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EVALUATION OF ANTI-INFLAMMATORY ACTIVITY OF MINOCYCLINE: AN EXPERIMENTAL STUDY

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ABSTRACT: Objective: Evaluation of anti-inflammatory activity of Minocycline: an experimental study. **Background:** Recently some studies have shown that minocycline may have pleiotropic biologic activities besides its antimicrobial activity. Due to these actions, minocycline may be useful in the treatment of pathological conditions in which acute or chronic inflammation is involved, such as rheumatoid arthritis, neurodegenerative and dermatological diseases. **Methods:** Wistar rats of either sex weighing 180-250 g were used for evaluating anti-inflammatory activity of minocycline (100mg/kg i.p.) by carrageenan induced rat paw edema and formalin induced arthritis models were used. **Results:** Minocycline in the dose 100mg/kg showed statistically significant anti-inflammatory activity in both acute and chronic model of inflammation i.e. Carrageenan- induced pawoedema and Formalin - induced arthritis model respectively. **Conclusion:** Minocycline possesses anti-inflammatory activity. However, further studies need to be carried out to evaluate its anti-inflammatory activity.

INTRODUCTION: Inflammation is a complex reaction to injurious agents such as microbes damaged and usually necrotic cells. It consists of a vascular response leading to accumulation of fluids, migration and activation of leukocytes and systemic reactions. Inflammation is fundamentally a protective response, with an aim is to get rid of both initial cause of injury and consequences of injury [1]. The tetracycline family of compounds is widely used as broad-spectrum antibiotics having antimicrobial activity against various bacteria, Mycoplasma, Rickettsiae and parasites [2].

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Recently, some studies have shown that, Minocycline may have pleiotropic biologic activities, besides its antimicrobial activity. Due to these actions, Minocycline may be useful in the treatment of pathological conditions in which acute or chronic inflammation is involved, such as rheumatoid arthritis, neurodegenerative and dermatological diseases [3, 4, 5].

Ala'a Ahmed 2005 *et al* shows that co-administration of Minocycline and Indomethacin an NSAIDS in hot plate method of analgesia and in monoarthritis model of inflammation, potentiates analgesic and anti-inflammatory activity of Indomethacin [6]. Even some chemically modified tetracyclines (CMTs), devoid of antibacterial activity, also attenuate some of the inflammatory response, 12S-hydroxy-1, 12-pyrazolino Minocycline (PMIN,) a derivative of Minocycline

may attenuate inflammation but devoid of antimicrobial activity [7]. In case of inflammation caused by infection, it needs treatment not only with antimicrobial /anti- parasitic drugs but also with anti-inflammatory agents. If the newer tetracycline possesses anti-inflammatory activity, they would be a useful addition to the existing anti-inflammatory drugs. Very few studies been carried out till date to evaluate the anti-inflammatory activity of Minocycline.

Aims & Objectives:

Aims: Evaluation of anti-inflammatory activity of Minocycline: an experimental study.

Objectives: To evaluate anti-inflammatory activity of Minocycline by Carrageen in induced rat paw edema and Formalin induced arthritis methods.

Animals, Material and Methodology: Wistar rats of either sex weighing 180-250 gm were used. Study was conducted after approval from the Institutional Animal Ethics Committee. The rats were grouped in separate cages with six animals in each cage. They were maintained in a colony room at ambient temperature of 23±1°C with help of air coolers and enough humidity on a 12-hour light – dark cycle. They had free access to food and water. Animals were randomly allocated into experimental groups. No blinding was done during drug administration or outcome measurement.

Chemicals: Aspirin, Carboxy Methyl Cellulose (CMC) and Minocycline pure powder form were obtained as gift samples from Medley and Cipla Pharmaceuticals, Mumbai. Carrageenan (1%) was procured from Yarrow Chem. Products and Unijules Life Sciences Limited. Carrageenan and Aspirin were suspended in Normal Saline using CMC.

Instruments: The fallowing instruments were used in the study, Plethysmometer, Dial Vernier Caliper, Rat Holder.

METHODS:

Evaluation of Anti-inflammatory Activity:

Acute Inflammation: Carrageenan – induced hind paw edema in rats [7].

Carrageenan – Induced Hind Paw Edema in Rats: Paw edema was induced by an intradermal injection of 0.1 ml of carrageenan (1% in normal saline) into the plantar surface of the right hind paw of the rats.

Animals were divided into following 3 groups:

1. Control group: Normal Saline Dose: 2ml/kg (i.p.)
2. Standard Group: Aspirin Dose: 100 mg/kg (i.p.) [8]
3. Test Group: Minocycline Dose: 100mg/kg (i.p.) [3]

The acute phase of inflammatory reaction i.e. edema volume was determined. Paw volume was measured using plethysmometer prior to and at 60 min, 120 min, 180 minutes after carrageenan injection. All the drugs were administered 30 min. prior to carrageenan.

Percentage inhibition of paw edema i.e. acute inflammation was calculated using the following formula:

$$\%It = (Vc-Vt) / Vc \times 100$$

Where, %It = % Inhibition at given time interval

Vc = Paw volume in control group

Vt = Paw volume in test group

Formalin Induced Arthritis in Rats [9]: Chronic phase of inflammation was induced by subcutaneous injection of 0.1 ml of 2% formalin under the plantar aponeurosis of right hind paw of albino rats on first and third day of the experiment.

Animals were divided into following 3 groups:

1. Control group: Normal Saline Dose: 2ml/kg (i.p.)
2. Standard Group: Aspirin Dose: 100 mg/kg (i.p.)
3. Test Group: Minocycline Dose: 100mg/kg (i.p.).

The drug to be tested was given daily for ten days. The linear cross section (LCS) immediately below the ankle joint of right hind paw was measured with Vernier Calliper.

The difference in LCS on day 1 and day 10 was calculated for all groups. Percentage anti – inflammatory effect of particular drug group was calculated by:

$$\% \text{ Anti-inflammatory Effect} = (LCSc - LCS_T) / LCS_C \times 100$$

Where, LCSc = Mean difference in linear cross-section (LCS) in the control group, LCS_T = Mean difference in linear cross-section (LCS) in the test group

Statistical Analysis: Data was expressed as Mean ± SEM (SD). Data was analyzed by using Graph Pad Prism software version 5.01.

Comparison between different groups was done by two-way ANOVA Repeated Measure ANOVA followed by Bonferroni posttest for comparison between multiple groups. The '*p*' valueless than 0.05 was considered statistically significant.

RESULTS:

TABLE 1: EFFECT OF DIFFERENT DRUGS ON PAW VOLUME IN CARRAGEENAN INDUCED PAW OEDEMA IN RATS

Groups, drugs & doses mg/kg , (n=06)	Increase in Paw Volume from Baseline (ml)		
	At 1 hr	At 2 hr	At 3 hr
Control (Normal Saline 2 ml/kg i.p.)	0.5667±0.08028(0.197)	1.100 ± 0.1238(0.303)	1.667 ± 0.08433(0.207)
Aspirin (100 mg/kg i.p.)	0.2167 ± 0.04014 (0.098)*	0.2500 ± 0.0500(0.122)** #	0.3667 ± 0.06146(0.151)** ##
Minocycline (100 mg/kg i.p.)	0.2833 ± 0.04014(0.098)*	0.6333 ± 0.06146(0.151)*	0.8000 ± 0.05164(0.126)**

Values are Mean ± SEM (SD). n = 06 in each group. ***** *p* value < 0.01 as compared to control. ** *p* value < 0.001 as compared to control. # *p* value < 0.05 as compared to Minocycline. ## *p* value < 0.01 as compared to Minocycline.

The **Table 1** shows increase in the mean paw volume from baseline in all the three groups at various time intervals in carrageenan induced paw edema model of acute inflammation in rats. At 1 hr interval, minocycline group had less increase in paw volume as compared to control group which was statistically significant. In aspirin treated group there was less increase in paw volume as compared to control and comparable with minocycline. At 2 and 3 hrs interval minocycline and aspirin attenuated increase in rat paw volume as compared to control, which was statistically significant. But in aspirin treated group caused more attenuation of rat paw volume as compared to minocycline which was statistically significant.

TABLE 2: EFFECT OF DIFFERENT DRUGS ON PAW VOLUME IN CARRAGEENAN-INDUCED PAW EDEMA IN RATS (% INHIBITION AT 3 HOURS)

Groups, drugs & doses, (n=06)	Differences in volume at 3 hrs (in ml)	% inhibition at 3 hrs.
Control (Normal Saline 2 ml/kg i.p.)	1.667 ± 0.08433(0.207)	----------
Aspirin (100 mg/kg i.p.)	0.3667 ± 0.06146(0.151)*#	78.0024%
Minocycline (100 mg/kg i.p.)	0.8000 ± 0.05164 (0.126)*	52.0095%

Values are Mean ± SEM (SD). n = 06 in each group**,** * *p* value < 0.001 as compared to control, # *p* value < 0.01 as compared to Minocycline

The **Table 2** shows the difference in paw volume at 3 hrs interval and percentage inhibition at 3 hours. At 3 hrs interval, the paw volume difference in Minocycline group and aspirin group was statistically significantly less as compared to control group. The difference in paw volume in aspirin group was significantly more as compared to Minocycline group. It was observed that percentage inhibition value at 3 hrs of aspirin group was 78.00 % which was significantly greater than Minocycline which was 52.00%.

TABLE 3: EFFECT OF DRUGS ON CHANGE IN LCS FROM DAY 1 TO DAY 10 IN FORMALIN-INDUCED ARTHRITIS (ENDPOINT ANALYSIS)

Groups (n=06 in each group)	Mean day 1	Mean day10	Mean Difference in LCS (mm)	% Anti-inflammatory effect
Control Group (Normal Saline 2ml/kg i.p.)	4.383 ± 0.07032(0.172)	7.883 ± 0.09458(0.232)	3.567 ± 0.1358(0.332)	
Aspirin (100 mg/kg i.p.)	4.300 ±	5.017 ±	0.7000 ±	80.37%

Minocycline (100mg/kg i.p.)	0.09661(0.237) 4.433 ± 0.1054(0.258)	0.09804(0.240)* 5.433 ± 0.2155(0.528)*	0.1770(0.433)* 1.000 ± 0.1238(0.303)*	71.96%

(Values are Mean S.E.M. (Standard error of Mean), n=06 in each group), *p value < 0.001 as compared to control

The **Table 3** shows that the least difference in the mean LCS was found in the aspirin group which was significantly (p<0.001) lower than that of control group.

The difference in the LCS in Minocycline group was also significantly less as compared to control group (p value<0.001).

The mean difference in LCS in Aspirin group and Minocycline group was statistically insignificant. The percentage anti-inflammatory effect was higher with aspirin group (80.37%) compared to Minocycline group (71.96%).

DISCUSSION: Minocycline is second generation synthetic broad-spectrum antimicrobial agent having longer plasma half-life and less renal toxicity than older tetracycline. In recent years, it has emerged that besides antimicrobial activity, tetracyclines may have various other properties such as anti-oxidant, analgesic, anti-inflammatory, gastroprotective, neuroprotective *etc* [10, 11].

In the model of acute inflammation i.e. carrageenan induced paw edema in rats, minocycline showed anti–inflammatory activity which was statistically significant as compared to control but less than aspirin.

The percentage inhibition of paw edema was maximum in the aspirin group 78.0024% and in Minocycline group it was 52.0095%.

Carrageenan induced edema shows a biphasic response. The first phase is mediated through the release of histamine, serotonin, and kinins, whereas the second phase is related to the release of prostaglandins and slow reacting substances such as leukotrienes [12].

Aladakatti *et al.* (2011) [13] reported anti-inflammatory activity of minocycline and doxycycline in carrageenan induced rat paw oedema. The proposed mechanisms of anti-inflammatory activity were inhibition of metalloproteinases like collagenase, gellatinase and others, phospholipase A2 –inhibition, suppression of T-lymphocytes as well as inhibition of cytokine production.

In formalin induced arthritis model of chronic inflammation maximum anti-inflammatory activity as indicated by percentage anti-inflammatory effect on tenth day (80.37%) was seen in aspirin treated animals. Percentage anti-inflammatory effect in minocycline group (71.96%) was significantly more when compared to control group.

Ala'a Ahmed *et al* (2010) [6] studied that mice with Lipopolysachride (LPS) induced monoarthritis which were treated with the combination of minocycline 50 mg/kg plus indomethacin 1 mg/kg had less weight bearing deficits.

Christopher *et al* (2011) [14] Minocycline has proven to be a very safe and moderately effective disease-modifying Antirheumatic drug (DMARD) in the treatment of Rheumatoid Arthritis.

Minocycline had anti-inflammatory activity in both acute and chronic model of inflammation i.e. Carrageenan induced rat paw oedema and formalin induced arthritis respectively. Also, some author suggested anti-inflammatory mechanism of minocycline may be due to anti-inflammatory effects on neutrophils, monocytes, microglial cells, and neurons [15]. Minocycline inhibits neutrophil-mediated tissue injury via inhibition of neutrophil migration and degranulation, as well as suppression of oxygen free radical formation [16].

Limitations: The study was conducted without blinding during drug administration and outcome assessment. The stusy did not evaluate histopathological changes and inflammatory biomarkers such as C-reactive protein, Erthrocyte sedimentation rate (ESR) and cytokines.

CONCLUSION: Minocycline in the dose 100mg/kg possesses significant anti-inflammatory activity. However, further studies need to be carried out to evaluate its anti-inflammatory activity.

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Declarations:

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Ethical Approval: The study was approved by the IAEC (Institutional Animal Ethics Committee) SRTR GMC AMBAJOGAI, letter no. 01 dated 2/12/2013.

CONFLICT OF INTEREST: There was no conflict of interest in this study.

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