

Study of evaluation of anti-inflammatory activity of macrolide antibiotics in rats: an experimental study

Punam A. Gosavi*, Jugalkishore B. Jaju, Vishal M. Ubale, Ganesh R. Pawar, Shrikant C. Dharmadhikari

Department of Pharmacology,
Government Medical College,
Latur, Maharashtra, India

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***Correspondence to:**

Dr. Punam A. Gosavi,
Email: gosavipunam@gmail.com

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ABSTRACT

Background: Inflammation is a complex and dynamic condition in which many changes take place at the site of inflammation, as well as systemically. In general, inflammatory response acts to protect the host, but many times it goes unchecked with tissue destruction leading to a spectrum of inflammatory disorders. Anti-inflammatory drugs have long been used to treat spectrum of inflammatory conditions. Anti-inflammatory agents, in use today, though have efficacy, cause a variety of side effects causing major problems during their clinical use. Amongst newer approaches to treat inflammation, macrolides, the anti-bacterial agents, seem to be beneficial in decreasing the inflammation. Still there is much speculation about the anti-inflammatory activity of macrolide antibiotics. So, we planned this study to assess anti-inflammatory activity of macrolide antibiotics (erythromycin, roxithromycin, azithromycin, and clarithromycin) and to compare their anti-inflammatory activity with control and indomethacin (standard non-steroidal anti-inflammatory drugs).

Methods: To assess anti-inflammatory activity of macrolides, we used acute (carrageenin-induced paw edema and turpentine oil-induced arthritis), as well as chronic model of inflammation (cotton pellet induced granuloma).

Results: All the macrolides, i.e., erythromycin, roxithromycin, azithromycin and clarithromycin showed significant ($p < 0.05$) anti-inflammatory activity in acute models of inflammation as compared to control group. However, macrolides showed insignificant activity as compared to indomethacin (acute and chronic models of inflammation) and as compared to control (chronic model of inflammation).

Conclusions: This study shows macrolide antibiotics have anti-inflammatory activity in animal models of acute inflammation.

Keywords: Anti-inflammatory, Macrolide antibiotics, Inflammation, Carrageenin

INTRODUCTION

Inflammation is defined as series of molecular and cellular responses acquired during evolution designed to eliminate foreign agents and promote repair of damaged tissues.¹

The mediators of inflammation are bradykinins, histamine, serotonin, leukotrienes, prostaglandins, lipoxins, and lysosomal enzymes.² In general, inflammatory response acts to protect the host (like in localization of abscess, decreasing the bacterial, and viral load), but many times it goes unchecked with tissue destruction leading to a spectrum of inflammatory disorders, and it is under these circumstances need to resort to drug therapy to dampen or abolish the unwanted inflammatory response arises.³

The current management of inflammation involves use of anti-inflammatory agents. Currently, the major groups

of anti-inflammatory drugs used are non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease modifying anti-rheumatic drugs (DMARDs).⁴ These currently available anti-inflammatory agents have different mechanisms of action to control inflammation, but they are also associated with unwanted side effects.⁴ It has been estimated that about 34-46% of the users of NSAIDs have sustained some gastrointestinal damage.^{4,5} Chronic use of NSAIDs is associated with nephrotoxicity and development of drug-induced hypertension.⁶ Recently, developed selective cyclooxygenase-2 inhibitors are gastric friendly but have a potential adverse effect of prothrombotic tendency leading to myocardial infarction and death.^{4,5} Glucocorticoids also produce an array of side-effects on chronic administration such as hypertension, Cushing's syndrome, hyperglycemia, osteoporosis, peptic ulceration, growth retardation, glaucoma, and adrenal insufficiency.⁷

DMARDs are associated with side effects such as exfoliative dermatitis, thrombocytopenia, peripheral neuritis, bone marrow depression, and anaphylaxis.⁸

So, constant effort is being put in to discover newer anti-inflammatory agents with improved efficacy and safety. Macrolide antibiotics have long been used as antibacterial agents in therapeutics.⁹ They have once a day administration, greater bioavailability and good tolerability.¹⁰ It has been shown that they possess anti-inflammatory activity in some animal models and human conditions.¹¹ Still there is much speculation about the anti-inflammatory effects of macrolide antibiotics. There is paucity of animal studies to evaluate the anti-inflammatory activity of macrolide antibiotics in general and of particular all four macrolide antibiotics.

So in the light of above information and evidence, we have undertaken this study to test the anti-inflammatory activity of macrolide antibiotics (erythromycin, roxithromycin, clarithromycin, and azithromycin) in various acute and chronic models of inflammation in comparison with the control, as well as standard drug indomethacin.

METHODS

Materials

Animals

Healthy adult albino rats of either sex weighing between 150 and 200 g were used in the experiment. The study was conducted after approval from the Institutional Animal Ethics Committee. The study was performed in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals guidelines.

The animals were acclimatized for 10 days under laboratory conditions. The animals were fed with standard diet and water *ad libitum* under strict hygienic conditions.

Drugs and chemicals

Drugs (erythromycin, roxithromycin, azithromycin, clarithromycin, and indomethacin) and chemicals (carrageenin, turpentine oil, formalin, and diethyl ether) were obtained from High Media, Mumbai.

- Indomethacin: The standard solution of indomethacin was prepared by dissolving 20 mg of the pure powder form in 10 ml of 1% carboxymethylcellulose (CMC)
- Erythromycin, roxithromycin, azithromycin and clarithromycin: The test solutions of each drug were prepared by dissolving 80 mg pure powder form in 20 ml of 1% CMC.
- Carrageenin: It was administered as a suspension (1% in 0.9% normal saline).¹²

Groups

The animals were divided into six groups containing six animals in each group.

Group I: Control: CMC in distilled water - Dose: 1 ml (p.o.).

Group II: Standard drug: Indomethacin dissolved in CMC⁹ - Dose: 10 mg/kg (p.o.).¹³

Group III: Test drug-1: Erythromycin dissolved in CMC - Dose: 40 mg/kg (p.o.).^{9,14}

Group IV: Test drug-2: Roxithromycin dissolved in CMC - Dose: 40 mg/kg (p.o.).⁹

Group V: Test drug-3: Azithromycin dissolved in CMC - Dose: 40 mg/kg (p.o.).⁹

Group VI: Test drug-4: Clarithromycin dissolved in CMC - Dose: 40 mg/kg (p.o.).⁹

Experimental methods

Carrageenin induced-rat paw oedema^{2,5,13,15,16}

Anti-inflammatory activity was evaluated by carrageenin-induced rat paw edema model, described by Winter et al. using mercury plethysmograph.¹⁵ Paw of each animal was marked with ink at the level of lateral malleolus. All the drugs were administered to the respective groups orally. After 1 hr of drug administration, paw edema was induced by an intradermal injection of 0.1 ml of carrageenin (1% in normal saline) into the planter surface of the right hind paw of the rats.¹⁶

Paw volume was measured as the displacement of mercury column on the mercury plethysmograph and was expressed in ml. The readings were taken at the baseline and at hourly interval up to 4 hrs after administering carrageenin.

The difference in paw volume was calculated by subtracting the 0 hr reading from the 4 hrs reading. Statistical analysis was done by comparing the mean difference in paw volume of control and drug-treated groups. Percentage inhibition of the edema for the test and control group was also calculated as a measure of anti-inflammatory activity by using the following formula.^{5,13}

$$\text{Percentage anti-inflammatory activity} = \frac{C - T}{C} \times 100$$

C = Mean increase in paw volume in the control group

T = Mean increase in paw volume in the drug treated group

Turpentine induced arthritis in rats^{13,17,18}

Knee joint of each animal was marked with ink. All the drugs were administered to the respective groups orally. 1 hr later, acute inflammatory joint edema was produced by injecting 0.05 ml of turpentine oil into the right knee joint cavity of rats.¹⁷ Lateral diameter of the knee joint was measured immediately after the injection of turpentine oil (0 hr reading) and after 4 hrs by using vernier caliper.^{13,18}

The change in lateral diameter of knee joint was calculated by subtracting the 0 hr reading from the 4 hrs reading. Statistical analysis was done by comparing the mean difference in lateral diameter of the knee joint of control and drug-treated groups. Percentage inhibition of arthritis for the test and control group was also calculated as a measure of anti-inflammatory activity by using the following formula.¹³

$$\text{Percentage anti-inflammatory activity} = \frac{C - T}{C} \times 100$$

C = Mean increase in lateral diameter of knee joint in the control group

T = Mean increase in lateral diameter of knee joint in the drug treated group

Cotton pellet granuloma in rats^{2,9,16,19,20}

On the 1st day, drugs were administered to respective groups orally. Then rats were anesthetized lightly with ether.¹⁹ The skin was disinfected with 70% ethanol. The small linear incisions of about 1 cm were made one near each axilla.² Two sterile cotton pellets weighing 10 mg each was implanted through small incisions in both the axilla.²⁰ The wounds were then sutured, and the animals were maintained in clean cages. Food and water were allowed throughout period of experimentation. Aseptic precautions were taken throughout the experiment. Drugs were administered to respective groups for 6 consecutive days.

On the 8th day, animals were anesthetized by diethyl ether. Cotton pellets with granulation tissue were removed. Wounds were sutured with black silk thread. Cotton pellets were cleaned of extraneous tissue and then dried in a hot air oven at 60°C for 18 hrs.¹⁶ The dry weight of the granuloma was calculated by noting the difference in the weight of the pellets recorded before and after implantation.

Statistical analysis was done by comparing the mean dry weight of granuloma for control and drug-treated groups. Percentage inhibition of mean dry weight of granuloma for the test and control group was also calculated as a measure of anti-inflammatory activity by using the following formula.^{2,9}

$$\text{Percentage anti-inflammatory activity} = \frac{W_c - W_t}{W_c} \times 100$$

W_c = Mean dry weight of granuloma in the control group

W_t = Mean dry weight of granuloma in the drug treated group

Statistical analysis

Data was analyzed by using Graph pad prism software version 5.01. Comparison between different groups was done by one-way ANOVA followed by Tukey's *post-hoc* test. The $p < 0.05$ was considered statistically significant.

RESULTS

Carrageenin induced rat paw edema

Mean paw volume increase is considered as a measure of inflammation and the ability to control this increase as compared to control suggests anti-inflammatory activity. In this model, at 4 hrs, all the macrolides showed statistically significant ($p < 0.05$) curtailment of mean paw volume increase as compared to control group (Table 1). Anti-inflammatory activity shown by macrolides was not significant ($p > 0.05$) as compared to indomethacin. Percentage inhibition of increase in mean paw volume shown by macrolides was less as compared to indomethacin (Table 1).

Turpentine oil-induced arthritis

Mean increase in lateral diameter of knee joint, is considered as a measure of inflammation and an ability to control this increase as compared to control suggests anti-inflammatory activity. Curtailment of increase in mean lateral diameter of knee joint is considered as anti-inflammatory action. In this model, at 4 hrs, all the macrolides showed statistically significant ($p < 0.05$) curtailment of increase in mean lateral diameter of knee joint as compared to control group (Table 2). Anti-inflammatory activity shown by macrolides was not significant ($p > 0.05$) as compared to indomethacin. Percentage inhibition of increase in mean lateral diameter of knee joint shown by macrolides was less as compared to indomethacin (Table 2).

Cotton pellet induced granuloma

Mean dry granuloma weight is considered as a measure of inflammation and an ability to decrease this mean dry granuloma weight as compared to control suggests anti-inflammatory activity. In this model, anti-inflammatory activity of macrolides as shown by decrease in mean dry granuloma weight was not significant ($p > 0.05$) as compared to control group (Table 3). Anti-inflammatory activity shown by macrolides was not significant ($p > 0.05$) as compared to indomethacin. Percentage inhibition of mean dry granuloma weight shown by macrolides was very less as compared to indomethacin (Table 3).

DISCUSSION

Inflammation is the integral part of the body's defense mechanism. It is known that the acute inflammatory response consists of three main vascular effects such as vasodilation, increased vascular permeability, and leukocytes migration to the injured tissue.²¹ Chronic inflammation includes proliferation of fibroblasts, increased connective tissue, and infiltration of mononuclear cells.²² These mediators of inflammation, if go unchecked, can cause tissue destruction also, leading to spectrum of diseases e.g. rheumatoid arthritis. Anti-inflammatory drugs have long been used to treat this

Table 1: Effect of different drugs on mean paw volume (ml) at 0 hr and 4 hrs in carrageenan-induced rat paw edema model.

Groups	Mean paw volume (ml)		Mean difference in paw volume	% inhibition
	At 0 hr	At 4 hrs	At 4 hrs (ml)	At 4 hrs
Control	0.27±0.02	0.95±0.07	0.67±0.06	
Indomethacin	0.36±0.05	0.61±0.03	0.25±0.02***	62.96
Erythromycin	0.30±0.04	0.68±0.03	0.38±0.02** [#]	43.21
Roxithromycin	0.28±0.01	0.67±0.07	0.39±0.06** [#]	41.97
Azithromycin	0.25±0.04	0.70±0.02	0.44±0.06** [#]	34.56
Clarithromycin	0.38±0.05	0.78±0.03	0.40±0.04** [#]	40.74

Values are expressed in mean±SEM, n=6 in each group, df=5,30. *p<0.05 as compared to control, **p<0.01 as compared to control, ***p<0.001 as compared to control, [#]p>0.05 as compared to indomethacin. SEM: Standard error of mean

Table 2: Effect of different drugs on mean lateral diameter of knee joint (mm) at 0 hr and 4 hrs in turpentine oil induced arthritis model.

Groups	Mean lateral diameter of knee joint (mm)		Mean difference in lateral diameter of knee joint	% inhibition
	At 0 hr	At 4 hrs	At 4 hrs (mm)	At 4 hrs
Control	7.02±0.27	8.78±0.22	1.76±0.25	
Indomethacin	6.21±0.34	6.86±0.35	0.64±0.23***	63.35
Erythromycin	7.13±0.20	7.94±0.22	0.81±0.04** [#]	53.82
Roxithromycin	6.95±0.30	7.77±0.31	0.82±0.03** [#]	53.20
Azithromycin	7.04±0.30	8.04±0.27	1.00±0.03** [#]	42.82
Clarithromycin	6.82±0.33	7.82±0.33	0.99±0.08** [#]	43.44

Values are expressed in mean±SEM, n=6 in each group, df=5,30. *p<0.05 as compared to control, **p<0.01 as compared to control, ***p<0.001 as compared to control, [#]p>0.05 as compared to indomethacin. SEM: Standard error of mean

spectrum of inflammatory conditions. Anti-inflammatory agents, in use today, though have efficacy, cause a variety of side effects causing major problems during their clinical use.

Amongst newer approaches to treat inflammation, macrolides, the anti-bacterial agents, not only reduces infection but seem to be beneficial in decreasing the inflammation. So, we planned this study to assess anti-inflammatory activity of macrolide antibiotics using acute (carrageenin-induced paw edema and turpentine oil-induced arthritis), as well as chronic models of inflammation (cotton pellet induced granuloma).

In carrageenin-induced hind paw edema model, there is 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.²³ In carrageenin-induced hind paw edema model, we assessed mean paw volume. Curtailment of mean paw volume increase is considered as anti-inflammatory action. In this model, at 4 hrs, all the macrolides showed statistically significant (p<0.05) curtailment of mean paw volume increase as compared to control group (Table 1). Anti-inflammatory activity shown by macrolides was not significant (p>0.05) as compared to indomethacin. Percentage inhibition of increase in mean paw volume shown by macrolides was less as compared to indomethacin (Table 1).

Table 3: Effect of different drugs on mean dry granuloma weight (mg) in cotton pellet induced granuloma model.

Groups	Mean dry granuloma weight (mg)	% inhibition
Control	41.00±3.07	-
Indomethacin	24.67±3.66**	39.82
Erythromycin	30.67±2.99 [#]	25.19
Roxithromycin	39.67±2.20 [#]	3.24
Azithromycin	34.50±2.56 [#]	15.8
Clarithromycin	38.00±3.38 [#]	7.31

Values are expressed in mean±SEM, n=6 in each group, df=5,30. **p<0.01 as compared to control, [#]p>0.05 as compared to control and indomethacin. SEM: Standard error of mean

Turpentine oil-induced arthritis is characterized by triphasic release of various inflammatory mediators such as histamine, serotonin, and kinin such as substance, cyclooxygenase, and lipoxygenase products. Inhibition of turpentine oil induced joint arthritis suggests the possible effect of macrolides on different phases of inflammation.²⁴ In turpentine oil-induced arthritis, we assessed mean lateral diameter of knee joint. Curtailment of increase in mean lateral diameter of knee joint is considered as anti-inflammatory action. In this model, at 4 hrs, all the macrolides showed statistically significant (p<0.05) curtailment of increase in mean

lateral diameter of knee joint as compared to control group (Table 2). Anti-inflammatory activity shown by macrolides was not significant ($p>0.05$) as compared to indomethacin. Percentage inhibition of increase in mean lateral diameter of knee joint shown by macrolides was less as compared to indomethacin (Table 2).

Cotton pellet-induced granuloma model divided into at least three response phases, i.e., transudative phase, exudative phase and proliferative phase. The proliferative phase is measured as the increase in dry weight of the granuloma.^{25,26} In cotton pellet-induced granuloma model, we assessed mean dry granuloma weight. Reduction in mean dry granuloma weight is considered as anti-inflammatory action. In this model, anti-inflammatory activity of macrolides as shown by decrease in mean dry granuloma weight was not significant ($p>0.05$) as compared to control (Table 3). Anti-inflammatory activity shown by macrolides was not significant ($p>0.05$) as compared to indomethacin. Percentage inhibition of mean dry granuloma weight shown by macrolides was very less as compared to indomethacin (Table 3).

Thus, all the macrolides, i.e., erythromycin, roxithromycin, azithromycin, and clarithromycin showed significant anti-inflammatory activity in acute models of inflammation as compared to control group. However, macrolides showed insignificant activity in acute models of inflammation as compared to indomethacin. Macrolides did not show significant activity in chronic model of inflammation as compared to control group and indomethacin group.

Various mechanisms have been proposed to explain this anti-inflammatory action of macrolides. Evidences indicate that macrolides are suggested to inhibit the production of many pro-inflammatory cytokines (interleukin [IL] 1, IL 2, IL 6), nitric oxide, tumor necrosis factor- α , leukotrienes, and prostaglandins. The most probable mechanisms of acute anti-inflammatory activity of macrolide antibiotics could be due to the inhibition of synthesis of prostaglandins, serotonin, histamine and other inflammatory mediators.^{9,14,27} Insignificant chronic anti-inflammatory activity of macrolides could be due to that, they do not inhibit fibroblast proliferation and synthesis of collagen in chronic inflammation.

Previous studies, such as Ianaro et al.,⁹ Prathima et al.,¹¹ Khobragade et al.,¹⁴ Scaglione and Rossoni,²⁷ and Agen et al.,²⁸ have also shown that macrolide antibiotics have anti-inflammatory activity using various animal models of inflammation. Our results correlate with the findings in above studies.

So from our study, we propose that macrolide antibiotics have anti-inflammatory activity. Furthermore, these drugs have advantages such as once a day administration, greater bioavailability, and good tolerability making them a potential new anti-inflammatory drug. Since this is an animal study, these results need to be confirmed in human studies for

further establishment of the role of macrolide antibiotics in the treatment of inflammation.

CONCLUSION

From this study, we conclude that macrolides have significant anti-inflammatory activity as compared to control in animal models of acute inflammation. Further studies need to be done to establish exact role of macrolides as anti-inflammatory agents.

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