

**Study of anti-inflammatory activity of omeprazole in complete Freund's adjuvant induced arthritic rats****Nadia Nausheen\*, Prabhakar Patil, Yatish Byndoor**

Department of Pharmacology,  
Navodaya medical college,  
Raichur, Karnataka, India

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Dr. Nadia Nausheen  
Email: museebrahman@  
yahoo.in

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**ABSTRACT**

**Background:** Rheumatoid arthritis (RA) is a chronic, progressive, and systemic inflammatory disease, characterized by synovial proliferation and joint erosions. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used as an important part of therapeutic regime to suppress the pain and inflammation associated with RA. The modern drugs both steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs) are used for the amelioration of the symptoms of the disease; however, they offer only temporary relief and also produce adverse effects. This study was done to evaluate anti-inflammatory activity of Omeprazole in CFA induced arthritic rats.

**Methods:** Animals were divided into five groups of six each, group I as control, group II as standard whereas groups III, IV and V as test groups (three doses). Anti-inflammatory effect of group II Diclofenac sodium (10 mg/kg orally) and group III, IV and V received Omeprazole (10mg/kg, 20mg/kg, and 30mg/kg bodyweight orally respectively) was evaluated in adult albino rats by Plethysmometer on 7th, 14th and 21st day post adjuvant injection.

**Results:** Group 3 produced a significant suppression of paw volume with P value (<0.05) and Group 4 produced a very significant suppression with P value (<0.001) compared to other groups.

**Conclusions:** Omeprazole, a PPI, has anti-inflammatory activity.

**Keywords:** CFA, NSAIDs, PPI, RA

**INTRODUCTION**

Rheumatoid arthritis (RA) is a chronic, progressive, and systemic inflammatory disease, characterized by synovial proliferation and joint erosions.<sup>1</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) are used as an important part of therapeutic regime to suppress the pain and inflammation associated with RA.<sup>2</sup> The modern drugs both steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs) are used for the amelioration of the symptoms of the disease; however, they offer only temporary relief and also produce adverse effects.<sup>3</sup> Proton pump inhibitors (PPIs) are substituted benzimidazoles that block gastric acid secretion by inhibiting H<sup>+</sup>, K<sup>+</sup>ATPase the proton pump of the gastric parietal cell.<sup>4</sup> PPIs are the most effective anti-secretory agents available, and they are among the most commonly used medications in the world.<sup>5</sup> Recent studies have elucidated a number of mechanisms whereby PPIs can exert anti-inflammatory effects unrelated to the inhibition

of gastric acid production.<sup>6</sup> Those anti-inflammatory properties of the PPIs, which have nothing to do with their effects on parietal cells, may contribute to the beneficial clinical actions of the PPIs, even in acid-peptic disorders. This study was done to evaluate anti-inflammatory activity of Omeprazole in CFA induced arthritic rats.

Rheumatoid arthritis (RA) is a long lasting disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly the wrist and hands are involved with typically the same joints involved on both sides of the body. The disease may also affect other parts of the body. Often symptoms come on gradually over weeks to months.<sup>7</sup>

The modern drugs both steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs) are used for the amelioration of the symptoms of the disease; however,

they offer only temporary relief and also produce adverse effects.<sup>3</sup>

Recent studies have elucidated a number of mechanisms whereby PPIs can exert anti-inflammatory effects unrelated to the inhibition of gastric acid production.<sup>6</sup>

Proton pump inhibitors may exert anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines that recruit inflammatory cells to diseased tissues. Gastric mucosal production of interleukin-8 (IL-8), a potent neutrophil chemo attractant, appears to play an important role in mediating gastric inflammation mediated by infection with *H.pylori*.<sup>8</sup> Handa et al.<sup>9</sup> observed that omeprazole and lansoprazole significantly blocked IL-8 production stimulated by HPE in a human gastric cancer cell line and in human umbilical vein endothelial cells, possibly by interfering with the nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathway. In rats treated with indomethacin, Kuroda found that lansoprazole significantly decreased the production of cytokine-induced neutrophil chemoattractant-1 (CINC-1, a rat homologue of IL-8) by the small intestine.<sup>10</sup> In cultured human tracheal epithelial cells, furthermore, lansoprazole was shown to decrease levels of a number of pro-inflammatory cytokines including IL-6, IL-8, and tumor necrosis factor- $\alpha$ .<sup>11</sup>

In eosinophilic esophagitis one mechanism that has been proposed for how acid reflux might attract eosinophils to the esophagus involves VCAM-1.<sup>12</sup> In human esophageal microvascular endothelial cells, acid exposure has been shown to induce the expression of VCAM-1<sup>13</sup>, an adhesion molecule that is recognized by ligands on the eosinophil cell surface.<sup>14</sup> As discussed above, PPIs have been found to inhibit the expression of VCAM-1 by endothelial cells.<sup>15</sup>

Thus, it is conceivable that PPIs may reduce esophageal eosinophilia, at least in part, by inhibiting VCAM-1 production by esophageal endothelial cells.

In this study we evaluated the anti-inflammatory activity of omeprazole in CFA induced arthritic rats. Adjuvant induced arthritis in rats is a chronic inflammatory disease characterized by infiltration of synovial membrane in association with destruction of joints resembles RA in humans.<sup>16</sup>

## METHODS

A quantitative experimental study in adult albino rats was conducted at Post graduate research laboratory, Department of Pharmacology, Navodaya medical college, Raichur according to ethical norms.

**Animals:** Wistar albino rats of either sex, weighing 150-200g obtained from the National Institute of Nutrition, Hyderabad and maintained at central animal house of Navodaya Medical College under suitable condition of

housing, ventilation and nutrition were used for study. Animals were fasted overnight before experiment with free access to water.

**Equipments:** Syringes, Plethysmometer

## Chemicals:

*Complete Freund's agent (CFA)*

CFA, most frequently used arthritic agents as 1% suspension in normal saline was used to induce arthritis in left hind paw. Not more than 0.1 ml was administered by intra plantar route. CFA was obtained from SIGMA – ALDRICH.

## Drugs

Omeprazole and Diclofenac Sodium were obtained from biocid pharmaceutical company.

## Induction of arthritis

Arthritis will be induced in rats by the intra plantar injection of 0.1 ml of CFA in the left hind paw. The adjuvant contained heat killed Mycobacterium tuberculosis in sterile paraffin oil (10 mg/ml).<sup>17</sup>

To induce arthritis 30 rats will be injected with 0.1 ml of complete Freund's adjuvant on their left hind paw. These rats then will be divided into 5 groups. Each group will receive different treatment as follows:

Group 1: Control - Receive 2ml of distilled water daily

Group 2: Standard - Receive diclofenac sodium 10 mg/kg/day orally

Group 3: Omeprazole 10 mg/kg orally

Group 4: Omeprazole 20 mg/kg orally

Group 5: Omeprazole 30 mg/kg orally

Edema formation in the injected hind paw peaked at 3-5 days after injection of the CFA and is measured by calculating percent inhibition of the edema volume of the injected paw.

$$\text{Percentage inhibition} = \frac{V_c - V_t}{V_c} \times 100.$$

Where

$V_c$  = Volume of paw edema in control animals.

$V_t$  = Volume of paw edema in treated animals.

Secondary lesions are immunologically mediated changes characterized by inflammation of the non-injected sites.

## Arthritis evaluation

### Primary and secondary lesions

Primary lesion refers to the edema formation in the injected hind paw that peaked 3-5 days after injection of the phlogistic agent and was measured on day 5 by calculating percent inhibition of the edema volume of the injected paw.

Secondary lesions are immunologically mediated changes characterized by inflammation of the non-injected sites (hind leg, forepaws, ears, nose and tail). Changes in Primary (lesions in adjuvant injected paw) and secondary (non-injected paw) lesions were assessed by using digital Plethysmometer (Marsap) before and on 7<sup>th</sup>, 15<sup>th</sup> and 21<sup>st</sup> day post adjuvant injection. Body weight was taken every 3<sup>rd</sup> day after adjuvant injection till 21<sup>st</sup> day.<sup>18</sup>

### Statistical analysis

Data were subjected to one-way analysis of variance (ANOVA) using SPSS 11.0 software. The results were expressed as "mean increase in paw volume ±SD". Analysis of variance (one way ANOVA) was followed by Dunnett's s t-test for control, standard and test group comparisons were used for statistical evaluation. P values <0.05 were considered as significant.

## RESULTS

Anti-inflammatory activity noted by Plethysmometer after administration of respective drugs.

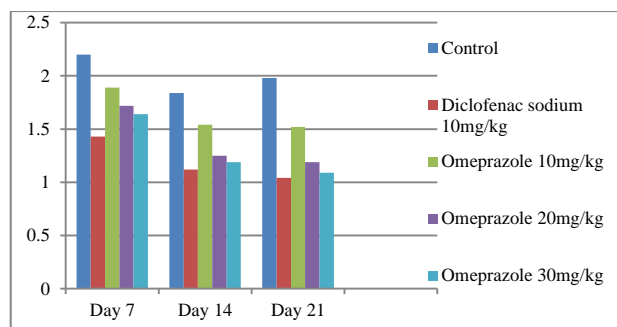
**Table 1: Percentage inhibition of paw volume edema.**

Treatment groups	Day 7	Day 14	Day 21
<b>Diclofenac sodium 10mg/kg (n=6)</b>	<b>23</b>	<b>45</b>	<b>60</b>
<b>Omeprazole 10mg/kg (n=6)</b>	<b>10</b>	<b>19</b>	<b>30</b>
<b>Omeprazole 20mg/kg (n=6)</b>	<b>15</b>	<b>28</b>	<b>44</b>
<b>Omeprazole 30mg/kg (n=6)</b>	<b>18</b>	<b>41</b>	<b>54</b>

The anti-inflammatory effect of omeprazole 20mg/kg was significant i.e. (p<0.05) and Omeprazole 30mg/kg was more significant (P<0.001) at time interval of 21 days.

## DISCUSSION

The present study was carried out to evaluate the anti-inflammatory property of omeprazole for this diclofenac sodium was selected as standard drug whereas omeprazole (10, 20, 30 mg/kg BW), where selected as test drugs.



**Figure 1: Paw volume edema (Mean±SD).**

Diclofenac sodium, Non-steroidal anti-inflammatory drug, whereas omeprazole anti-inflammatory drug by suppresses induction of inflammatory mediators like TNF- $\alpha$ <sup>19,20</sup>, IL-1 $\beta$ <sup>19</sup>, IL-6<sup>20</sup> and induces protective enzyme Heme-oxygenase-1(HO-1)<sup>21</sup> and by decreasing proinflammatory cytokines release from the phagocytes.

Total rats were divided into 5 groups, Group 1 rats were considered as controls and treated with normal saline, Group 2 rats as standard and treated with diclofenac sodium 10mg/kg, Group 3 rats as test-1 and treated with omeprazole 10mg/kg, Group 4 rats as test-2 treated with omeprazole 20mg/kg and Group 5 rats as test-3 and treated with omeprazole 30mg/kg BW.

The readings were recorded using Plethysmometer and results were analysed using Anova test.

## CONCLUSION

From the above study it was concluded that Omeprazole possess significant anti-inflammatory activity. The anti-inflammatory activity of Omeprazole was not better than that of the standard drug, Diclofenac sodium in plethysmometer. The mechanism of anti-inflammatory activity is unclear. Other researchers can do further study on its mechanism.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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