

## THE ROLE OF FREE RADICALS IN EXPERIMENTALLY INDUCED INDOMETHACIN ULCER

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### SUMMARY

**Purpose :** In this experimental study, the roles of allopurinol - xanthine oxidase inhibitor - and superoxide dismutase (SOD) - free radical scavenger - in the prevention of indomethacin-induced acute mucosal lesions were investigated. **Methods :** Thirty rats from both sexes weighing 90-130 gr. were used. Six of them were used to investigate the effect of 48 hours fasting on ulcer occurrence. In the control group (n=8), subcutaneous indomethacin was administered to form acute mucosal lesion. Other two groups, each consisting of eight rats, were given SOD and allopurinol, respectively. **Results:** In the indomethacin group, the ulcer score was found to be  $22.4 \pm 2.8$  mm., while it was  $13.5 \pm 2.5$  mm. and  $7.6 \pm 3.0$  mm. in the allopurinol and SOD group respectively.

Compared with the control group, allopurinol and SOD groups were found to be statistically significant in reducing ulcer formation. Moreover, SOD was also found to be more effective than allopurinol in preventing ulcer formation. **Conclusion:** According to these results, it can be assumed that the free oxygen radicals (FOR) generated through the lipooxygenase and xanthine oxidase pathways have an important role in the pathogenesis of indomethacin-induced ulcer besides the other humoral mediators.

**Key Words :** Indomethacin-Induced Ulcer, Free Radicals.

### INTRODUCTION

The pathogenesis of gastric ulcer is still obscure because of its complicated mechanisms. Several humoral factors - like autonomic nervous system mediators, prostanoids, leukotrienes, histamine, gastrin and bombesin - have been identified on the ulcer pathogenesis (1). In recent ten years, the FOR are claimed to play a role in the pathogenesis of this disease ( 2, 3, 4, 5 ).

This study is under taken to investigate the role of FOR in ulcer formation and whether SOD and

allopurinol have a preventive effect on indomethacin-induced gastric lesion.

### MATERIAL AND METHODS

In this study, rats from both sexes and weighing 90-130 gr. were used. Two of them died during experiment and therefore were excluded from the study.

The experiment were held in three groups. In each group, the rats were fasted for 48 hours and were allowed to drink water ad libitum. In the first group, 6 rats were fasted for 48 hours to see the

effects of fasting on ulcer formation, and at the end of this period the rats were sacrificed by cervical dislocation. The abdominal cavity was opened and gastrectomy was performed. The stomach was opened along the lesser curvature and ulcer scoring was made by using the method described by Cho and Ogle (6).

In the control group, 20 mg/kg indomethacin (SIGMA, St. Lois, USA) was administered subcutaneously (sc) to each of the eight rats three hours later and after cervical dislocation, the abdominal cavity was opened, gastrectomy was performed, and ulcer scoring was made by the same route.

In the third group (the first group), allopurinol (SIGMA, St. Lois, USA) 10 µg/kg was intraperitoneally (ip) administered to all rats and indomethacin-induced ulcer was formed in 30 minutes. And then the ulcer scoring was made by the mentioned route.

In the last phase of the study (the second group), 500 U/kg SOD (SIGMA, St. Lois, USA) ip was administered to all rats and indomethacin-induced ulcer was formed in 30 minutes. The the ulcer scoring was made again. The control and the study groups are listed in Table 1.

Values are presented as means ± SE and statistical analysis was performed by using Mann-Whitney U nonparametric test.

## RESULTS

In the 48 hours fasted group, ulcer formation was observed in only one rat and the ulcer score in this group was 0.4±0.3 mm. The results are shown in Table 2.

The allopurinol and SOD pretreated groups, compared with their own controls, both were found to have significantly reduced ulcer scores (p<0.001). When SOD and allopurinol pretreated groups were compared, the prevention of the ulcer formation was found to be more effective in the SOD pretreated group compared with allopurinol pretreated group (p<0.05).

## DISCUSSION

Indomethacin is thought to increase H<sup>+</sup> permeability of gastric mucosal membrane, inhibit prostanoïd synthesis, affect mucosal defense mechanism, inhibit mucus production and alkaline secretion (7, 8, 9) and thus cause ulceration. Ashley (10) and Gana (11) have previously shown that nonsteroidal antiinflammatory drugs reduced gastric mucosal blood flow. Our findings in this study clearly show that, SOD and xanthine oxidase inhibitor allopurinol significantly reduced indomethacin - induced ulcer formation, SOD being more effective. Indomethacin by inhibiting cyclooxygenase pathway and causing a shift in the lipoxygenase and monooxygenase pathway of arachidonic causes the formation of FOR (1, 12). SOD effectively prevents indomethacin-induced ulcer as a scavenger. This finding also correlates well with the previous study of Pihan who shown that SOD and catalase decrease the aspirin-induced mucosal damage (13).

Xanthine dehydrogenase is rapidly converted to xanthine oxidase during the reduced gastric blood flow and this enzyme mediates the release of superoxide radicals in large amounts. For this reason, allopurinol prevents indomethacin-induced ulcer. But the statistically significant difference between the preventive effects of allopurinol and

	Control group (n)	Allopurinol (n)	SOD (n)
48 hours fasting	6	-	-
Indomethacin-induced ulcer	8	8	8

Table 1 : Control and study groups (n=number of rats).

	Control group (n)	Allopurinol (n) pretreated (10 µ/kg)	SOD (n) (500 U/kg)
48 hours fasting	0.4 ± 0.3	-	-
Indomethacin-induced ulcer	22.4 ± 2.8 <sup>a</sup>	13.5 ± 2.4 <sup>b</sup>	7.6 ± 1.3 <sup>c</sup>

a-b : p < 0.001      a-c : p < 0.001      b-c : p < 0.05

Table 2 : The comparative results of ulcer scoring (mm) of the control, allopurinol pretreated, and SOD pretreated groups.

SOD may suggest that indomethacin can be more effective through the leukotrienes, lipoxins and FOR pathways.

### CONCLUSION

Our data in this study state that; besides other humoral mediators, FOR - resulting from the lipoxygenase and monooxygenase pathways of arachidonic acid and less dominantly from the xanthine oxidase pathways - play an important role in the pathogenesis of indomethacin-induced ulcer.

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