for damage quantified using the ulceration index (UI) and the preventive index (PI) of the drug used and a stomach tissue was then used for spectrophotometric determination of the enzymatic activities of superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) level.

Results: All animals exposed to cold-restraint stress with or without DXM administrations had gastric ulcers of varied extent and severity, irrespective of the administration of MLK. However, prophylactic MLK administration in groups III and V significantly reduced UI compared to group II and IV, respectively. Prophylactic MLK administration showed a dose-dependent PI that was significantly higher in animals received MLK in a dose of 30 mg compared to those received 3 or 10 mg dose with significantly higher PI in those received 10 mg compared to those received 3 mg. Prophylactic administration of MLK significantly reduced CAT and improved SOD activities and improved GSH level in gastric tissue extract compared to animals did not receive MLK prophylaxis.

Conclusion: Prophylactic administration of MLK could ameliorate the ulcerogenic effect of variant ulcerogenic agents with high preventive index of 10 mg MLK once daily on the ulcerogenic effect of DXM. Thus, MLK administration in addition to its role as therapeutic modality for asthma patients could provide prophylaxis whenever corticosteroid therapy is indicated.

Key Words: Montelukast – Cold-restraint stress gastric ulcer – Dexamethasone – Rats.

Introduction

INHALED corticosteroids are considered the most effective therapy currently available for persistent asthma and are the guideline-recommended first-line treatment for all patients requiring controller medication; however, the potential for oropharyngeal and systemic adverse events can be a barrier to their use, [1]. Despite the fact that, most of the patients with asthma are found to be successfully treated with conventional therapy. However, there are a small proportion of asthmatic patients who fail to respond to corticosteroids even at high doses or with supplementary therapy. In addition, even high doses of corticosteroids have a minimal effect on the inexorable decline in lung function in chronic obstructive pulmonary disease and only a small effect in reducing exacerbations. Corticosteroid-insensitivity therefore presents a profound management problem, [2].

Cysteinyl leukotrienes, leukotrienes C4, D4, and E4 (LTC4, LTD4, and LTE4), are secreted mainly by eosinophils, mast cells, monocytes, and macrophages and perform a number of pathogenic actions during periods of inflammation. [3]. The cysteinyl leukotriene cysLT1 receptor (cysLT1R) is present on the eosinophil cell surface, [4] and may have a role in eosinophil adhesion, as stimulation of the receptor by LTD4 was shown...
to up-regulate eosinophil binding to recombinant human vascular cellular adhesion molecule-1, [5].

Multiple studies evaluated the effect of LTC4 on gastric mucosal injury and various drugs and herbals were tried to minimize such effects. Kim et al. [6], investigated the gastro-sparing effects of a herbal mixture on the gastric mucosa injury induced by diclofenac, a conventional NSAID, and celecoxib, a cyclooxygenase-2 (COX-2) specific inhibitor and reported significantly decreased gastric and blood leukotriene B4 and concluded that the used herbal mixture could spare the gastric mucosa through significantly suppressing gastric leukotriene synthesis. Okazaki et al. [7], attributed the significant gastric-mucosa-protecting effect of proton-pump inhibitors to the significantly increased PGE2 and decreased LTB4 levels in comparison to the H2-blocker group during the ulcer-healing stage.

The cysteinyl leukotriene cystLT1 receptor (cysLT1R) antagonists, including Montelukast (MLK), are the first new class of anti-asthma drugs to be introduced in the past 30 years. Overall, they are less effective than steroids, but some asthmatic subjects show a striking improvement and a steroid-sparing effect has been demonstrated, [8]. Verini et al., [9] and Joos et al., [10] found montelukast effective as add-on therapy for asthmatic patients who remain uncontrolled with low, moderate or high doses of inhaled corticosteroid monotherapy. Moreover, Maspero et al., [11] found montelukast was effective as monotherapy for patients with mild asthma who remain uncontrolled or unsatisfied while on inhaled corticosteroid monotherapy.

Furthermore, MLK inhibits the transmigration of eosinophils across human umbilical vein endothelial cells under static conditions, [12] and cysLT1R activation has been shown to increase pro-inflammatory cytokine release from eosinophils. MLK not only reduced this cytokine release but also down-regulated expression of cysLT1R, [13]. Moreover, MLK blocked plasma protein extravasation and eosinophil accumulation in small, intraparenchymal bronchi of sensitized guinea pigs, [14]. Although antagonism of the cysLT1R likely explains the majority of the anti-inflammatory properties of MLK, some effects may be independent of receptor blockade, [15].

The present study aimed to evaluate experimentally the impact of prophylactic administration of MLK on the ulcerogenic effect of exposure to cold-restraint stress with and without administration of dexamethasone (DXM) in rat model.

**Material and Methods**

The present study was conducted at Pharmacology department, Faculty of Medicine, Benha University and included 64 adult male Sprague Dawley rats weighing 150-200 gm. Rats were acclimatized to standard laboratory conditions (12:12-h light-dark cycle, environmental temperature, free access to food and water) for 7 days before use. All experiments were performed during the same time of the day to avoid variation due to diurnal rhythms of putative regulators of gastric functions. The rats were deprived of food but not water for 24 hours before initiation of the restraint procedure and were placed in individual cages with a wide wire mesh bottoms to avoid coprophagy.

**Drugs:** Montelukast sodium (MKL), was supplied as white powder (Merk Sharp and Dohme, USA), Dexamethasone phosphate (Merk Sharp and Dohme, USA). They were suspended in distilled water and were given orally to the rats.

**Dosage:** Doses of MKL used were the average doses documented by Marusova et al., [16] and Dengiz et al., [17]. Dexamethasone was provided in two dosage regimen; 0.25 mg/kg orally which was more relevant to that used clinically, [18] and 0.5 mg/kg as a trial dose.

**Animal grouping:**

- **Group I** (Negative Control group): Included 8 rats that neither received any medications nor exposed to any forms of stress.
- **Group II** (Positive Control group): Included 8 rats that were exposed to cold-restraint for inducing stress gastric ulcer and received only distilled water (0.5-1 ml/rat).
- **Group III** (MLK-pretreated group): Included 24 rats that were pretreated with MLK in 3-variant doses, 30 minutes before the start of 3-hrs of acute cold-restraint stress and subdivided equally according to the dose into 3 subgroups:
  - **a- Subgroup III a:** Included rats given MLK in a dose of 3mg/kg p.o.
  - **b- Subgroup III b:** Included rats given MLK in a dose of 10mg/kg p.o.
  - **c- Subgroup III c:** Included rats given MLK in a dose of 30mg/kg p.o.
- **Group IV** (DXM group): Included 16 rats that received DXM in 2-variant doses, 30 minutes before the start of 3 hrs of acute cold-restraint stress and subdivided equally according to the dose into 2 subgroups.
a- Subgroup IV a: Included rats given DXM in a dose of 0.25 mg/kg orally.
b- Subgroup IV b: Included rats given DXM in a dose of 0.5mg/kg orally.

• Group V (MLK- pretreated DXM group): Included 8 rats that received MLK in a dose of (10mg/kg p.o.) concomitant with DXM in a dose of 0.5mg/kg orally 30 minutes before the start of 3 hrs of acute cold-restraint stress.

Method:

Cold and restraint are two stresses that act synergistically, [19] for induction of gastric ulcer; the animals were immobilized in open wire restraint cages and placed at 4 ± 1°C for 3 hours, [20].

After cold restraint, the animals were sacrificed by decapitation. Immediately after laparotomy, the gastroesophageal and pylodudenal junction were clamped, the stomach was excised en block, opened along the greater curvature, cleaned with isotonic cold saline and spread over a cold place to allow the mucosa to be everted and examined macroscopically for damage.

Assessment of gastric ulceration:

1- The Ulceration index (UI) was determined using the formula: Ulcer index = 10/X; where X = Total mucosal area/Total ulcerated area, [21]. Lesion size (mm) was measured along its greatest length and for assessing the area of petechiae, each 5 petechiae were considered equivalent to 1 mm ulcer, [22].

2- The preventive index (PI) of a drug was calculated from the formula: PI = 100 x [(UI of control stressed group-UI of treated group)/UI of control stressed group], [23].

3- Color photographs of the mucosal surface were obtained using digital camera and the image was magnified ten times than normal for documentation and assurance of assessment.

Gastric tissues extract levels of biomarkers:

Preparation of stomach tissue homogenates: stomach tissues were ground with liquid nitrogen, then the ground tissues (0.5 g each) were homogenized in 10 mg/mL ice-cold phosphate-buffered saline to get a concentration of 10% (W/V) using a homogenizer for 15 min. Homogenates were filtered and centrifuged by using a refrigerated centrifuge at 4°C, [24]. Then, the supernatant was used for spectrophotometric determination of the enzymatic activities of superoxide dismutase (SOD), [25], catalase (CAT), [26] and glutathione (GSH) level, [27]. All assays were carried out at room temperature.

Statistical analysis:

Obtained data were presented as mean ± SD, ranges, numbers and ratios. Results were analyzed using unpaired t-test. Statistical analysis was conducted using the SPSS (Version 10, 2002) for Windows statistical package. p value <0.05 was considered statistically significant.

Results

Macroscopic gastric examination:

All animals exposed to cold-restraint stress with or without DXM administrations had gastric ulcers of varied extent and severity, irrespective of the administration of MLK. However, group IV animals showed significantly higher UI compared to group II (p<0.001). Prophylactic MLK administration significantly reduced UI compared to group II (p<0.001) and compared to group IV (p<0.001).

There was dose-dependent reduction of UI with administration of MLK manifested as significantly (p<0.05) reduced UI in groups IIIb and IIIc compared to group IIIa with significantly lower UI in group IIIc compared to group IIIb (p<0.05). Also, DXM showed dose-dependent ulcerogenic effect with significantly higher UI in group IVb compared to group IVa, (p<0.001). Also, MLK administered in dose of 10 mg showed significantly (p<0.001) reduced UI in group IIIb compared to group V, (Table 1, Fig. 1).

Fig. (1): Mean UI recorded in studied groups.
Montelukast Ameliorates Dexamethasone Effect

Table (1): Mean ulcer index (UI) reported in studied groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
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<td></td>
<td></td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>a</td>
</tr>
<tr>
<td>Mean</td>
<td>4.6 ± 1.1</td>
<td>2.6 ± 0.67</td>
<td>2.1 ± 0.21</td>
<td>1.75 ± 0.24</td>
<td>6.4 ± 0.6</td>
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<tr>
<td>$P_2$</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>$P_3$</td>
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<tr>
<td>$P_4$</td>
<td></td>
<td>&lt;0.05</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
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<tr>
<td>$P_5$</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
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<tr>
<td>$P_6$</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tbody>
</table>

$p_2$: significance versus Group II  
$p_3$: significance versus Group IIIa  
$p_4$: significance versus Group IIIb  
$p_5$: significance versus Group IVa  
$p_6$: significance versus Group IVb

Prophylactic administration of MLK showed a dose-dependent preventive index against ulcerogenic effect of cold-restraint stress that was significantly higher in groups IIIb ($p_2 < 0.05$) and IIIc ($p_3 < 0.05$) compared to group IIIa with significantly higher preventive index in group IIIc compared to group IIIb ($p_4 < 0.05$). For evaluating effect of administration of DXM in addition to cold-restraint stress in animals administered 10 mg MLK prior to ulcer-induction showed non-significantly lower PI in those administered DXM compared to those exposed to cold-restraint stress only. (Table 2, Fig. 2).

Gastric tissues extract levels of biomarkers:

All studied animals showed significantly ($p_1 < 0.001$) lower gastric tissue extract levels of SOD compared to control animals. Exposure to cold-restraint and received DXM (Group IV) showed lower SOD levels that were non-significant ($p_2 > 0.05$) in group IVa but were significant ($p_2 < 0.05$) in group IVb compared to those exposed to cold-restraint only, with significantly ($p_5 < 0.05$) lower SOD level in those received higher dose of DXM (Group IVb) compared to those received lower dose (Group IVa). Combined administration of MLK ameliorated significantly ($p_2 < 0.05$) the effect of cold-restraint on SOD levels and showed dose response effect, where SOD levels were significantly higher in groups IIIb and IIIc, ($p_2 < 0.05$ & $< 0.001$, respectively) compared to group IIIa with significantly ($p_5 < 0.001$) higher SOD levels in group IIIc compared to IIIb.

Similarly, MLK significantly ($p_5 & p_6 < 0.001$) improved SOD levels in animals exposed to cold-restraint and received DXM compared to those did not received MLK. The effect of combined administration of MLK was dependent on multiplicity of ulcerogenic agents as gastric tissue extract SOD levels in animals received MLK in dose of 10 mg and exposed to cold-restraint were significantly ($p_4 < 0.05$) higher compared to those exposed to cold-restraint and received DXM, (Table 3, Fig. 3).

Ulcerogenic agents induced significantly ($p_1 < 0.001$) increased CAT activity in gastric tissue, irrespective of administration of MLK, compared to control animals. Moreover, animals received DXM in addition to cold-restraint stress showed significantly higher ($p_2 < 0.001$) CAT activity compared to those exposed to cold-restraint stress only and in those received high DXM dose compared to those received lower dose ($p_5 < 0.001$). MLK combination in group III significantly ($p_2 < 0.001$)
reduced CAT activity in comparison to group II
and in group V compared to group IV (p5 & p6 <
0.001) and showed dose-dependent effect mani-
fested as significant reduction in group IIIb and
IIIc compared to group IIIa (p3 <0.001) and in
group IIIc compared to group IIIb (p4 <0.05). Also,
DXM showed dose-dependent elevation of CAT
activity that was significantly higher in group IVb
compared to group IVa (p5<0.001). However, MLK
in dose of 10 mg significantly (p4 <0.001) reduced
CAT activity in group IIIb compared to group V,
(Table 4, Fig. 4).

Table (3): Mean (±SD) gastric tissue extract levels of SOD (nmol/mg tissue) estimated in studied groups.

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>Group III a</th>
<th>Group III b</th>
<th>Group IV a</th>
<th>Group IV b</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>127.2±1.4</td>
<td>93.2±1.8</td>
<td>98.1±1.9</td>
<td>103.1±1.3</td>
<td>88.4±1.7</td>
<td>85.2±2</td>
</tr>
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<td>p1</td>
<td>&gt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>p2</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
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<tr>
<td>p3</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
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<tr>
<td>p4</td>
<td>&gt;0.001</td>
<td>&lt;0.001</td>
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<td>p5</td>
<td>&gt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
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<tr>
<td>p6</td>
<td>&gt;0.001</td>
<td>&lt;0.001</td>
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</table>

p1: significance versus Group I  p2: significance versus Group II  p3: significance versus Group IIIa
p4: significance versus Group IIIb  p5: significance versus Group IVa  p6: significance versus Group IVb

Table (4): Mean (±SD) gastric tissue extract levels of CAT (nmol/mg tissue) estimated in studied groups.

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>Group III a</th>
<th>Group III b</th>
<th>Group IV a</th>
<th>Group IV b</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>12.7±0.3</td>
<td>19.8±0.33</td>
<td>18.5±0.1</td>
<td>17.6±0.25</td>
<td>17±0.3</td>
<td>20.5±0.28</td>
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<tr>
<td>p1</td>
<td>&gt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>p2</td>
<td>&gt;0.001</td>
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<td>p3</td>
<td>&gt;0.001</td>
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<td>p4</td>
<td>&gt;0.001</td>
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<td>p5</td>
<td>&gt;0.001</td>
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<td>p6</td>
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p1: significance versus Group I  p2: significance versus Group II  p3: significance versus Group IIIa
p4: significance versus Group IIIb  p5: significance versus Group IVa  p6: significance versus Group IVb
Gastric tissue extract GSH levels were significantly decreased in animals exposed to cold-restraint stress \((p_1<0.05)\) and those received additionally DXM \((p_1<0.001)\) compared to control animals with non-significantly \((p_5 & p_6>0.05)\) lower levels in those received higher versus lower DXM. Animals administered MLK prior to cold-restraint stress ulcer-induction showed significantly higher GSH levels compared to their counterpart positive control group \((p_2<0.05)\) and non-significantly lower levels compared to negative control animals \((p_1>0.05)\). However, animals administered MLK prior to cold-restraint stress and DXM administration showed less evident effect and showed non-significantly higher GSH levels compared to their counterpart positive control group \((p_2<0.05)\) and significantly lower levels compared to negative control animals \((p_1<0.05)\). There was a non-significant between animals received 10 mg MLK, but in favor of group IIIb,

(Table 5, Fig. 5).

![Fig. (5): Gastric tissue extract GSH levels estimated in studied groups.](image)

Table (5): Mean (±SD) gastric tissue extract levels of GSH (nmol/mg tissue) estimated in studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
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<tbody>
<tr>
<td>Mean±SD</td>
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<td>3.6±0.2</td>
<td>3.8±0.2</td>
<td>3.95±0.2</td>
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\(p_1: \) significance versus Group I  
\(p_2: \) significance versus Group II  
\(p_3: \) significance versus Group IIIa  
\(p_4: \) significance versus Group IIIb  
\(p_5: \) significance versus Group IVa  
\(p_6: \) significance versus Group IVb

![Photograph (1): Normal gastric mucosa in control group (group I).](image)  
![Photograph (2): Gastric mucosa in cold-restraint stress group (group II). The black arrow shows gastric erosions while green arrow directed to area of hyperaemia.](image)
Photograph (3): Gastric mucosa in group III a (MLK in a dose of 3mg/kg p.o.30 min. before cold-restraint stress exposure). The black arrow shows small gastric erosions while green arrow directed to area of hyperaemia.

Photograph (4): Gastric mucosa in group III b (MLK in a dose of 10mg/kg p.o.30 min. before cold-restraint stress exposure). The black arrow shows small gastric erosions while green arrow directed to area of hyperaemia.

Photograph (5): Gastric mucosa in group III c (MLK in a dose of 30mg/kg p.o.30 min. before cold-restraint stress exposure). The green arrows directed to areas of hyperaemia.

Photograph (6): Gastric mucosa in group IVa (DXM 0.25 mg/kg orally 30 min. before cold-restraint stress exposure). The black arrow shows gastric erosions while green arrow directed to area of hyperaemia.

Photograph (7): Gastric mucosa in group IVb (DXM 0.5 mg/kg orally 30 min. before cold-restraint stress exposure). The black arrows show massive gastric erosions while green arrow directed to areas of hyperaemia.

Photograph (8): Gastric mucosa in group V (dexamethasone in a dose 0.5 mg/kg orally concomitant with MLK in a dose 10 mg/kg p.o. 30 min. before cold-restraint stress exposure). The black arrow shows small gastric erosions while green arrow directed to small area of hyperaemia.
Discussion

The current study included only male rats to spare the effect of gender on ulcer-induction or treatment associated biomarker changes depending on the previous work of Uslu et al., [28] who found sex differences do not interfere with stress ulcer formation, but SOD activity in rat gastric tissue has varied significantly by hormonal milieu. Also, all animals were stressed and received medication at fixed time of the day to guard against effect of circadian changes previously documented by Savran et al., [29] who reported in experimental models of ulceration that the circadian time of application of the ulcerogenic stimulus must be considered as an important experimental factor. Moreover, the protective effectiveness of antiulcer drugs can express time-dependent differences and must also be taken into account in investigative research, [29].

The study presented two models of gastric ulceration induction; cold-restraint stress ulcer-induction alone and combined with administration of DXM; one of the effective therapeutic modalities for asthma especially in cases with status asthmaticus. Cold-restraint model was previously documented by Landeira-Fernandez, [30] who found hypothermia resulting from cold-water exposure has a deleterious effect on gastric ulceration and the animal’s conscious activity during the cold-water immersion increases the severity of gastric mucosal damage and concluded that cold-restraint is a useful procedure for the study of the underlying mechanisms involved in stress-induced ulceration.

All animals exposed to stress with or without DXM administrations had gastric ulcers of varied extent and severity, however, animals exposed to cold and restraint stress in addition to administration of DXM showed significantly higher UI compared to those exposed to cold and restraint stress only with significantly higher UI in those administered higher dose of DXM compared to those administered the lower dose. These data point to a fact that the impact of ulcerogenic agents was variant and in drug-induced ulcers was dose-dependent, and both may act synergistically. These findings could be attributed to the facts that specific brain pro-opiomelanocortin gene products; adrenocorticotropic (ACTH) and beta-endorphin modulate gastric mucosal integrity in response to stress, [31] and exposure to cold-restraint for 3 hr was found to exhaust these products as documented by Filar et al., [32] who found gastric erosions elicited in male rats by 3-h cold-restraint or water-restraint stresses were increased by pretreatment with a rabbit antiserum to ACTH 30 min before stress. On contrary, dexamethasone makes the mucosa prone to ulceration by inhibiting the activity of prostaglandin synthetase to block the gastroprotective action of prostaglandin and also by inhibiting the peroxidase, thereby elevating the endogenous H2O2 level to generate more reactive hydroxyl radical responsible for the mucosal damage, [33].

Animals administered prophylactic MLK prior to ulcer-induction showed significantly lower UI compared to their counterpart positive control group. This finding was in line with that reported by Dengiz et al., [17] who investigated the gastroprotective effect following oral administration of montelukast, lansoprazole, famotidine, and ranitidine, respectively, in rats with indomethacin-induced ulcers and found that all reduced the development of indomethacin-induced gastric damage, with this reduction occurring at a greater magnitude for montelukast, famotidine, and lansoprazole than for ranitidine.

The protective effect of prophylactic administration of MLK was found to be dose-dependent as shown by the significantly higher ulcer PI in animals received MLK in a dose of 30 mg compared to those received 3 or 10 mg dose with significantly higher PI in those received 10 mg compared to those received 3 mg. Such effect goes in hand with that documented clinically by Bronsky et al., [34] who found montelukast caused dose-related protection against exercise-induced bronchoconstriction at the end of a once-daily dosing interval.

Such protective effect of MLK could be attributed to its anti-oxidant properties; in support of this assumption, prophylactic administration of MLK significantly reduced CAT activity and improved SOD activity and level of GSH in gastric tissue extract compared to their levels in animals did not receive MLK prophylaxis. These findings go in hand with that documented clinically by Bronsky et al., [35] who found treatment with montelukast almost completely reversed the low contractile responses of rat urinary bladder to carbachol and decreased lipid peroxidation and myeloperoxidase activity of the bladder tissues and the significant decrease in tissue glutathione level in the ischemia/reperfusion injury group compared with controls was also prevented by montelukast and concluded that MLK treatment prevented oxidative tissue damage following ischemia/reperfusion injury.

An another explanation for the reported preventive effect of MLK on experimentally induced ischemia/reperfusion injury.
gastric ulceration; MLK may act as anti-inflammatory agent against the local effect of DXM. Such assumption coincided with that previously reported by Holma et al., [36] who supposed that Cysteinyl leukotrienes play a part in inflammatory processes such as inflammatory bowel diseases and found that montelukast significantly reduced the occult blood in the faeces/ gross bleeding, maintained normal body weight gain and tended to decrease the ratio of leukotriene B_{4}/prostaglandin E_{2} production in the colon in vitro and concluded that montelukast has some potential to ameliorate mild experimental colitis induced by dextran sulphate sodium.

In support of MLK anti-inflammatory effect; Tahan et al., [37] found that montelukast inhibits tumor necrosis factor-alpha-stimulated IL-8 expression through changes in nuclear factor-kappaB p65-associated histone acetyltransferase activity and drugs targeting these enzymes may enhance the anti-inflammatory actions of montelukast.

It could be concluded that prophylactic administration of MLK could ameliorate the ulcerogenic effect of variant ulcerogenic agents with high preventive index of 10 mg MLK once daily on the p65-associated histone acetyltransferase activity. 

References


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