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Screening of the drug Amiodarone for its Antiinflammatory potential in albino rats

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Abstract

Adult albino rats of either sex weighing 150-200 grams were randomly divided into 3 groups of 6 each. The control, standard and test group received Gum acacia 2g%, indomethacin 10 mg/kg and amiodarone 24 mg /kg respectively. Acute inflammatory activity was assessed by carageenan induced paw oedema, Turpentine induced arthritis and Sub Acute activity was assessed by cotton pellet induced granuloma model. The anti-inflammatory activity was expressed as percentage of inhibition. In carageenan induced paw oedema, percentage of inhibition of paw oedema by indomethacin and amiodarone with respect to control were 51% and 30% respectively. Hence the anti-edema effect of the test group was good and comparable with standard. The percentage of inhibition of paw oedema by the test group considering the percentage of inhibition of standard as 100 % was 70.37%.Thus Amiodarone showed good anti-inflammatory activity compared with the standard drug indomethacin in carageenan induced rat paw oedema model.

Key-Words: Amioadarone, Antinflammatory, Indomethacin, Carrageenan, Turpentine, Cotton pellet

Introduction

Inflammation is the basic strategy of any host defense mechanism to combat or overcome the invading pathogen or the foreign particles. The most common presentation of a patient to the doctor is pain and inflammation[1].

Therapy of inflammation is a debate and is also incomplete since long. The introduction of sodium salicylate, acetyl salicylic acid (ASPIRIN), cortisone, gold salts and phenylbutazone for the treatment of inflammatory disorders is an important milestone in the development of clinically useful anti-inflammatory agents [2] and the newer ones like selective COX-2 inhibitors, Oxyprofen, aceclofenac, etc. The currently used 3 major groups of anti-inflammatory drugs include: NSAIDs, Glucocorticoids and Disease modifying anti-rheumatic drugs (DMARDs).[3]

Currently available anti-inflammatory agents are associated with unwanted side effects and have their own limitations. It has been estimated that about 34-46% of the users of NSAIDs will sustain some gastrointestinal damage due to the inhibition of the protective COX enzyme in gastric mucosa.[4]

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Recently developed selective COX-2 inhibitors are gastric friendly but have a potential adverse effect of prothrombotic tendency leading to MI and death. Glucocorticoids also produce an array of side-effects upon chronic administration.

Of late we are establishing the anti-inflammatory activity in other groups of agents also which are not designated as conventional anti-inflammatory drugs i.e., new indications of the older drugs like chloroquine was found to be effective in the therapy of Rheumatoid arthritis, D-Penicillamine ,a chealating agent used as a Disease modifying agent in rheumatoid arthritis ,Methotrexate an anticancer agent used as immunosuppressants.The mediators of inflammation are Bradykinin,c3,c5a,plasmin,thrombin,histamine serotonin interferon,oxygen derived free radicals,NO,PAF,Interleukins,NF kappa B , Leukotrines,TNF Alpha,IL-1,INF Gamma,Prosthoglandins,lysosomal enzymes[5].

The drug Amioadarone has been used to treat arrhythmias .It is a class 3 antiarrythmic Agent.[6]The drug is known to have anti-inflammatory activity due to its different action relating to mediators of inflammation such as reducing polymorphonuclear leukocytes,inhibition of phospholipase A_2,reduction in free radical production,proteolytic enzyme release[7] and increasing antioxidative enzymes such as catalase and

glutathione s transferase [8]hence in this study an earnest attempt is made to explore its activity.

Objectives of the study

1. To evaluate the Anti-inflammatory activity of the drug Amiodarone in acute and sub acute inflammatory animal models.
2. To compare the Anti-inflammatory activity of the drug Amiodarone with standard in both acute and sub acute inflammatory models.

Material and Methods

Source of data: Adult albino rats of either sex weighing between 150 to 250 grams were randomly selected from central animal facility, J S S Medical College, Mysore after getting prior approval from institutional animal ethical commitee.

Inclusion criteria: Rats of either sex weighing 150-250 grams.

Exclusion criteria: Pregnant and Diseased animals are not included in this study.

Chemicals used: Amioadarone (24mg/kg), Indomethacin (10mg/kg) of body weight, Turpentine, 1% Carrageenan, Cotton pellets, Ether.

Instruments required: Mercury Plethsmograph, Screw gauge, Tuberculin syringe, Feeding tube, mouth gag.

Models of experiment

The animals will be randomly divided into 3 groups of 6 each, one group will serve as control and will receive 2% gum acacia suspension orally (without drug). Other two groups will receive drug Indomethacin10mg/kg of body weight and Amioadarone 24 mg/kg of body weight respectively. Each rat is fed with respective drug one hour prior to the administration of Phlogestic agent.

Methodology

Carrageenan induced rat paw edema Animal Model: [9]

0.1 ml of 1% Carrageenan is injected into the subplantar surface of right hind

paw of each group. Paw volume is measured by Mercury Plethysmograph at '0'hour and at the end of '4' hours. The difference between the Zero and 4 hours gives the actual edema.

From the mean paw oedema volume the percentage inhibition of oedema was calculated between the test and the control group .Percentage of inhibition of oedema=100(1-vt/vc) where Vt and Vc represent average paw oedema volume in test and in control group.

Turpentine induced Arthritis Animal Model: [10]

0.1ml of turpentine oil is injected into the right knee joint of each rat .Then the lateral diameter will be measured by screw gauge at '0' hour and at the end of '4' hours. Change in lateral diameter will be noted. From the mean difference in lateral diameter the percentage of inhibition of arthritis was calculated between the test and the control group .Percent antiarthritic effect =100(1-Dt/Dc) where Dt and Dc represent mean lateral diameter in test and control group.

Cotton pellet induced Granuloma Animal Model: [11]

Four sterile cotton pellets weighing 10mg each will be implanted subcutaneously in each axilla and groin in each rat of control standard and test group. Each rat is fed with respective drug for 14 days.The cotton pellet is inserted after 14th day and oral feeding of the drugs are continued for 6 days ,then cotton pellets will be removed along with granulation tissue on 21st day, cleaned and dried in hot air oven for24 hrs and dry granulation tissue weight will be determined.From the mean difference in dry granulation tissue weight the percentage of inhibition of granuloma was calculated between the test group and the control.Percent antigranuloma ctivity =100(1-wt/wc),where wt and wc represent dry granulation tissue weight of the test group and control.

Statistical methods applied

The effect of the drug under study was presented by calculating mean and SD of the outcome parameters.one way anova and post hoc test was applied to see the differences between any two groups at a time.Test of significance were carried out at 5%level.SPSS for windows(version 21) was applied in the statistical analysis.

Results and Discussion

The drug Amiodarone have been investigated in this study for their anti-inflammatory potential and compared with the standard reference drug Indomethacin.

In the present study the acute experimental inflammatory models studied includes, Carrageenan rat paw oedema, Turpentine induced arthritis. The sub acute inflammatory model includes Cotton pellet induced granuloma model. In all the experimental inflammatory models, Indomethacin was used as Standard drug and sumatriptan was used as test drug.

The percentage inhibition of carageenan induced rat paw oedema by Indomethacin compared with control was 51% while that of test drug was 30%. Hence the anti-edema activity of the test group was comparable with that of the standard.The percentage inhibition of paw oedema by the test group considering the inhibition of paw oedema by standard as 100% was 70.37%.Thus sumatriptan showed good anti-inflammatory activity comparable with standard drug

Indomethacin in Carrageenin induced rat paw oedema model.

The percentage inhibition of Turpentine induced knee arthritis by standard compared with control was 60%and that of test group was 32% respectively.Therefore sumatriptan showed a good antiarthritic activity as compared to the standard drug. The percentage inhibition of knee arthritis by the test group considering the percentage inhibition of standard as 100% was 58.8%.Thus sumatriptan showed moderate degree of anti-inflammatory activity comparable with standard drug Indomethacin in Turpentine induced arthritis model.

The percent inhibition of cotton pellet induced dry granulation tissue weight by Indomethacin compared with control was 50% and that of the test group was 42%. Sumatriptan showed antigranuloma effect of moderate degree as compared to the standard drug. The percentage inhibition of dry granuloma weight by the test group considering the percentage inhibition of standard as 100% was 85.72%.Thus sumatriptan showed significantly good anti-inflammatory effect comparable with standard drug Indomethacin in Cotton pellet induced granuloma model.

The anti-inflammatory activity of the Standard drug was significant in cotton pellet induced granuloma model and carageenan induced paw oedema model and good in turpentine induced arthritis model.

The anti-inflammatory activity of Amiodarone was good in carageenan induced paw oedema model and moderate in turpentine induced arthritis model and significantly good in cotton pellet induced granuloma model.

This study was in accordance with the study 'Amioadarone has anti-inflammatory and antioxidative properties:.An experimental study with carageenan induced rat paw oedema model,wherein amioadarone was found to cause decrease in paw oedema,increase in antrioxidative enzymes,catalase,glutathione –s-transferase.[7]

This study was supported by the study .The role of polymorphonuclear leucokocyte in the mechanism of anti-inflammatory effect of amiodarone. Wherein amiodarone was found to exhibit protective effects histopathologically in Histamine induced inflammatory model in rats due to reduction in neutrophil movement, inhibition of phospholipase A_2, reduction in free radical and proteolytic enzyme release[8].

Different assays based on other inflammation parameters like erythema, pain, etc needs to be done. Further studies are required to support these findings in humans as the animal data cannot be directly extrapolated on humans.

Hence Amioadarone can be used to combat inflammation alone or with other conventional anti-inflammatory agents apart from its conventional use as an antiarrythmic agent.

Concluion

1. There are only a few studies on Amiodarone which showed anti-inflammatory properties**.**
2. In the present study, Amiodarone has showed good to moderate anti-inflammatory activity in acute models and significantly good anti-inflammatory activity in sub-acute model of inflammation, in comparison to the standard Indomethacin**.**
3. The anti-inflammatory property of Amiodarone is due its ability to prevent the production of pro-inflammatory mediators like neutrophils, phospholipase A_2 antioxidative enzymes like catalase, superoxide dismutase, glutathione s transferase .etc.
4. The present study envisaged that the use of Amiodarone either as monotherapy or along with the conventional medications may have an added benefit of anti-inflammatory activity in various inflammatory disorders.
5. This study is valuable for identifying lead compounds for anti-inflammatory drugs, keeping in mind the side effects of NSAIDs and corticosteroids.
6. Further studies need to done in various other acute and chronic inflammatory models along with the human studies to strengthen the results and prove their efficacy of long term administration Amioadarone as potential anti-inflammatory agent in routine clinical practice.

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Table 1: Carrageenan -induced Rat Paw Oedema Method

Table showing the Mean rat paw volume (cm) at 0hr and 4hr and difference between the groups, ANOVA, independent t test resultsand percentage of inhibition of inflammation with respect to control and standard

GROUPS	0hr (mean+/- SD)	4hr (mean+/- SD)	Mean difference in paw oedema in cms	ANOVA	Independent T TEST	% of inhibition of oedema of test and standard with respect to control	% of inhibition of oedema of test group with respect to standard
CONTROL	0.69+/- 0.16	8.42+/- 0.45	7.73	F=2427.7. P=0.001	t=26.95 P=0.001	-	-
STANDARD	1.3+/- 0.28	5.13+/- 1.03	3.83			51%	-
TEST	1.5+/- 0.35	6.9+/- 0.90	5.4			30%	70.37%

The table indicates that Amioadarone shows good antiinflammatory acvtivity, ANOVA Analysis suggest that there was a statistical significance between the group, independent t test suggest that the there is a statistical significant difference between the standard and the test

Table 2: Turpentine Induced Arthrtis model

Table showing the mean lateral knee diameter (mm) at 0 hr and 4hr and difference between the groups, ANOVA, Independent t test results and percentage inhibition of inflammation with respect to control and standard

GROUPS	0hr (mean+/- SD)	4hr (mean+/- SD)	Mean difference in lateral diameterin mm	ANOVA	Independent T TEST	% of inhibition of oedema with respect to control	% of inhibition of oedema with respect to standard
CONTROL	3.33+/- 0.51	8.05+/- 0.23	4.71	F=1733.7 P=0.001	t=27.8 P=0.001	-	-
STANDARD	3.5+/- 0.54	5.4+/- 0.35	1.9			60%	-
TEST	3.7+/- 0.08	6.93 +/- 0.64	3.23			32%	58.8%

The table indicates that Amioadarone shows moderate antiinflammatory activity, ANOVA Analysis suggest that there was a statistical significance between the group, independent t test suggest that the there was a statistical significant difference between the standard and the test.

Table 3: Cotton Wool Pellet Induced -Granuloma Model

Table showing the mean dry granulation tissue weight in different drug groups, ANOVO, Independent t test results, percentage of anti-inflammatory activity of the test group with respect to control and standard

GROUPS	Mean dry granulation tissue in mgs	ANOVA	Independent T TEST	% of inhibition of dry granulation with respect to control	% of inhibition of dry granulation tissue with respect to standard
CONTROL	**90.33**	**F=1163.2 P=0.001**	**t=11.82 P=0.001**	**-**	**-**
STANDARD	**46**			**50%**	**-**
TEST	**53.66**			**42%**	**85.72%**

The table indicates thatAmiodarone shows significantly good antiinflammatory activity, ANOVA Analysis suggest that there was a statistical significance between the group, independent t test suggest that the there was a statistical significant difference between the standard and the test

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