The high risk of developing gastric ulcers by various non-steroidal anti-inflammatory drugs has affected their common application in the treatment of collagen diseases like arthritis. Indomethacin, a potent anti-inflammatory agent, has been found to induce gastric irritation and ulceration (1). In humans, it is expected that pregnancy which may exert physiologic stress would aggravate gastric ulcer. Instead, pregnant mothers are protected from gastric ulceration under normal conditions. Stress or restraint has been found also to induce ulcers in laboratory animals (2, 3). In the mechanism of indomethacin-induced ulcers, Djahanguiri et al. (4) found adrenalectomy to have no effect, while Urushidani (5) contrasted these findings by implicating the deficiency of glucocorticoids. In another study, Vane (6) proposed the inhibition of prostaglandin biosynthesis as a mechanism of action for aspirin-like drugs. Several other drugs have been claimed to aggravate or suppress indomethacin-induced ulcers (4). The present study was undertaken to investigate the ulcerogenic effects of indomethacin in pregnant rats and to suggest a possible mechanism.

Forty mature female Wistar rats (150–190 g) were kept with mature males capable of mating (number of females were more than males). Vaginal smears were examined on the following morning, and the day on which sperms were detected in the smear was considered to be the first day of pregnancy (7). The animals were separated into two groups: 20 were treated during mid-term (9–10 days of pregnancy), and the other 20 mice treated with drugs during late pregnancy (19–20 days of pregnancy). Ten mice from such a group served as the control, while the other ten mice received the drug. Indomethacin (Polfa) at a dose of 15 mg/kg in 1% CMC suspension containing a trace of Tween 80 was used to induce ulcers using the method of Urushidani. The method of Main and Whittle (8) was used to determine the ulcer index. The control group was treated with 0.5 ml/kg of 1% CMC suspension containing a trace of Tween 80. Results are shown in Table 1 as the mean ulcer index ± S.E. The study was repeated with 20 nonpregnant rats. Ten of them received single s.c. doses of 15 mg/kg of the drug, while the rest served as the control and were treated with 0.5 ml/kg containing a trace of Tween 80 in 1% CMC. The results were compared with the previous work by Aguwa and Mittal (9). The significance of the data was evaluated using Students’ t-tests.

The effects of pregnancy on indomethacin-induced ulcers are shown in Table 1. At mid pregnancy (9–10 days), indomethacin induced ulcers in 100% of the animals as compared with 40% in the control group. The ulcer index was 2.26±0.20 and 0.10±0.05, respectively. The difference is highly significant (P<0.01). At term (19–20 days), ulcers occurred in 30% of the control animals and in 100% of the group treated with indomethacin. Again, the ulcer index was statistically significant (P<0.01). Furthermore, when the ulcer indices of the pregnant rats, 2.26±0.20 at mid pregnancy and 2.56±0.12 at term, were compared with the ulcer index of nonpregnant rats, (1.22±0.15), the difference is highly significant. During pregnancy, there is an elaboration of several adrenal hormones-steroids, some of which have been associated with peptic ulcer (10). However, in humans, pregnancy has been reported to have a beneficial effect against ulceration. Estrogens have been implicated in this “protective” effect (11). The present study has shown increased incidence and
degree of peptic ulcer in pregnant rats as compared with nonpregnant ones treated with the same drug. An acceptable explanation at this time may be that indomethacin potentiates the ulcerogenic effects of stress, and this may overcome the protective effect of estrogens in pregnant rats. Additionally, hyper-function of the adrenal gland may result in excess hormones which may sensitize the stomach to respond to increased acid secretion (12). Adreno-cortical steroids increase pepsinogen excretion, and ulcer patients have been found to have high incidence of adrenal hyperplasia which really should exist in pregnancy. According to Gray (13), increased adrenal activity may produce gastro-intestinal ulceration by either increasing erosive action of acid and pepsin or decreasing mucosal resistance to vascular and metabolic disturbances.

In conclusion, pregnancy-induced stress with adrenal hyperplasia may potentiate the ulcerogenic activity of indomethacin in rats as found in this study. However, it is desirable to confirm these observations.

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Table 1. Effects of pregnancy on indomethacin-induced ulcers in rats

<table>
<thead>
<tr>
<th>Group treated</th>
<th>No. of rats used</th>
<th>Days of pregnancy</th>
<th>No. of animals having ulcers</th>
<th>% of animals having ulcers</th>
<th>Ulcer index ±S.E.</th>
<th>Degree of significance <em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. (Control) 0.5 ml/kg 1% CMC containing a trace of Tween 80</td>
<td>10</td>
<td>9–10</td>
<td>4</td>
<td>40%</td>
<td>0.10±0.05</td>
<td></td>
</tr>
<tr>
<td>B. 15 mg/kg Indomethacin</td>
<td>10</td>
<td>9–10 (Mid-pregnancy)</td>
<td>10</td>
<td>100%</td>
<td>2.26±0.20</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>C. (Control) 0.5 ml/kg 1% CMC containing a trace of Tween 80</td>
<td>10</td>
<td>19–20</td>
<td>3</td>
<td>30%</td>
<td>0.54±0.20</td>
<td></td>
</tr>
<tr>
<td>D. 15 mg/kg Indomethacin</td>
<td>10</td>
<td>19–20 (Late-pregnancy)</td>
<td>10</td>
<td>100%</td>
<td>2.56±0.12</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

S.E.: Standard error

References


