THERAPEUTIC POTENTIAL OF TRIMETAZIDINE ON ANTI–INFLAMMATORY ACTIVITY ON RATS

Puja Kumari*, Vipin Kumar Soni, Vishweshar Bhagat, Vinod Kumar and Jagdish Rathi

Department of Pharmacology, NRI Institute of Pharmaceutical Sciences, 3, Sajjan Singh Nagar, Opp. Patel Nagar Raisen Road, Bhopal, MP, India.

ABSTRACT

The present study was designed to elucidate the effects of Trimetazidine and their administered drug in formalin-induced paw edema model inflammatory model. Male Lewis rat (divided into 4 groups with 6 animals each) were treated with Group1-control, Group 2-Negative control, Group 3- Diclofenac 50 mg/kg, Group 4-Trimetazidine 25 mg/kg. On the 28th day, evaluate various behavioral tests such as Hind paw volume and edema, body weight, arthritis scale and locomotor activity. Data was analyzed using One way ANOVA followed by Dunnette’s test (p<0.05) was considered statistical significant. Arthritic control group significantly (p< 0.05) impaired Hind paw volume and edema, body weight and locomotor activity as compared to negative and therapeutic. Trimetazidine (25mg/kg; orally) significantly (p< 0.05) reduced hind paw volume and edema, improved body weight and improved locomotor activity. Further, trimetazidine (25 mg/kg) significantly (p < 0.05) potentiated the anti-inflammatory as compared to their effects alone. The present study to investigate the trimetazidine has as antioxidant, anti-inflammatory activity and energy homeostasis hence a could be a promising strategy to treat inflammation.

KEYWORDS: anti-arthritis, locomotors activity, trimetazidine, antioxidant, anti-inflammatory.

INTRODUCTION

Inflammation is part of the biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is response that involves various
immune cells, blood vessels, and mediators. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the inflammatory process, and to also initiate tissue repair. The signs of acute inflammation are pain, heat, redness, swelling, and loss of function. Inflammation is a generic response, and that considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen.

Inflammation can be classified as acute and chronic. Acute inflammation is defined as initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood into the injured tissues. A series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process. Several causes such as physical factor, chemical factor and biological.

MATERIALS AND METHODS

Formalin preparation

Formalin –induced rat paw edema model is a suitable test for evaluating anti-inflammatory drugs, which has frequently been used to assess the anti-edematous effect of the drug. The rat formalin test, which causes a local tissue injury of the paw, has been used as a model for acute pain. These are two phases of the response. While the stimulus during the early phase is a chemical stimulation of the nociceptor, that during the late phase involves inflammation. It is an interesting aspect of this test that two principally different stimuli are employed in the same test. Formalin induced pain is caused primarily by peripheral tissue inflammation. A central sensitization of dorsal horn neurons occurs during the inflammation. Acute inflammation lasts a relatively short duration; only for minute, several hours, or a few days and its main characteristics are the exudation of fluid and plasma proteins and the emigration of leukocytes, predominantly neutrophils.[6]

Selection of drugs

Meloxicam is used to treat arthritis. It reduces pain, swelling, and stiffness of the joints. Meloxicam is known as a non-steroidal anti-inflammatory drug (NSAID). Trimetazidine, a piperazine derivative is a serum level of inflammatory markers, including interleukin-6,
interleukin-1beta and tumor necrosis factor-α, were detected to evaluate the extent of systemic inflammation. That’s why we selected these drug to see the effect of Meloxicam in combination Trimetazidine on Rheumatoid arthritis.\textsuperscript{[7]}

**Acute study by Formalin-induced paw edema model**

The formalin test was carried out in a 30×30×60 cm-sized clear transparent plastic chamber. The formalin was made of commercially available 37% formaldehyde solution further diluted in isotonic saline. Conscious rats received a subcutaneous injection of formalin solution in to the planter surface of the right hind paw with a 26-gauge needle.

The drugs were administered an hour before inducing paw edema with 0.1 ml formalin which was injected into the sub-planator aspect of left hind paws. Measurements of the paw volumes (ml) were made by plethysmometer 0, 1, 2,4,6,24,48 hours after formalin injection. The percentage inhibition of paw inhibition of paw volume was calculated. To evaluate the accuracy of the method, objects with bizarre shapes and different volumes (1 to 6 ml) were dipped into the mercury using a mechanical driver. The values on the digital balance were recorded. Thereafter, according to the mercury gravity the expected measures were calculated and compared with the observed value. The formula used for this measurement is $V = \frac{W}{p}$, in which $V$ stands for volume, $W$ for weight and $p$ for gravity. The procedure was repeated twice.\textsuperscript{[8]}

**Hind paw volume and edema**

Hind Paw edema and volume measurement using mercury column plethysmometer The HPV increase was calculated as the percentage increase on 0,1,3,7 days in HPV on the experimental day 28 relative to the HPV at the beginning of the experiment and beginning more inflammatory changes spreads systemically.

**Weight loss**

Weight loss after induction of arthritis and on subsequent days was observed and measure till the volume heals completely. Weight loss in various treatment groups will be compare on 0th to 7\textsuperscript{th} day.\textsuperscript{[9]}

**Locomotor activity**

The locomotors activity can be an index of wakefulness [alertness] of mental activity. Locomotor activity [horizontal activity] can be easily measured using an actophotometer.
which operates on photo cells which are connected in circuit with a counter when beam of light following on the photocell is cut off by the animals a count is recorded.[10]

RESULT AND DISCUSSION
Therapeutic potential of Trimetazidine against negative control was established by observing the general behavior such as paw volume, body weight and locomotor activity.

The formalin induced acute paw model negative control animals exhibited prominent swellings in hind paw as well as in for paw. The treatment TMZ significantly reduced the swellings which was also evident in (shown in table No.1). The mean and standard deviation of the values recorded for 7th hour was subject to one way ANOVA with repeated measures followed by Dunnett’s test. The ‘P’ values were obtained. The inhibition was significantly different as compared to negative control animals treated with saline.

Weight loss after induction of inflammation and on subsequent days was observed and measure till the volume heals completely. Induction of inflammation significantly maintain body weight and improved locomotor activity.

Table 1.1: Effect of Trimetazidine on body weight

<table>
<thead>
<tr>
<th>Treatment change</th>
<th>Initial body weight</th>
<th>Final body weight</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham control</td>
<td>178±0.04</td>
<td>185±0.06</td>
<td>........</td>
</tr>
<tr>
<td>Negative</td>
<td>199±2.77</td>
<td>168±0.09</td>
<td>-16%±0.05</td>
</tr>
<tr>
<td>Standard</td>
<td>189±0.49</td>
<td>184±0.08</td>
<td>-3.0%±0.06</td>
</tr>
<tr>
<td>TMZ (25 mg/kg) (Therapeutic)</td>
<td>176±0.77</td>
<td>170±0.08</td>
<td>-4.0%±0.08a</td>
</tr>
</tbody>
</table>

Data was analysed as Mean±SEM using one way ANOVA followed Dunnett’s test. The P values a=p<0.05 against negative control, b= p< 0.05 against positive control.

Table 1.2: Effect of Trimetazidine formalin-induced paw volume % inhibition (paw volume)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>..............</td>
</tr>
<tr>
<td>Standard</td>
<td>40.01±0.08</td>
</tr>
<tr>
<td>TMZ (25 mg/kg) (Therapeutic)</td>
<td>45.99a,b±0.04</td>
</tr>
</tbody>
</table>

Group-1-sham control, Group-2-Negative control, Group-3-Standard (Diclofenac sodium 50 mg/kg), Group-4-Treatment -1- Trimetazidine 25 mg/kg.

Data was analysed as Mean±SEM using one way ANOVA followed Dunnett’s test. The P values a=p<0.05 against negative control, b= p< 0.05 against positive control.
The percentage inhibition of paw volume edema using formalin as inducing agent was estimated. The mean and standard deviation of the values recorded for 3rd day was subject to one way ANOVA with repeated measures. The ‘P’ values were obtained.[11]

Seven day administration of drug to Lewis rats induced with formalin in hind paw on day 3rd day showed maximum inhibition. The inhibition was significantly (p<0.05) different as compared to negative control animals treated with saline.

**Effect of Treatment on Paw Volume Inhibition**

![Graph showing % inhibition]

Fig- 1.1- Lane -1- Negative control,Lane-2-Standard (Diclofenac sodium 50 mg/kg), Lane -3- Trimetazidine 25 mg/kg.

**Table 1.3: Effect on locomotor activity**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0th day</th>
<th>7th day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham control</td>
<td>133±0.04</td>
<td>140±0.08</td>
</tr>
<tr>
<td>Negative</td>
<td>132±2.77</td>
<td>122±0.05</td>
</tr>
<tr>
<td>Standard</td>
<td>129±0.49</td>
<td>129±0.06</td>
</tr>
<tr>
<td>TMZ (25 mg/kg) (Therapeutic)</td>
<td>132±0.49</td>
<td>135±0.08a</td>
</tr>
</tbody>
</table>

Group-1- sham control, Group-2-Negative control, Group-3-Standard, Group-4-Treatment -1- Trimetazidine 25 mg/kg.

Data was analyses as Mean±SEM using one way ANOVA followed Dunnett’s test. The P values a=p<0.05 against negative control, b= p< 0.05 against positive control.
The therapy is well known for anti-inflammatory properties in various experimental models.\textsuperscript{[12]} It has also been shown to protection against functional impairment produced by formalin in rat model of arthritis. In the present study, evaluated the effect of therapy on the level of inflammatory mediators, induced inflammatory model and compared with diclofenac. Paw swelling is an index of measuring the anti-arthritic activity of various drugs and it is employed here to determine the activity of combination therapy. The drug administered in groups showed marked reduction in paw volume when compared with the arthritic control group\textsuperscript{[13]} found that there was significant weight maintained, the day following the injection of the adjuvant, but there after continued to show normed weight gain in rats. The result of the present study also indicates that there is a close relationship between the extent of inflammation and loss of body weight.

**CONCLUSION**

A comparative study on the therapy and diclofenac for anti-inflammatory affect was performed. The experiments that drug are processing better anti-inflammatory activity as comparison to negative group. The present study to investigate the Trimetazidine has as antioxidant, anti-inflammatory activity and energy homeostasis hence aoptimum and Trimetazidine could be a promising strategy to treat anti-inflammatory.

**ACKNOWLEDGEMENT**

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REFERENCE


