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Research Article

The Protective Effect of Testosterone on Indomethacin Induced Gastric Ulcer in Female Sprague Dawley Rats

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Gastric ulcer has shown association with changes in sex hormones, with impact exacerbated in males. Also, males are known to be more exposed to ulcer risk factors. This study investigates the effect of testosterone on indomethacin induced gastric ulcers in adult female rats. Eighteen female rats (225 ± 25 g body weight) were randomly assigned to 3 groups under standard laboratory condition. After acclimatization, animals fasted for 40 hrs but were given water *ad libitum*. Group A served as control while group B served as the ulcer control, in which ulcer was induced without treatment using indomethacin (40 mg/kg single orally dose). Group C was pretreated with testosterone (1 mg/kg IM) eight hours before ulcer induction. Eight hours after ulcer induction, animals were sacrificed and the stomach was harvested for analysis. Results showed a significant reduction in mucus content in groups C (0.79 ± 0.11 g) and B (0.87 ± 0.02 g) compared to A (1.11 ± 0.03 g). Gastric mucus pH was significantly acidic in group B (4.40 ± 0.55) compared to C (5.20 ± 0.45) and A (5.80 ± 0.45). There was a significantly higher ulcer index in group B (4.60 ± 0.55 mm) compared to C (3.60 ± 0.89 mm) and testosterone pretreatment resulted in a 21.74% ulcer inhibition. Although weak, the findings suggest that testosterone might protect the gastric mucosa against NSAIDs in females.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been implicated in ulcer aetiology and employed in several animal studies for gastric ulcers induction [1–4]. Indomethacin is a commonly used type of NSAIDs in animal experiment whose proposed mechanism of stomach damage has been reported to be through local/topical and systemic actions. The topical mechanism involves those of acidic nature which directly kill epithelial cells [5, 6]. In the topical action, gastric ulcerogenic action of NSAIDs is reported to be due to their local inhibitory effect on gastric prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2) that are the main inhibitors of gastric acid secretion [7] as well as induction of osmotic lysis subsequent to trapping of charged NSAIDs with the epithelial cells [8] and death of the epithelial cell subsequent to uncoupling of oxidative phosphorylation [9]. Also, NSAIDs have been said to diminish the ability of Epithelial Growth Factor to promote epithelial repair, and thus inhibition of epithelial proliferation appears to involve a reduction of EGF binding to its receptor [10] and inhibition of EGF signalling pathways [11, 12].

The development of peptic ulcer has been said to be influenced by various aggressive and defensive factors [13–15], inadequate dietary habits, cigarette smoking, excessive ingestion of nonsteroidal anti-inflammatory agents, stress, hereditary predisposition, *Helicobacter pylori* infection [1, 3, 16–18], free radicals formation [19], and decreased prostaglandin synthesis [20]. Although several pharmaceutical products have been employed and have resulted in decreased rate of mortality and morbidity of gastric ulcers, none, however, is completely effective [21]. According to studies, the available drugs used for the treatment of gastric ulcers are not without adverse effects and limitations [22–25]. Thus, there is a growing interest in alternative therapies with promising outcomes and nontoxic effects to other organs or systems.

Interestingly, there has been an observation that "peptic ulcers occur more frequently among men than women at reproductive age" [26, 27]. By implication, this gives rise to the question "could testosterone (a major androgen and male

sex hormone) be responsible for this effect?" Nevertheless, males are known to be more exposed to stress, cigarette smoking, excessive ingestion of alcohol, and inadequate dietary habits, which are known to be implicated in the development of gastric ulcers. Hence, the assumption that testosterone could be responsible for the frequency of peptic ulcers among men than women at reproductive age is questionable. However, according to Kirsner [28], sex differences in peptic ulcer have not been adequately explained and it is presumably said that the greater exposure of men to environmental influences predisposing to ulcer and the development of ulcers in women subjected to comparable or similar tensions suggest the role of other factors.

Although existing facts suggest that gastric acid secretion, gastroduodenal mucosa integrity, and gastric ulcerations are associated with changes that occur within hormonal cycles, especially those related to sex hormones [26], the possible deleterious effects of the androgenic hormones remain to be investigated. The possible protective influence of female sex hormones thus far has not been established and the course of peptic ulcer in women during various phases of the reproductive period might be expected to provide information pertinent to this.

Considering that studies have reported antiulcer drugs side effects to include disturbance of plasma hormone levels [29–33] is an indication suggesting the relationship between hormonal difference and the development of gastric ulcers. Despite these facts that relate sex hormones and ulcer development, little literature exists regarding the effect of male sex hormone on ulcer prevention. This study investigates the protective effect of testosterone on indomethacin induced gastric ulcer in female rats.

2. Materials and Methods

2.1. Experimental Animals. Eighteen adult female rats of comparable weight (225 ± 25 g) were obtained from the Animal House of Anthonio Research Centre and transported to the experiment site where they were housed in a well-ventilated room under a 12/12 hours' light/dark cycle and fed with feed (Vital feed, Plateau State, Nigeria) and water *ad libitum*.

2.2. Drug of Study. Testosterone (testosterone propionate USP 25 mg made in India by Laborate pharmaceutical) was purchased from a Pharmacy in Ekpoma, Nigeria.

2.3. Experimental Grouping. Following standard laboratory animal care, the rats were randomly divided to three groups (A, B, and C) of 6 rats each; group A served as the control, B as the ulcer control, and C as the test group.

2.4. Ulcer Induction. Ulcer was induced by a single oral dose of indomethacin (40 mg/kg/bwt) as previously reported by Akpamu et al. [34].

2.5. Experimental Design. Following a 2-week period of acclimatization, animals in group A received no treatment (control). After 40 hours of fasting, animals in group B were given intramuscularly tween 80 and at the 48th hour, they received orally indomethacin (40 mg/Kg). After 40 hours of fasting, animals in test group C were pretreated with 1 mg/kg IM testosterone [26]. Eight (8) hours later, ulcer was induced with indomethacin (40 mg/kg single dose orally). Eight (8) hours after the induction of ulcers in groups B and C, the animals were prepared for sample collection.

2.6. Sample Collection. At the end of the treatments, the rats in each group were sacrificed under mild chloroform anesthesia and the stomach was obtained following standard laboratory procedures as described by Abdulla et al. [35] and Ketuly et al. [36].

2.7. Sample Analysis. The stomach was opened along the greater curvature and the content emptied. It was then rinsed with saline water and gastric mucus was obtained by gentle scraping of the mucosa with a glass slide and then weighed using an electronic weighting balance.

Also, the acidity of gastric mucus was determined using litmus paper with colour indicator. Gastric mucosal lesions were then examined macroscopically using dissecting microscope for ulcer index analysis. Gross gastric lesions severity was measured as described by Wilhelmi and Menasse-Gdynia [37] using the 1 to 5 scoring system (severity factor 1 = 1 or 2 minutes, sporadic, punctuate lesion; 2 = several small lesions; 3 = one extensive lesion or multiple moderate sized lesions; 4 = several large lesions; 5 = several large lesions with stomach perforation). The UI for each group was taken as the mean lesion score of all the rats in that group [35]. The percentage ulcer inhibition (% UI) was calculated by the equation of Hano et al. [38].

$$\%\ \text{UI} = \left[\frac{(\text{UI of ulcer control} - \text{UI of treated})}{(\text{UI of ulcer control})}\right] \times 100\%. \quad (1)$$

2.8. Data Analysis. This was by the one-way analysis of variance (ANOVA) which was performed using SPSS version 17 software. The post hoc test carried out was LSD and the significance level was set at $p < 0.05$.

3. Results

Ulcers of the gastric mucosa appear as inflammation and haemorrhagic lesions on the wall of the stomach. There was a significant reduction ($p < 0.05$; $F = 50.4117$) in mucus content in groups C (0.74 ± 0.10 g) and B (0.87 ± 0.02 g) compared to the control (1.11 ± 0.03 g). Similarly, the mucus content of group B was significantly higher ($p < 0.05$) compared to group C (Figure 1). Gastric mucus pH was significantly acidic ($p < 0.05$; $F = 10.571$) in group B (4.40 ± 0.55) compared to group C (5.20 ± 0.45) and control (5.80 ± 0.45) (Figure 2). The results showed significantly higher ($p < 0.05$; $F = 79.818$) ulcers index in group B (4.60 ± 0.55) compared to group C (3.60 ± 0.89). Pretreatment with testosterone resulted in a 21.74% ulcer inhibition in group C (Table 1).

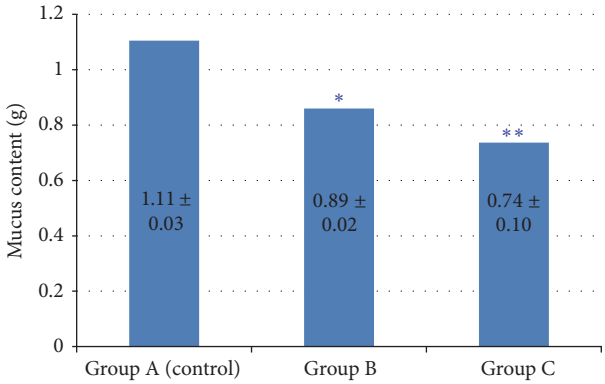

Figure 1: Mucus content (gram) of treatments and control. ∗ denotes significant different compared to control and ∗∗ compared to group B (test control) at the $p < 0.05$ level ($n = 6$).

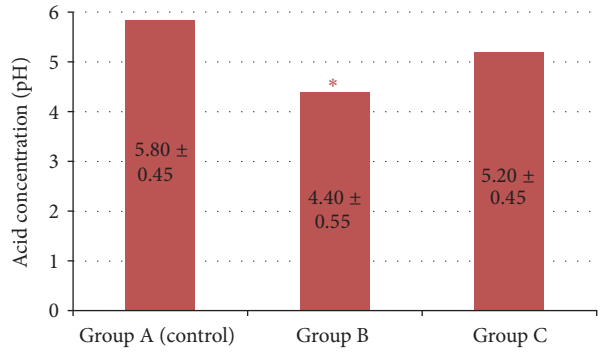

Figure 2: Acid concentration (pH) of treatments and control. ∗ denotes significant different compared to control at the $p < 0.05$ level ($n = 6$).

Table 1: Evaluation of gastric ulcer index and inhibition by testosterone in indomethacin induced gastric ulcer in female rats treated with testosterone.

Physical observations	Group A (Control) ($n = 6$)	Group B (Ulcer control) ($n = 6$)	Group C (Testosterone) ($n = 6$)
Severity factor	—	S	MS
Ulcer index	0^a	4.60 ± 0.55^b	3.60 ± 0.89^c
% UI	100^b	0^b	21.74^c

Means in a row with different superscripts are significantly different at the $p < 0.05$ level.
Key: — = absent; MS = mildly severe; S = severe; % UI = percentage ulcer inhibition.

4. Discussion

On the influence of testosterone treatments on indomethacin induced gastric ulcers in female rat, the present study showed testosterone pretreatment to significantly reduced mucus content (Figure 1) and nonsignificantly reduced gastric acidity (Figure 2) compared to group B; in which ulcer was induced without treatment. Also, pretreatment with testosterone was observed to result in a milder ulcer compared to that without treatment (group B; Table 1) and resulted in a 21.74% ulcer inhibition when compared to that in group B. These findings in the present study indicate that pretreatment with testosterone may be gastroprotective in female rats. Worrisome, however, is the significant reduction in gastric mucus production observed in the present study. Hence, the findings on the effect of testosterone in this study further support the hypothesis by El-Tawil [39] that sex hormones may act through potentiating the effect of other cofactors in inducing or modulating pathogenesis of gastrointestinal disorder.

Estrogens have been shown to inhibit gastric acid secretion in female human and animal studies [40–44]; the finding of this study on the effect of testosterone on gastric acidity showed that testosterone may neutralise gastric acidity induced by indomethacin, at least in female rat. This estrogenic effect observed in human and animals [40–44] was exhibited by testosterone in female rats considering the similar and nonsignificant ($p < 0.05$) difference in gastric acid concentration between pretreatment with testosterone and control and the significant difference ($p > 0.05$) between pretreatment with testosterone and group B. This is in accordance with considering that it has been demonstrated that androstenedione and testosterone can be aromatized to estrone and estradiol [45–47]. Thus, the observed estrogenic effect by testosterone may be that testosterone was converted to estradiol by the enzyme aromatase. In another line of thought, testosterone may have similar effect of estrogen to bring about the increased mucus acidity in female observed in this study.

Considering the observed ulcer indices in the present study, pretreatment with testosterone was shown to be gastroprotective against indomethacin induced gastric ulcerations. Previous studies have shown the administration of testosterone receptor blockers (cyproterone acetate) to attenuated gastric haemorrhagic erosions in intact male rats following ethanol challenge [48, 49]. A study has previously reported that administration of testosterone in the presence of testes significantly protected intestinal tissue against postischemia/reperfusion mucosal injuries, while the opposite occurs in the absence of testes [50]. Comparatively, the protective effect of testosterone observed in the presence of testes in the study by Albayrak et al. [50] was similar to the finding of this study in female rats.

Although the mechanism by which pretreatment with testosterone resulted in the protection of gastric damage by indomethacin is not studied, it may however be that it interferes with the mechanism by which indomethacin caused damage to the stomach. It may be that testosterone stimulates gastric prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2) considering the observed inhibition of gastric acidity in this study. Recall that indomethacin inhibits PGE2 and PGI2 that are the main inhibitors of gastric acid secretion [7]. Thus, our assertion that testosterone may stimulate PGE2 and PGI2 is in line with considering the restoration of gastric acid to that of the control by pretreatment with testosterone in the present study (Figure 2). In another line of thought, the 21.74% ulcer inhibition by testosterone pretreatment in the present study suggests testosterone may inhibit gastric tissue

damage induced by indomethacin via coupling oxidative phosphorylation and potentiating the ability of epidermal growth factor (EGF) or stimulating EGF signalling pathways to promote epithelial repair. This assertion is based on the facts that NSAIDs, for example, indomethacin, induced death of the epithelial cell by reduction of EGF, which promote epithelial repair and proliferation [10], or inhibition of EGF signalling pathways [11, 12] and/or uncoupling of oxidative phosphorylation [9].

In this regard, pretreatment with testosterone in female may be gastroprotective against indomethacin challenge via stimulating gastric prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2) or acting on EGF signalling pathways to promote production or uncoupling of oxidative phosphorylation. Although weak, the findings suggest that testosterone might protect the gastric mucosa against NSAIDs in females. Conclusively, judging by the ulcer inhibition capacity exhibited by pretreatment with testosterone on indomethacin induced gastric ulcer, coupled with the potentials in maintaining mucus pH in comparison with the control, testosterone treatment or hormonal therapy may be promising in the management of ulcer in females. Its ability in reducing mucus content is inquisitorial and thus further studies are required. The need to further investigate the effect of testosterone in ovariectomy to eliminate the effect of female hormones in the findings of the present study is recommended.

5. Limitation of Study

This study did not consider the effect of testosterone acting alone on gastric integrity in nonulcer rat, or the effect of ovariectomy in female rats treated with testosterone and indomethacin, and did not put the phase of the estrous cycle of the female rats into consideration. However, the female rats used in this study were nonpregnant and where not in contact with male rats at least 28 days before the study commenced.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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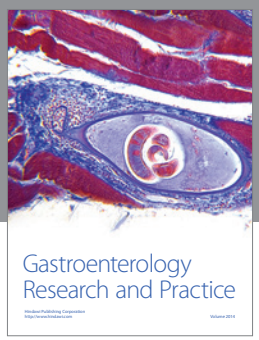

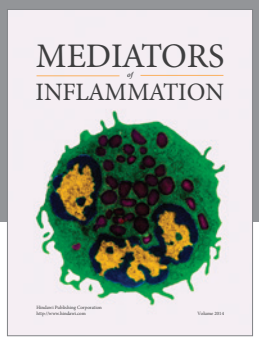

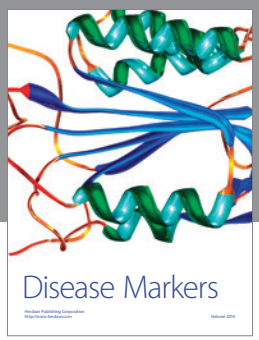

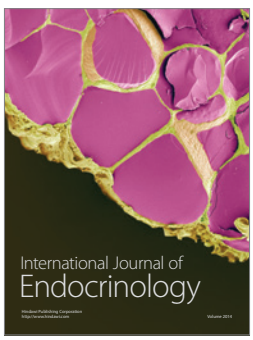

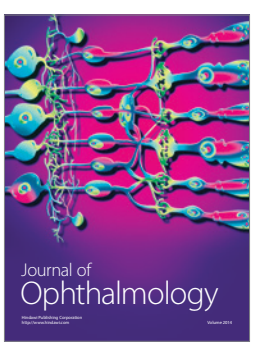

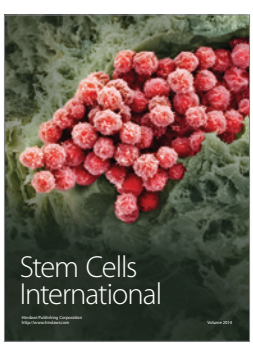

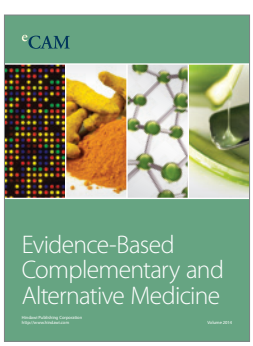

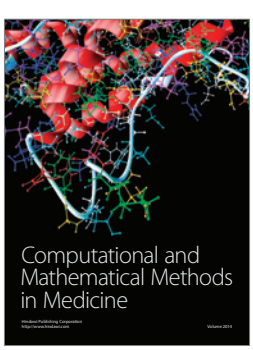

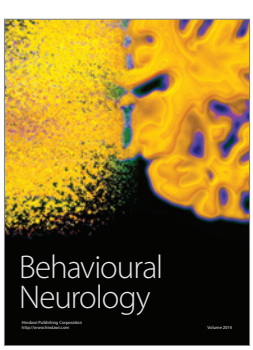

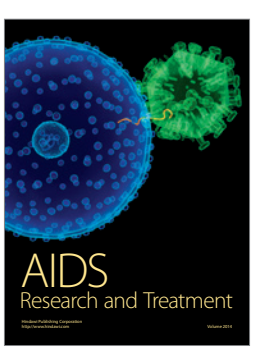

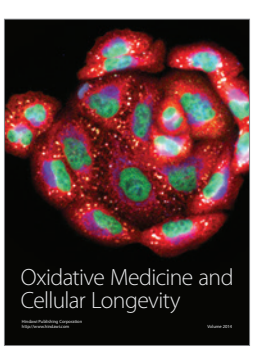

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