IMMUNOMODULATORY EFFECT OF ETORICOXIB AND MELOXICAM IN S. TYPHI 'O' ANTIGEN TREATED RABBITS

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ABSTRACT

Introduction: Non-steroidal anti-inflammatory drugs are commonly prescribed in cases of inflammatory conditions. Earlier little was known about the immunomodulatory role of Nsaids, particularly selective Cox-2 inhibitors as immunosuppressants. This study was conducted to observe the in vivo effect of Cox 2 inhibition on immune response.

Material & methods: Albino Rabbits of either sex were divided into three groups of six animals each and were administered Meloxicam (2 mg/kg, OD, p.o), Etoricoxib (17 mg/kg O.D, p.o) and Normal Saline (acting as Control) for seven days starting one day prior to immunization by S. Typhi Antigen (0.5 ml in each thighs). The antibody titre were measured weekly for one month using Widal Agglutination test.

Results: The antibody titre in the first week were found raised in all the groups but the response was more marked in treated group as compared to Control group. After 1st week antibody titre fell markedly in the treated groups. Etoricoxib administration caused higher antibody suppression in comparison to Meloxicam treated group.

Conclusions: Our results suggest that NSAIDs and significantly Cox-2-selective drugs attenuate antibody production. Use of NSAIDs may therefore be beneficial in decreasing autoantibody production in autoimmune diseases and may be harmful in response to antigenic challenge/vaccination as they dampen humoral immunity.

Key words: Antibody production, Immunomodulators, Etoricoxib, Meloxicam.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are mainstay treatment in cases of inflammatory conditions and they are effective in relieving pain, reducing fever and inhibiting inflammation. NSAIDs acts by inhibiting enzyme known as cyclooxygenases. Cyclooxygenases (Cox-1 and Cox-2) catalyze the conversion of arachidonic acid to prostaglandin H2 (PGH2) which is metabolized by tissue-specific isomerases to other prostanoids (PGD2, PGE2, PGF2α, PG12) and thromboxanes. Classically, Cox-1 is constitutively expressed in most tissues and cells and a play a role in homeostasis, while Cox-2 enzyme is inducible means they generates PGs during inflammation1,2.

Prostaglandins are critical mediators of inflammation that affect both humoral and cell-mediated immune response. Prostaglandins, which play a role in immune-regulating activity, have been shown to promote antibody formation to sheep red blood cells in mice (3). Some studies have shown that PGE2 enhances antibody production and promotes type 2 immune responses 3, 4. Cox-2 is the predominant isoform contributing to high levels of PGE2 found in chronic inflammatory conditions 5.

Earlier studies have shown evidences that NSAIDs have immunomodulatory effects by interfering with human monocyte and T lymphocyte activation, proliferation and cytokine synthesis6-8. Some studies shown that PGE2 suppressed all B-cell functions except for IgG synthesis9,10. IgG synthesis rather increased by PGE2. Therefore, drugs inhibiting PGE2 production will have opposite effect on B-cell. The synthesis of IgM was increased and of IgG was decreased10. Therefore this study was done to compare the immunosuppression caused by Selective Cox-2 inhibitors and Non-selective Cox inhibitors.

In our study we have chosen Etoricoxib, Selective Cox-2 inhibitor and Meloxicam of the oxicam class which shows preferential inhibition of cyclo-oxygenase-2.

MATERIAL & METHODS

The study was done in department of Pharmacology in collaboration with Microbiology department. The study was approved by institutional animal ethics committee. The study was conducted on healthy adult Albino rabbits of either sex weighing 1000 – 1500 G.

The rabbits were divided into 3 groups of 6 animals each. One group serving as control was given normal saline (1 ml/kg p.o), while the other groups as test were administered Meloxicam (2 mg/kg, OD, p.o), and Etoricoxib (17 mg/kg O.D, p.o) for seven days starting one day prior to immunization.

All animals were immunized with Salmonella typhi 'O' antigen obtained from the Department of Microbiology of our Medical College. One ml of antigen contained 1×10⁸ bacteria of which 0.5 ml was injected intramuscularly in each gluteal region once only.

Blood samples (2 ml each) were withdrawn from marginal ear vein on 1st (before inoculation), 7th, 21st, and 28th days of immunization and were titrated for antibody level against S. Typhi 'O' antigen by modified Widal test.

DRUGS USED

MELOXICAM: (Unibiotic India Private Limited, Noida)
15 mg Meloxicam dissolved in 7.5ml of distilled water to give strength of 2mg/ml and was administered in suspension form.

ETORICOXIB (Amoli Organics Private Limited, Mumbai)
120 mg Etoricoxib dissolved in 7ml of distilled water to give approximately strength of 17mg/ml. It was given in suspension form.

The drug solutions were administered with the feeding canula per orally once daily. Care was taken so that rabbit do not spit the drug solution.

Statistical Analysis

The data was compared by Kruskal-Wallis test for comparison between individual samples. 2 tailed P value < 0.05 was considered as significant and P value < 0.005 was considered as highly significant.

RESULTS

The antibody titres in all the groups were found raised in the first week but more marked in treated groups as compared to Control...
In treated groups, antibody titres in the first week were highly raised in Etoricoxib treated rabbits than Meloxicam group (Table 1, Figure 1). Later on antibody titres were found significantly low in the treated groups at 7th, 14th, 21st, and 28th day in comparison to control (P< 0.005). Amongst the treated group, selective Cox 2 inhibitor (Etoricoxib) administration caused significantly higher antibody suppression in comparison to Non-selective Cox inhibitor Meloxicam, the suppression being significantly higher at day 14. (Table 1, figure 1).

Table 1: Effect of NSAIDS on Antibody Titres

<table>
<thead>
<tr>
<th></th>
<th>7th Day</th>
<th>14th Day</th>
<th>21st Day</th>
<th>28th Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROL (Normal Saline)</td>
<td>58.3±20.4</td>
<td>466.6±163.3</td>
<td>333.3±242.2</td>
<td>233.3±81.6</td>
</tr>
<tr>
<td>MELOXICAM (2 mg/kg p.o)</td>
<td>183.3±40.8</td>
<td>100.0±77.4</td>
<td>91.6±58.4</td>
<td>37.5±20.9</td>
</tr>
<tr>
<td>ETORICOXIB (17 mg/kg p.o)</td>
<td>500.0±244.9</td>
<td>58.3±20.4</td>
<td>83.3±60.5</td>
<td>37.5±20.9</td>
</tr>
</tbody>
</table>

P value .002 .000 .018 .001

aP< 0.005 in comparison to control.
bP< 0.05 in comparison to control.
cP< 0.005 in comparison to Meloxicam.

DISCUSSION

Since NSAIDs are used widely nowadays as over the counter drugs and have varying inhibitory effect on Cox-1 and Cox-2, it was considered worth to perform comparative study of various commonly used NSAIDs including specific Cox-2 inhibitors on immune response in animal model to make rational use of these agents in various conditions.

Our Study shows that NSAIDS enhances antibody production after a week of immunization whereas during second and third week antibody titres are markedly low as compared to Control. This also becomes evident from earlier studies which have shown that PGE2 suppressed all B-cell functions except for IgG synthesis[15]. Therefore drugs inhibiting Prostaglandin PGE2 will have opposite effect, increasing IgM antibody production and decreasing IgG production.

Disturbances in immune function found in several human conditions and diseases have been linked to changes in PGE mediated immunoregulation. A major role of PGE2 in the pathogenesis of Osteoarthritis has been already established which shows that chondrocytes isolated from patients with Osteoarthritis produce 50-fold more PGE2 than chondrocytes from patients without Osteoarthritis[11-13]. Interestingly, elevated Cox-2 levels have been reported in autoimmune diseases, such as systemic lupus erythematosus, where chronic inflammation persists at multiple sites in the body. This explains the clinical utility of highly selective Cox-2 inhibitors such as Etoricoxib to reduce the pain associated with inflammation. The drawback with this study is that we have used Widal test which is now obsolete; we should have gone for ELISA.

CONCLUSIONS

Our finding of reduced antibody production by Etoricoxib, specific Cox-2 inhibitor and Meloxicam suggests that these agents may be suppressing autoantibody production via direct effects on B cells.

The findings reported herein also have important implications for the use of NSAIDs following vaccinations, where the goal is to promote a humoral immune response. Although these drugs are commonly used to alleviate the pain associated with injection of vaccine, our findings suggest that there may be an adverse effect on antibody production and/or the immune response following secondary exposure.

REFERENCES

