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Abstract: Misoprostol (Cytotec, Searle, England), a prostaglandin E1 analogue, is indicated for protection of peptic disease induced by cyclo-oxygenase inhibitors. Since vaginal bleeding was reported during misoprostol use previously, we hypothesized that misoprostol might cause endometrial stimulation. Therefore, we investigated the effects of misoprostol on the endometrium of ovariectomized (OVX) rats to investigate any endometrial changes. Thirty-two, four month-old, parous female Sprague-Dawley rats were used in this study. All rats underwent ovariectomy at the beginning of the study. Sixty days after the ovariectomy six rats were sacrificed to remove the uterus and the remaining 26 rats were divided into three groups. Group I (six rats) was treated with vehicle (1 cc of distilled water orally) for 60 days. Groups II and III (ten rats each) were treated with oral 100 and 200 μg/day misoprostol, respectively, for 60 days. At the end of the treatment laparotomy was performed and the uteri of all the rats were removed. Histopathologic examination of the endometrium 60 days after ovariectomy revealed endometrial atrophy. But after misoprostol administration a minimal endometrial proliferation was encountered regardless of the dose of misoprostol.

The present study demonstrated that misoprostol can cause a proliferation in the endometrium after 60 days of administration. Long term studies are needed to evaluate if this proliferation leads to hyperplasia and cancer, especially in postmenopausal women.

Key Words: misoprostol, endometrium, menopause

Introduction

Misoprostol is a synthetic prostaglandin E 1 analogue that replaces the protective prostaglandins consumed with prostaglandin-inhibiting therapies e.g., nonsteroidal anti-inflammatory drugs (1). It has been shown that misoprostol induces uterine contractions when given to pregnant women and causes abortion or preterm labor (2, 3). Vaginal bleeding was observed as an adverse effect in misoprostol treated patients for gastric mucosa protection (1). For this reason, this study was planned to investigate whether misoprostol causes any changes in the endometrium. To the best of our knowledge this is the first study investigating the endometrial effects of misoprostol.

Materials and Methods

A total of 32, four month-old female Sprague Dawley rats weighing approximately 250 g were used in this study. The research protocol for this study was approved by the ethics committee of the İnönü University, School of Medicine, Malatya, Turkey. The rats were fed standard laboratory chow and water ad libitum. They were acclimated to local conditions for one week and housed in pairs in plastic cages. The rats were anesthetized with ketamine hydrochloride (50 mg/kg) and then ovariectomized. Sixty days after ovariectomy, six rats were sacrificed to remove the uterus to demonstrate endometrial atrophy and the remaining rats were divided into three groups. Group I (six rats) was treated with vehicle (1 cc of distilled water orally) for 60 days. Groups II and III (ten rats each) were treated with oral 100 and 200 μg/kg/day misoprostol respectively, for 60 days. Misoprostol was administered orally via metal rat feeding cannula. At the end of the treatment, laparotomy was performed and the uteri of all the rats were removed. All uterine materials were fixed in 10% phosphate buffered neutral formaline and several sections were taken from

tissues. Materials were processed using routine operations, embedded in paraffin and 5-micron thick sections were deparaffinized and stained with hematoxylin-eosin. Histopathologic examination was performed under a light microscope. The thickness of endometrium and endometrium+myometrium was measured using an oculometer. Results were expressed as means ± SD. Statistical analysis was performed with the X^2 test or Fisher's exact test for group comparisons. A p value of < 0.05 was considered statistically significant.

Results

Histopathological examination revealed atrophic endometrium 60 days after the ovariectomy. In the vehicle treated group, endometrial atrophy was encountered as well. A few small tubular glands were embedded in inactive spindled stroma. Glands were lined with monolayered spingle epithelial cells. There was no mitotic activity (Figure 1). In both of the misoprostol treated groups, minimal endometrial proliferation was detected. Tubular endometrial glands were embedded in active stromal cells and some glands were lined with cuboidal epithelial cells (Figure 2).

Figure 1. Endometrial atrophy (Hematoxylin-Eosin X2).

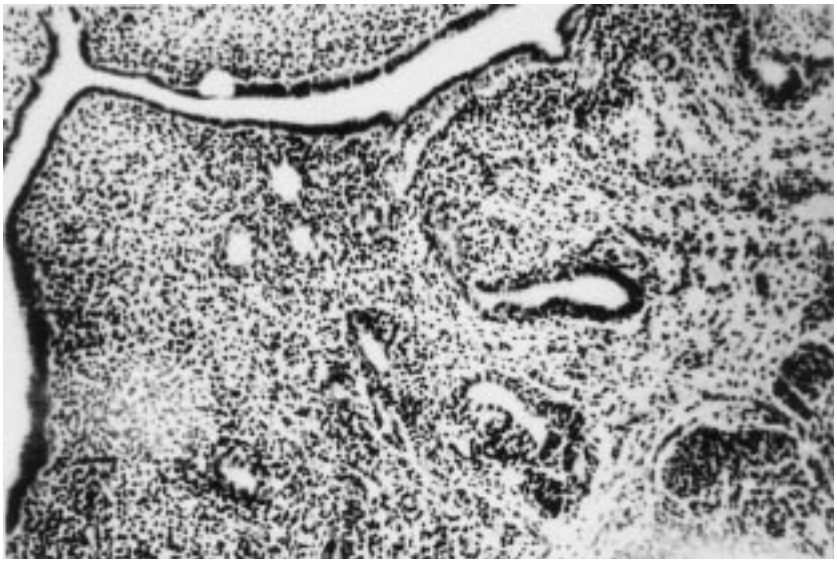

Figure 2. Minimal proliferation in endometrium (Hematoxylin-Eosin X2).

In the vehicle treated group, the thickness of the endometrium was measured as 0.58 ± 0.11mm (n=6) and the thickness of the endometrium+myometrium was 0.9 ± 0.14 mm. In the 100 μg/kg/day misoprostol treated group, the endometrial thickness was 0.68 ± 0.07mm (n=10) and the thickness of the endometrium + myometrium was 1.01 ± 0.09 mm (n=10). In the 200 μg/kg/day misoprostol treated group, the endometrial thickness was 0.69 ± 0.07mm (n=10) and the thickness of the endometrium + myometrium was 1.02 ± 0.11 mm (n=10). The difference the between vehicle administrated and misoprostol treated groups was not statistically significant (p>0.05), (Table 1).

Table 1. Effect of misoprostol on endometrial thickness

	vehicle	100μg/kg/day misoprostol	200μg/kg/day misoprostol	p
Thickness of endometrium	0.58 ± 0.11	0.68±0.07	0.69±0.07	NS
Thickness of endometrium+myometrium	0.9±0.14	1.01±0.09	1.02±0.11	NS

Discussion

In this study, we found that misoprostol caused minimal proliferation in the endometrium independent of the dose of the drug. Although misoprostol has a contractile effect on myometrium in very small doses, a reasonable effect was not found in endometrium. Moreover, it is very difficult to comment on this subject because of the effects of all prostaglandins are not clearly defined (4). Misoprostol has been shown to produce uterine contractions that may endanger pregnancy (2, 3). In clinical trials, some gynecologic disorders have been reported in women who received misoprostol such as spotting (0.7%), uterine cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). It was not evident whether bleeding disorders were due to the contraction anomalies or to the endometrial changes. In order to clarify if misoprostol has a direct effect on endometrium, it was administered for two months to the ovariectomized rats whose endometrium have been shown to be atrophic histologically. At the end of the treatment period, a proliferative endometrium was the only histologic finding. Even this minimal proliferation suggested that bleeding disorder during misoprostol treatment was due to endometrial stimulation. The mechanism causing this proliferative effect should be further investigated. It may be speculated that if misoprostol is an endometrial proliferative agent, its chronic use may cause an endometrial hyperplasia. This may be a serious problem for elderly patients who use non-steroidal anti-inflammatory drugs for pain relief together with misoprostol for its protective effects against gastric mucosa irritation (5). These patients need to be evaluated for endometrial thickness increase by ultrasonography and if they experience an abnormal vaginal bleeding, sampling of the endometrium is indicated.

On the other hand, in our previous study misoprostol was found to reduce bone loss in ovariectomized rats (6).

In conclusion, further long-term studies are needed to evaluate the possible adverse effects of misoprostol on the endometrium, especially in elderly women. If it is demonstrated to cause endometrial hyperplasia, its use must be restricted in postmenopausal patients provided that appropriate pathological follow up is performed using standard procedures.

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