Possible Effect of Mosapride on Gastric Mucosa and Indomethacin Induced Gastric Ulcer in Male Albino Rats

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Abstract: Background: Mosapride, a gastroprokinetic agent that acts as a selective 5HT\textsubscript{4} agonist, is used for the treatment of gastritis, gastro-oesophageal reflux disease, functional dyspepsia and irritable bowel syndrome. Non-steroidal anti-inflammatory drug (NSAID) commonly used as a prescription medication to reduce fever, pain, stiffness, and swelling. Peptic ulcer is a major side effect of NSAIDs. In this study we tested the effect of oral administration of mosapride 0.25, 0.5, 0.75, 1.25, 2.5 and 5mg/kg on gastric mucosa and on NSAIDs induced gastric ulcers in rats.

Methods: Acute gastric ulcers were induced in rats by the oral administration of indomethacin.

Results: Mosapride had no effect on gastric mucosa but increased the prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) level. Pretreatment with mosapride at 0.25 and 0.5 mg/kg prevented the mucosal damage induced by indomethacin. The higher doses, from 0.75 up to 5mg/kg, had no effect on indomethacin-induced gastric ulcer.

Conclusion: Mosapride had no effect on gastric mucosa but increased PGE\textsubscript{2} and demonstrated anti-ulcer effect in small doses only. This effect could be partially mediated through increased prostaglandin E\textsubscript{2}.

Key Words: ProstaglandinE\textsubscript{2}, mosapride, peptic ulcer, ulcer, ulcer index, prokinetic

INTRODUCTION

Peptic ulcer is one of the world’s major gastrointestinal disorders, embracing both gastric and duodenal ulcers, and affecting 10% of the world population (Zapata-Colindres et al., 2006). The pathophysiology of peptic disease is attributed to the imbalance between aggressive factors like acid, pepsin, Helicobacter infection, and the local mucosal defenses like bicarbonate secretion, mucus, prostaglandins (Jain et al.,2007) and nitric oxide, as well mucosal blood flow (Parente and Parretti, 2003).

NSAIDs at high dose constitute the principal therapy for the majority of arthritis patients; however, these drugs frequently cause upper gastric discomfort, dyspepsia and gastrointestinal ulcer after prolonged usage (Villegas et al., 2004). NSAIDs damage the stomach by suppressing synthesis of gastric prostaglandins while, gastric acid exacerbates this effects by deepening superficial lesions and impairing the ulcer healing process (Malfertheiner et al., 2009).

Serotonin 5-HT\textsubscript{4} receptors are located on enteric cholinergic neurons and regulate peristalsis. 5-HT\textsubscript{4} receptors on primary afferent neurons have been postulated to modulate visceral sensation (Bharucha, 2000).

Mosapride is a second-generation 5HT\textsubscript{4} receptor agonist with no affinity for other subtypes of 5-HT receptors except for 5-HT\textsubscript{3} receptor, which is weakly antagonized by the metabolite of mosapride (Curran and Robinson, 2008). The drug is used for the treatment of acid reflux, irritable bowel syndrome and functional dyspepsia (Mizuta et al., 2006).

Fujisawa et al (2010) reported that, mosapride has a gastric mucosal protective action which could be mediated by an action on immune cells through the acceleration of ACh release from parasympathetic nerves via the activation of 5-HT\textsubscript{4} receptors. The present study aimed to explore the effect of mosapride on gastric mucosa, prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) production and its effect on the progression of mucosal ulcer induced by indomethacin.
2. MATERIALS AND METHODS


2.2. Animals: Adult male albino rats weighing 180-200 gm were obtained from National Research Laboratory, Cairo, Egypt. These animals were divided into 4 main treatment categories and each has 7 groups comprising of 6 animals for each. They were housed under hygienic and standard environmental conditions (22±1 °C) and 12h light-dark cycle. They were allowed free access to food and water ad-libitum. The animals were deprived of food but allowed free access to tap water for 24 h prior to the experiment. During fasting, rats were housed each in a separate cage with raised mesh bottom to prevent coprophagy. All experimental protocols were approved by the ethics committee of Zagazig University.

2.3. Experimental categories:

2.3.1. Studying the effect of mosapride on gastric mucosa, which includes 7 groups: Control group (0.5% carboxy methyl cellulose), three groups were treated with small doses of mosapride citrate (0.25, 0.5 and 0.75 mg/kg) groups according to Fujisawa et al. (2010) and another three groups for large doses of mosapride citrate (1.25, 2.5 and 5mg/kg), these doses are around the equivalent prokinetic human dose which is 15mg/60kg human (Hideki et al., 2003) and converted according to FDA (2005).

2.3.2. Shay rat category for studying the effect of mosapride on gastric secretions, which further divided into 7 groups: Control group (0.5% carboxy methylcellulose) and six groups treated with mosapride citrate 0.25, 0.5, 0.75, 1.25, 2.5 and 5mg/kg groups.

2.3.3. Studying the effect of mosapride on indomethacin-induced gastric ulcer which further divided into 7 groups: A group to induce gastric ulcer, pretreated with indomethacin 10 mg/kg, p.o. (Fujisawa et al. (2010). Six groups were pretreated with mosapride citrate in doses of 0.25, 0.5, 0.75, 1.25, 2.5 and 5 mg/kg p.o., one hour before indomethacin.

2.3.4. Shay rat groups for studying the effect of mosapride on indomethacin-induced changes on gastric secretions, which further divided into 7 groups: Indomethacin, 10 mg/kg, group, indomethacin, 10 mg/kg, plus mosapride citrate 0.25, 0.5, 0.75, 1.25, 2.5 and 5mg/kg groups.

2.4. Experimental models

2.4.1. Indomethacin induced gastric ulcer: indomethacin 10mg/kg was administered by gavage. The animals were sacrificed 6 h later under deep ether anesthesia; the stomachs were removed then opened along the greater curvature (Fujisawa et al., 2010).

The ulcer score was determined according to the 1 to 5 scoring system devised by Wilhelmi and Menasse-Gdynia (1972). The incidence of ulceration was calculated. The ulcer index (U.I) was calculated by the following equation: U.I = Mean ulcer score of similarly treated group X percentage of ulcerated animals of the same group (Radwan and Ghaleb, 1974).The preventive effect of mosapride on the severity of ulceration was calculated according to the method of Hano et al. (1976).

2.4.2. Shay rats: Gastric secretion was tested by Shay rats “pylorus ligated” technique (Shay et al., 1945). The volume of gastric juice after 4 hours of ligation was measured, and then centrifuged at 2000 r.p.m. for 10 min. The supernatant fluid was then analyzed for titratable acidity. In this model indomethacin or mosapride were given p.o., 2 hours before ligation while mosapride is given 1 hour before indomethacin in the interaction groups.

Determination of titratable acidity: The one end point method was used as described by Grossman (1963). The acid concentration was calculated as milli-equivalent per litre.

<table>
<thead>
<tr>
<th>Score</th>
<th>Histopathological finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>epithelial cell damage</td>
</tr>
<tr>
<td>2</td>
<td>Glandular disruption, vasocongestion or edema in the upper mucosa</td>
</tr>
<tr>
<td>3</td>
<td>Haemorrhagic damage in the mid to lower mucosa</td>
</tr>
<tr>
<td>4</td>
<td>deep necrosis and ulceration</td>
</tr>
</tbody>
</table>

Each section was evaluated on a cumulative basis to give the histological index, the maximum score thus being 10. All determinations were performed in a randomized manner with both transparencies and histological sections coded to eliminate observer bias (Whittle et al, 1990).

STATISTICAL ANALYSIS: All data were collected, tabulated, entered, checked and analyzed using statistical program for social science (SPSS) for windows version 14 (Swinscow, 1994). The obtained data were tabulated as means ± SEM. Comparison
between different groups were made using one way analysis of variances (one-way ANOVA) followed by Tukey post-hoc test to determine the difference between treatment groups. Statistical comparisons for non-parametric data (ulcer and pathological scores) were analyzed by Dunnet’s C multiple comparison test. The differences were considered to be significant when \( p < 0.05 \).

3. RESULTS

3.1. The effect of mosapride on gastric mucosa, mucosal mucous & PGE\(_2\) concentrations and gastric secretions (volume, acid concentration and acid output) of male albino rats: After administration of mosapride in doses of 0.25, 0.5, 0.75, 1.25, 2.5 and 5mg/kg, the incidence of ulceration, the mean ulcer score and the calculated ulcer index were zero, mean PGE\(_2\) concentrations were increased (\( p < 0.5 \)) in relation to the control group while the mucus concentrations, the mean volumes, acid concentrations and acid output were insignificantly changed in relation to each other and to the control group (table 1 & photo 1, 2).

3.2. Effect of mosapride on indomethacin-induced gastric ulcer, mucosal mucous & PGE\(_2\) concentrations and gastric secretions (volume, acid concentration and acid output) in male albino rats: In the control group, the incidence of ulceration, the mean ulcer score and the calculated ulcer index were zero. After administration of indomethacin in a dose of 10 mg/kg, the incidence of ulceration was 100%, the mean ulcer score and the ulcer index were increased (\( p < 0.05 \)) (Table 2 & Photo 3). Administration of mosapride in a dose of 0.25 mg/kg one hour prior to indomethacin decreased the incidence of ulceration from 100% in indomethacin group to 83.3%, the mean ulcer score was reduced (\( p < 0.05 \)) and the ulcer index decreased in relation to indomethacin-treated group (Table 2 & photo 4). Mosapride 0.5 mg/kg administered one hour prior to indomethacin did not change the incidence of ulceration but, the mean ulcer score was reduced (\( p < 0.05 \)) in relation to indomethacin-treated group but not to mosapride 0.25mg/kg group and the ulcer index decreased in relation to indomethacin-treated group but, increased in relation to that of mosapride 0.25mg/kg group (Table 2& photo 5). Mosapride in a dose of 0.75, 1.25, 2.5 and 5 mg/kg did not change the incidence of ulceration but, the mean ulcer score was increased (\( p < 0.05 \)) in relation to mosapride 0.25 and 0.5 mg/kg groups but not to the indomethacin-treated group while, the ulcer index increased in relation to indomethacin-treated group and also that of mosapride 0.25, 0.5 mg/kg groups (Table 2& photo 6). The preventive index of mosapride in a dose of 0.25 mg/kg was 78.9%; this index was decreased to 63.1, 0, -5.05, -10.41 and 15.5% with mosapride doses 0.5, 0.75, 1.25, 2.5 and 5 mg/kg respectively (Table 2).

Administration of indomethacin decreased PGE\(_2\) and mucus concentrations (\( p < 0.05 \)) in relation to control group. After administration of mosapride in different doses one hour prior to indomethacin, the PGE\(_2\) concentrations were increased (\( p < 0.05 \)) in relation to indomethacin-treated group but, decreased (\( p < 0.05 \)) in relation to the control group, however, the mucus concentrations were not changed in relation to each other and to indomethacin-treated group and significantly decreased (\( p < 0.05 \)) in relation to the control group (Table 2).

Neither administration of indomethacin alone nor mosapride prior to indomethacin changed the mean volume of gastric secretion. Indomethacin increased (\( p < 0.05 \)) the acid concentration and output in relation to control group. They were increased (\( p < 0.05 \)) after administration of mosapride in different doses of one hour prior to indomethacin in relation to control group but not in relation to each other and the indomethacin-treated group (Table 2).

3.3. Histopathological Findings

3.3.1. Light microscopic examination of gastric tissues after administration of mosapride:

In the control group, light microscopic examination of gastric tissues showed normal gastric biopsy with intact mucosal surface and mucosal gland and the mean histopathological score was zero. Light microscopic examination of gastric tissues after administration of mosapride in different doses also showed normal gastric biopsy with intact mucosal surface and mucosal gland and the mean histopathological score was zero (Table 3 & Microphotograph 1& 2).

3.3.2. Light microscopic examination of the effect of mosapride 0.25, 0.5, 0.75, 1.25, 2.5 and 5 mg/kg on indomethacin-induced changes on gastric tissues:

Light microscopic examination of gastric tissues after administration of indomethacin showed epithelial damage (1) total necrosis of mucosal glands (4), marked congestion of the mid mucosa and sub-mucosa (2) and hemorrhagic damage of the mid and lower mucosa and sub-mucosa (3) (Table 4, Microphotograph 3). Comparing the effect of different doses of mosapride on the histo-pathological changes of gastric tissue, it was found that the smallest dose (0.25 mg/kg) of mosapride was the most effective in protection against ulcer followed by the 2nd dose (0.5 mg/kg). These doses decreased \( p < 0.05 \) the mean pathological score compared to indomethacin group. The other doses of mosapride didn’t affect in the mean
Pathological score compared to indomethacin group (Table 4 & Microphotograph 4, 5 and 6).

Table (1): Effect of oral administration of mosapride (0.25, 0.5, 0.75, 1.25, 2.5 and 5 mg/kg) on gastric mucosa, mucosal mucus, PG\(_E2\) concentration and gastric secretion (mean volume, acid concentration and acid output) in male albino rats (n=6).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Parameters</th>
<th>Control</th>
<th>Mosapride Small doses</th>
<th>Mosapride Large doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.25 mg/kg</td>
<td>0.5 mg/kg</td>
<td>0.75 mg/kg</td>
</tr>
<tr>
<td>Incidence of ulceration (%)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean ulcer score</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ulcer index</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean PG(_E2) concentration ng/g wet tissue + S.E.M.</td>
<td>144.7±4.47</td>
<td>190.33±4.6</td>
<td>177.6±5.35</td>
<td>182.6±3.9</td>
</tr>
<tr>
<td>Mean mucous concentration mg% hexose + S.E.M.</td>
<td>169.75±1.7</td>
<td>155.83±5.1</td>
<td>152.47±4</td>
<td>150.65±5.4</td>
</tr>
<tr>
<td>Mean volume ml/4hr + S.E.M.</td>
<td>15.17±0.31</td>
<td>15.3±0.31</td>
<td>15.17±0.38</td>
<td>15.5±0.56</td>
</tr>
<tr>
<td>Mean acid concentration m.Eq/L + S.E.M.</td>
<td>5±0.23</td>
<td>4.87±0.08</td>
<td>4.72±0.14</td>
<td>4.88±0.11</td>
</tr>
<tr>
<td>Mean acid output µEq/h + S.E.M.</td>
<td>18.91±0.55</td>
<td>18.7±0.55</td>
<td>17.85±0.33</td>
<td>19.02±0.52</td>
</tr>
</tbody>
</table>

Data are presented as means±SEM; n=number of rats in each group. The control group received 0.5% carboxy methyl cellulose. Mosapride doses were administered p.o.. The animals were sacrificed 6 h later under deep ether anesthesia. Statistical analysis was done using one-way ANOVA followed by Tukey post-hoc test for all parameters except mean ulcer score Dunnet’s test was utilized. * Significantly different from control group at P<0.05.
Table (2): Effect of oral administration of mosapride (0.25, 0.5, 0.75, 1.25, 2.5 and 5 mg/kg rat) on indomethacin-induced gastric ulcer, mucosal mucous, PGE2 concentrations and gastric secretions (volume, acid concentration and acid output) in male albino rats: in male albino rats (n=6).

<table>
<thead>
<tr>
<th>Groups Parameters</th>
<th>Control (Vehicle)</th>
<th>Indomethacin</th>
<th>Indomethacin + mosapride</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Small doses</td>
<td>Large doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25 mg/kg</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>Incidence of ulceration (%)</td>
<td>0</td>
<td>100</td>
<td>83.3 ± 0.17*</td>
</tr>
<tr>
<td>Mean ulcer score ± S.E.M.</td>
<td>0</td>
<td>3.17 ± 0.17*</td>
<td>0.83 ± 0.17*</td>
</tr>
<tr>
<td>Ulcer index</td>
<td>0</td>
<td>317</td>
<td>66.6 ± 5.1±</td>
</tr>
<tr>
<td>Preventive index (%)</td>
<td></td>
<td>78.9%</td>
<td>63.1%</td>
</tr>
<tr>
<td>Mean PGE2 concentration ng/g wt. tissue ± S.E.M.</td>
<td>144.7 ± 4.47</td>
<td>109.5 ± 3.7*</td>
<td></td>
</tr>
<tr>
<td>Mean mucous concentration mg% hexose ± S.E.M.</td>
<td>169.7 ± 1.7</td>
<td>112.5 ± 4.1*</td>
<td></td>
</tr>
<tr>
<td>Mean volume ml/4hr ± S.E.M.</td>
<td>15.17 ± 0.31</td>
<td>14.25 ± 0.25</td>
<td></td>
</tr>
<tr>
<td>Mean acid concentration m.Eq/L ± S.E.M.</td>
<td>5 ± 0.23</td>
<td>7.65 ± 0.3*</td>
<td></td>
</tr>
<tr>
<td>Mean acid output µEq/h ± S.E.M.</td>
<td>18.91 ± 0.55</td>
<td>28.5 ± 0.55*</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as means ±SEM; n=number of rats in each group. The control group received 0.5% carboxy methyl cellulose by gavage. Gastric ulceration was induced by administration of indomethacin (10mg/kg, p.o.). Pretreatment with mosapride doses was done 60 min before indomethacin. The animals were sacrificed 6 h later under deep ether anesthesia. Statistical analysis was done using one-way ANOVA followed by Tukey post-hoc test for all parameters except mean ulcer score Dunnet’s C test was utilized. * Significantly different from control group at P<0.05. # Significantly different from indomethacin group at P<0.05 versus.
Table (3): Effect of oral administration of mosapride 0.25, 0.5, 0.75, 1.25, 2.5 and 5 mg/kg on the mean histopathological score in gastric tissues of male albino rats (n=6).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control</th>
<th>Mosapride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Small doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25 mg/kg</td>
</tr>
<tr>
<td>Mean Histopathological Score</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are presented as means of histopathological score; n=number of rats in each group. 1; epithelial cell damage; 2; Glandular disruption, vasocongestion or edema in the upper mucosa; 3; Haemorrhagic damage in the mid to lower mucosa; 4; deep necrosis and ulceration. Each section was evaluated on a cumulative basis to give the histological index, the maximum score thus being 10. All determinations were performed in a randomized manner with both transparencies and histological sections coded to eliminate observer bias (Whittle et al, 1990). Statistical analysis was done using one-way ANOVA followed by Dunnet’s C post-hoc test.

Table (4): Effect of oral administration of mosapride (0.25, 0.5, 0.75, 1.25, 2.5 and 5 mg/kg rat) on indomethacin-induced changes in histopathological score in gastric tissues of male albino rats (n=6).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control (Vehicle)</th>
<th>Indomethacin</th>
<th>Indomethacin + Mosapride</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Small doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.25 mg/kg</td>
</tr>
<tr>
<td>Mean histopathological score ± S.E.M.</td>
<td>0</td>
<td>$9±0.63^*$</td>
<td>$2.83±0.17^*$</td>
</tr>
</tbody>
</table>

Data are presented as means of histopathological score±SEM; n=number of rats in each group. 1; epithelial cell damage; 2; Glandular disruption, vasocongestion or edema in the upper mucosa; 3; Haemorrhagic damage in the mid to lower mucosa; 4; deep necrosis and ulceration. Each section was evaluated on a cumulative basis to give the histological index, the maximum score thus being 10. All determinations were performed in a randomized manner with both transparencies and histological sections coded to eliminate observer bias (Whittle et al, 1990). Statistical analysis was done using one-way ANOVA followed by Dunnet’s C post-hoc test. * Significantly different from control group at P<0.05. # Significantly different from indomethacin group at P<0.05 versus.
Photo (1): Gastric mucosa of rat from the control group. The incidence of ulceration, the mean ulcer score and the calculated ulcer index were zero.

Photo (2): Gastric mucosa after administration of mosapride in dose of 5mg/kg. The incidence of ulceration, the mean ulcer score and the calculated ulcer index were zero.

Photo (3): Gastric mucosa of rat received indomethacin 10mg/kg showing ulcers which appear as dark spots of variable sizes, the incidence of ulceration was 100%, the mean ulcer score and the ulcer index were increased.
Photo (4): Gastric mucosa of rat received mosapride (0.25 mg/kg) one hour before indomethacin. The incidence of ulceration, the mean ulcer score and the ulcer index are decreased in relation to indomethacin-treated group.

Photo (5): Gastric mucosa of rat received mosapride (0.5 mg/kg) one hour before indomethacin. No change in the incidence of ulceration but, the mean ulcer score and the ulcer index were decreased in relation to indomethacin-treated group.

Photo (6): Gastric mucosa of rat received mosapride (0.75 mg/kg) one hour before indomethacin. No change the incidence of ulceration, the mean ulcer score or index in relation to the indomethacin-treated group.
Photo (7): Gastric mucosa of rat received mosapride (1.25 mg/kg) one hour before indomethacin. No change the incidence of ulceration, the mean ulcer score or index in relation to the indomethacin-treated group.

Photo (8): Gastric mucosa of rat received mosapride (2.5 mg/kg) one hour before indomethacin. No change the incidence of ulceration, the mean ulcer score or index in relation to the indomethacin-treated group.

Photo (9): Gastric mucosa of rat received mosapride (5 mg/kg) one hour before indomethacin. No change the incidence of ulceration, the mean ulcer score or index in relation to the indomethacin-treated group.
Possible Effect of Mosapride on Gastric Mucosa and Indomethacin Induced Gastric Ulcer in Male Albino Rats

Microphotograph (1): Gastric biopsy from a rat in control group shows intact mucosal surface and mucosal gland in control rat. (Score 0) H&E x400.

Microphotograph (2): Gastric biopsy from a rat treated with mosapride in doses of 0.5 mg/kg showing intact mucosal surface and mucosal gland in rat taking (Score 0) H&E x400.

Microphotograph (3): Gastric biopsy from a rat treated with indomethacin (10 mg/kg). This slide shows epithelial damage (1), necrosis of mucosal glands (4), congestion of the mid mucosa and sub-mucosa (2) and hemorrhagic damage of the mid and lower mucosa and sub-mucosa (3) (Score 10). H&E x400.
Microphotograph (4): Gastric biopsy from a rat treated with mosapride in a dose of 0.25 mg/kg one hour before indomethacin showing mild mucosal (1), and sub-mucosal congestion and edema (1), (score 2). H&E 400.

Microphotograph (5): Gastric biopsy from a rat treated with mosapride in a dose of 0.5 mg/kg one hour before indomethacin showing epithelial damage (1) and glandular disruption (2) (Score 3) H&E 400.

Microphotograph (6): Gastric biopsy from a rat treated with mosapride in a dose of 0.75 mg/kg one hour before indomethacin showing epithelial damage (1), full mucosal ulceration (4), mucosal and sub-mucosal congestion, edema (2) and hemorrhage (3) (Score 10) H&E 400.
Possible Effect of Mosapride on Gastric Mucosa and Indomethacin Induced Gastric Ulcer in Male Albino Rats

**Microphotograph (7):** Gastric biopsy from a rat treated with mosapride in a dose of 1.25 mg/kg rat one hour before indomethacin showing epithelial damage (1), full mucosal ulceration (4), hemorrhagic damage of the mid and lower mucosa (3) and mucosal and submucosal congestion, edema (2) (Score 10) H&E x400.

**Microphotograph (8):** Gastric biopsy from a rat treated with mosapride in a dose of 2.5 mg/kg one hour before indomethacin showing epithelial damage (1), marked glandular disruption and mucosal and submucosal congestion (2), necrosis (4) and hemorrhagic damage of the mid and lower mucosa (3) (Score 10) H&E x400.

**Microphotogram (9):** Gastric tissue in rat taking mosapride in a dose of 5 mg/kg one hour before indomethacin showing epithelial damage 1, glandular disruption, mucosal and sub-mucosal congestion2, necrosis 4 and hemorrhage of the mid and lower mucosa and sub-mucosa 3 (Score 10) H&E x400.
4. DISCUSSION

Previous studies demonstrated that mosapride in doses below that required for increasing gastric emptying could protect from indomethacin-induced ulcer. The present work was constructed to detect the effect of the drug on gastric mucosa and on indomethacin-induced ulcer. Indomethacin induces gastric damage via inhibiting the release of protective factors like PGE2, bicarbonate, and mucus; increasing aggressive factors like acid (Suleyman, 2010). The present study assessed the effect of mosapride on most of these parameters.

The results of our work revealed that, mosapride in different doses produced no effect on gastric mucosa or mucus concentration while, PGE2 concentrations were increased. The drug did not change the volume of gastric secretion, acid concentration and acid output. These results are in parallel with Fujisawa et al. (2010) who found that mosapride (up to 3 mg/kg) induced no visible damage in the glandular part of stomach and confirmed the results of Shuurke and Neuten (1988) who shown that cisapride, a 5HT4 agonist, does not affect gastric acid secretion.

NSAID-induced ulcers could be due to topical and systemic effects and the latter may be prostaglandin-dependent (through COX inhibition) or prostaglandin-independent (Musumba et al., 2009). In present study, indomethacin produced gastric ulcerations mainly in the glandular portion of rat’s stomach and reduced the mucosal mucous and PGE2 concentration. Concerning the effect of indomethacin on gastric secretion, we found that the drug increased the acid concentration, and acid output while, no change in the volume. Our findings cope with Wallace (2008), who reported that NSAIDs induce inhibition of COX-1 activity causing microvascicular dysfunction, mucosal ischemia and tissue necrosis. Tissue necrosis causes chemotaxis of immune cells such as neutrophils and macrophages, which release proinflammatory cytokines to activate local fibroblasts and endothelial cells, leading to a final stage of gastric ulcer. Moreover, Sanders, (1984) reported that PGE2 inhibition promotes contraction in circular muscles of the stomach, while the longitudinal muscles are suppressed. This action may cause gastric motility abnormalities. Also, Wyse et al. (2001) indicated that NSAIDs induced hypercontractility of gastric smooth muscle, which may partially contribute to the mucosal damage through impairment of the microcirculation.

In the present work, we found that oral administration of mosapride in doses of 0.25 and 0.5 mg/kg elicited a significant protective effect on gastric ulcer induced by indomethacin, while this effect was lost with the higher doses of the drug. In the same context, the histopathological examination of gastric tissue revealed that the smallest dose (0.25 mg/kg) of mosapride was the most effective in reducing pathological changes followed by the dose (0.5 mg/kg). In the higher doses histopathological changes were insignificant in relation to indomethacin group. These results confirm the work of Fujisawa et al. (2010) who demonstrated that mosapride at doses of 0.1–0.75 mg/kg attenuated gastric mucosal damage in a rat indomethacin gastric mucosal injury model. Also, Tsukamoto et al. (2012) who demonstrated that mosapride (1 mg/kg) ameliorated prednisolone-induced gastric mucosal injury in dogs. Furthermore Katao et al. (2012) reported that, in mice, mosapride in doses of 0.1, 0.3 and 1mg/kg prevented the occurrence of the indomethacin-induced intestinal lesions, the maximal effect being observed at a dose of 0.3 mg/kg.

The results of the present study showed that mosapride increased PGE2 concentration in relation to indomethacin treated group. On gastric secretion, the drug did not change the volume, acid concentration and acid output in relation to indomethacin treated group. These results are in parallel with Muller-Lissner and Fraas (1986) who have demonstrated that the antulcer effect of cisapride has no antisecretory mechanism. In addition, Takeuchi et al. (1997) reported that, cisapride had no effect on gastric acid secretory activity in the presence of indomethacin. They have examined the effects of several prokinetic drugs on gastric motility and ulcerogenic responses in the rat stomach both in absence and presence of PG deficiency and concluded that, gastric prokinetic drugs caused hemorrhagic lesions in the stomach under PG-deficient conditions at doses that enhance gastric motility and emptying supporting the importance of gastric motility as the pathogenic element of gastric lesions and that high-amplitude stomach contractions may weaken the mucosa, while PG deficiency is a prerequisite for increasing mucosal susceptibility to injury caused by gastric hypermotility.

The present findings indicated that, the mucosal protective action of small doses of mosapride could be mediated partially by the increased prostaglandin secretion and decreased titratable acidity. Fujisawa et al. (2010) reported that this anti-ulcerogenic action of mosapride was mediated through cholinergic anti-inflammatory pathway via activating acetylcholine release from the enteric nervous system by 5-HT4 receptor activation, which finally acts on alpha7 nicotinic acetylcholine receptor (α7nAChR) expressed on immune cells especially monocytes and macrophages, an effect which was observed at a lower dose than that induced motility activation. They also
suggested that one possible explanation for the different responsiveness of the motility and antulcerogenic actions is that the sensitivity to Ach released from parasympathetic nerve terminals is different in smooth muscle cells and immune cells. They also reported that the activation of 5-HT3 receptors worsens intestinal lesions via enhancement of inflammatory responses. So, the 5-HT3 antagonistic action of mosapride may partly contribute to this anti-inflammatory protective action. Moreover, Katoa et al. (2012) reported that, both 5-HT3 and 5-HT4 receptors were significantly increased after the administration of indomethacin, they concluded that endogenous 5-HT exerts a dual role in the pathogenesis of indomethacin-induced small intestinal lesions and that the severity of the lesions was dose dependently suppressed by ondansetron and ramosetron, 5-HT3 receptor antagonists, and was significantly aggravated by GR113808, a 5-HT4 receptor antagonist.

In the same context, Yasuda et al. (2011) concluded that low dose metoclopramide ameliorate indomethacin-induced small intestinal ulceration in mice and it is possible that the protective effect of this agent is partly mediated by the activation of 5-HT4 receptors in addition to D2 receptor antagonism.

In conclusion: Mosapride had no effect on the gastric mucosa but increased the PGE2 secretion. The small doses of the drug had protective effect against indomethacin-induced gastric ulcer which could be attributed partially to the increased PGE2 secretion and decreased titratable acidity. The higher doses of the drug lack this protective effect might be due to increased stomach contractions which weaken the mucosa or release of mediators that antagonize the beneficial effect of increased prostaglandins. Further experimental studies are needed to explore the mechanisms of proulcerogenic potential of the high doses of mosapride.

7. REFERENCES


