

A study on the modification of anti-inflammatory and analgesic action of aspirin by nifedipine

Patowary S

Assistant Professor, Department of Clinical Pharmacology, College of Medical Sciences, Bharatpur, Nepal

Abstract

Introduction

Aspirin has been used as an analgesic from time immemorial. But the recent advances on various aspects of it in reducing risk of various fatal and non fatal diseases warrant a re-look.

Objective:

This study has been undertaken to assess the anti inflammatory and analgesic action of aspirin and Nifedipine alone as well as in combination and their individual and synergistic effect as anti-inflammatory and analgesic drug.

Materials and methods:

The anti - inflammatory and anti - nociceptive effect of aspirin and nifedipine was studied in a group of albino rats of Sprague Dowly strain. Anti - inflammatory action of the drugs were tested in experimentally produced inflammatory model by injecting turpentine oil in to the synovial cavity of knee joint of rats and anti - nociceptive effect was studied by hot plate method .

Results

From the study it was observed that nifedipine alone was a better anti - inflammatory drug causing 40.10 percent reduction of experimentally produced inflammation in the studied rats on the 12th day of observation compared to aspirin alone(33.80 %) and aspirin - nifedipine combination (39.82%) but as an analgesic nifedipine alone (51.20%) was not found to be as effective as aspirin(88.96%) at 90 minutes of observation. However, when nifedipine was combined with aspirin, it potentiated the anti - nociceptive action of aspirin (107.64 %) at 90 minutes of observation which was statistically significant ($P < 0.01$).

Conclusion:

The above finding demonstrated that the dose of Non Steroidal Anti – inflammatory Drugs (NSAIDs) probably could be reduced when it is combined with Calcium Channel Blockers (CCBs) and thus the adverse effect of NSAIDs could be reduced considerably. Student's t test was applied for statistical analysis.

Key words: Anti inflammatory, anti - nociceptive, synergistic action.

Aspirin is an age-old drug widely used as an analgesic, which alleviates pain without affecting consciousness. It was introduced by Dr. Henrich Dresser as an analgesic but its anti-inflammatory action was demonstrated only after the demonstration of anti-inflammatory action of cortisone in 1948. Now it is referred to as NSAIDs. Recent advances on various actions of aspirin on different symptoms warrants a re-look in to its exciting new possibilities like its role in reducing the risk of fatal and non-fatal heart attacks, strokes, migraine, cataract, colorectal carcinoma and in control of pre-eclampsia of pregnancy. CCBs are also widely used in various clinical and cardiovascular conditions like in ischemic heart disease, angina pectoris, cardiac arrhythmias, migraine, Raynaud's phenomenon, oesophageal spasm and so on. Few recent studies^(1,2,3) have revealed the anti - inflammatory and analgesic property of CCBs and its synergistic action with some drugs in human being as well as in experimental model but these studies are very limited and they are still in preliminary stage. Hence this study

was undertaken to find out if there was any synergistic action between nifedipine and aspirin in experimental model.

Objectives

The study was undertaken:

1. To assess the anti - inflammatory and analgesic activities of
 - a. Aspirin and Nifedipine alone
 - b. Aspirin and Nifedipine in combination
2. To find out their individual and synergistic effects as an anti-inflammatory and analgesic drug.

Correspondence

Dr. Susmita Patowary,

Assistant Professor

Dept. of Clinical Pharmacology, Agartala Government Medical College,

P.O. Kunjaban, Agartala, Tripura (South), India.

E-mail: suspat@rediffmail.com

Material and methods:

Experiments were carried out in 64 albino rats of either sex. They were divided randomly into two broad groups:

- a) Anti - inflammatory group
- b) Anti - nociceptive group

The anti - inflammatory group comprised of 24 rats, which was further sub divided into four sub groups and each sub group comprising of six rats. Before starting the experiment the rats were weighed and lateral diameter of knee joints were measured with a vernier caliper and recorded. The model of inflammation was produced in experimental animals by injecting turpentine oil in dose of 0.1ml in the synovial cavity of the right knee joint. On the third day prior to administration of drugs, lateral diameter of the rat's knee joints were measured and examined for inflammatory changes. The groups were given continuous number as Group I, II, III and IV. Group I which acted as control was given normal saline. Group II, III and IV received aspirin, nifedipine and aspirin - nifedipine combination respectively. Aspirin was given in the dose of 100mg/kg body weight and nifedipine in the dose of 5mg/kg body weight.⁽⁴⁾ All the drugs were given orally with the help of stomach tube for ten days and the groups were kept separately. The animals were followed on 4th, 7th, 10th, 12th, 14th and 17th day after administration of drugs and the knee joints were examined to observe the inflammatory changes and the measurement of the knee joints were taken and recorded.

The anti – nociceptive group consisted of 40 rats which was also divided into four sub groups, each sub group consisted of 10 rats and they were given a continuous number as group V, VI, VII and VIII. To study the anti -

nociceptive effects of drugs the Hot Plate Method⁽⁵⁾ was used. Before starting the experiment the weight of the rats were taken and recorded. The reaction time of the rats to thermal pain was recorded prior to the administration of drugs. To observe the reaction time of the rats the animals were dropped gently on a hot plate, which was maintained at 50 degree centigrade. The rats reacted to the thermal stimuli by jumping and squeaking. The time taken between the dropping of the rats on the hot plate and jumping was taken as the reaction time. The reaction time for each rat was recorded with a stopwatch to the nearest fifth of a second. The drugs i.e. aspirin, nifedipine and aspirin - nifedipine combination were given to the group VI, VII and VIII respectively. The group V that served as control for these groups was given only normal saline. All the drugs were given subcutaneously. The reaction time for each group was at interval of 30 min, 45min, 60min, 90min, 120min and 180min was recorded and based on the reaction time the efficacy of analgesic property of the drugs were calculated. The dose dependant study in both the experiments could not be performed due to paucity of time.

Results

To observe the anti - inflammatory action of the tested drugs the swelling of the rat knee joints were measured on successive follow up days. The reduction was of the highest percent in nifedipine group (41.0%), and was observed on 12th day of follow up whereas on the same day it was 33.80% for aspirin and 39.82% for aspirin and nifedepine combined was statistically not significant. The second highest reduction (41.30%) was observed in aspirin - nifedipine group on 17th day and for aspirin group the highest reduction (39.01%) was observed on 17th day of follow up (Table - I & Fig. I).

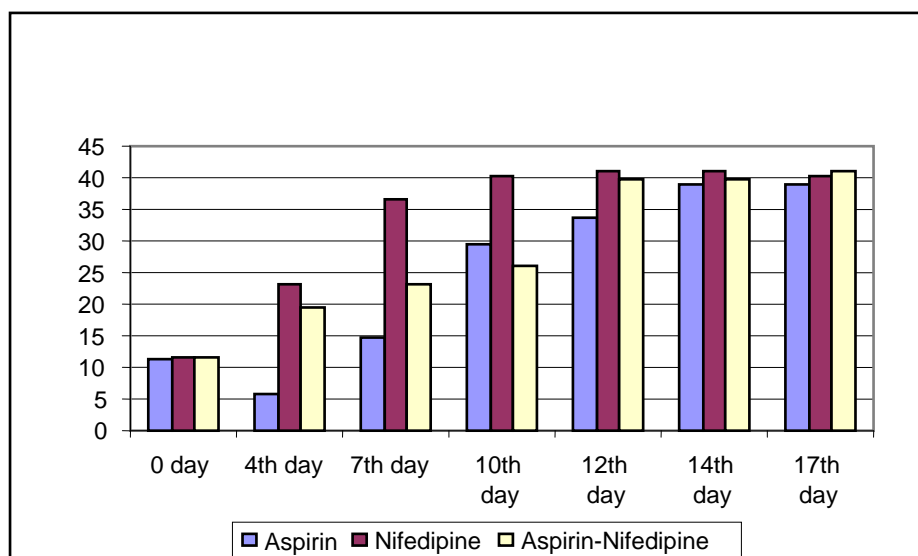
Table 1: Percentage of reduction of inflammatory swelling in experimental group

Follow up days	Aspirin	Nifedipine	Aspirin - Nifedipine
0	11.33	11.58	11.50
4th day	5.91	23.05	19.56
7th day	14.73	36.70	23.21
10th day	29.39	40.24	26.00
12th day	33.80	41.00	39.82
14th day	38.95	41.00	39.82
17th day	39.01	40.24	41.03
Mean \pm SD	24.7 \pm 15.84	33.4 \pm 11.54	28.7 \pm 11.66

Control group (n =6) mean \pm SD = 6.67 \pm 0.12

N.B: The reduction of inflammatory swelling in the different drugs and their combination was not statistically significant (P> 0.05), Table 2.

Fig 1: Percentage reduction of inflammatory swelling following drug treatment

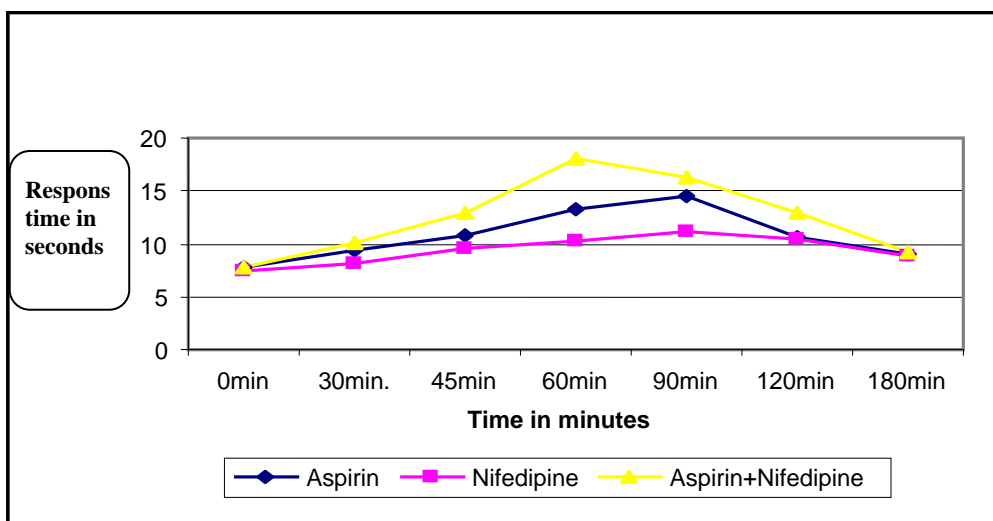


In this study an attempt was also made to observe the anti - nociceptive effects of these tested drugs in the rats by calculating the percentage of inhibition of anti - nociceptive effect. The highest inhibition of nociception (129.30%) was observed with aspirin - nifedipine combination after 60 minutes of follow up, followed by aspirin group (88.96%) at 90 minutes. Nifedipine group (51.02%) at 90 minutes showed the least inhibition. These differences were statistically significant ($p < 0.01$) (Table II & Fig. II).

Table 2: Percentage in Parenthesis depicts increase in reaction time in the rats to painful thermal stimuli after administration of analgesic drugs

Groups	Average reaction time in seconds at interval (minutes)							Remarks
	Before drugs	30	45	60	90	120	180	
V control (N/S)	7.8	7.7 (-1.28)	7.7 (-1.28)	7.3 (-6.40)	7.6 (-2.56)	7.7 (-1.28)	7.6 (-2.56)	Statistically no differences $p > 0.05$
VI Aspirin	7.7	9.35 (21.00)	10.85 (40.90)	13.25 (70.07)	14.55 (88.96)	10.65 (38.31)	8.95 (16.23)	Statistically significant $p < 0.05$
VII Nifedipine	7.35	8.15 (10.88)	9.55 (26.93)	10.30 (40.13)	11.10 (51.20)	10.50 (44.48)	8.85 (20.40)	Statistically not significant $p > 0.05$
VIII Aspirin + Nefidipine	7.85	10.15 (29.29)	12.95 (64.96)	18.00 (129.30)	16.30 (107.64)	13.00 (65.60)	9.15 (16.56)	Statistically significant $p < 0.01$

Fig 2: Anti-nociceptive effect of Aspirin, Nifedipine and Aspirin combined with Nifedipine



Discussion

The anti-inflammatory action of nifedipine started earlier and higher than aspirin and aspirin nifedipine combination group. The trend of quicker and better action of nifedipine was continued in successive follow up days and maximum anti-inflammatory action of nifedipine was observed on 12th day. The anti-inflammatory action of aspirin and aspirin - nifedipine combination groups started from 4th day onwards but the action was slow and maximum anti-inflammatory action was observed on 17th day of follow up.

The anti-inflammatory action of aspirin - nifedipine was better than aspirin alone on 4th and 7th day of follow up. But by 10th day the anti-inflammatory action of aspirin was found to be more than aspirin - nifedipine combination. However, this is not statistically significant ($p > 0.05$). This finding corroborates with the findings of several other authors. In their preliminary study on anti-inflammatory effect of CCBs Aditya et al^(1,2) observed a significant dose dependent inhibition of carrageenin induced hind paw oedema in rats. They also found nifedipine to be more potent in their experiment. In another study by the same authors observed that the combination of nifedipine with aspirin or with another NSAIDS had synergistic effect in inhibition of the experimentally produced rat paw oedema and this inhibition was higher than the algebraic sum of inhibition produced by individual drugs when it is used separately. So it can be concluded that the anti-inflammatory action of nifedipine is more potent and quick in its action.

As regards the nociceptive effect of aspirin compared to nifedipine, it was revealed that the anti-nociceptive

action of aspirin was more than nifedipine from 30 minutes onwards and the maximum effect was observed at 90 minutes in both the groups. Whereas the anti-nociceptive action of aspirin - nifedipine combination group as compared to aspirin alone was more and the maximum effect was observed at 60 minutes. From this findings the anti-nociceptive action of aspirin - nifedipine combination was found to be more effective than aspirin alone. The anti-nociceptive action of CCBs was also observed by several authors^(6, 7). They observed that CCBs act as anti-nociceptive agent either directly or by modulation of analgesic activities of another endogenous substance. The relative nociceptive efficacy of these three tested drugs were worked out by measuring the percent inhibition of anti-nociceptive effect to thermal (pain) stimuli. The highest inhibition of nociception (129.30%) was observed in aspirin - nifedipine combination after 60 minutes of follow up followed by aspirin group (88.96%) at 90 minutes and this was not statistically significant ($P > 0.05$). The nifedipine group (51.02%) at 90 minutes showed least inhibition. These differences were statistically significant ($p < 0.01$). It can be inferred from this finding that anti-nociceptive action of aspirin was probably potentiated by nifedipine.

Conclusion

The present study showed that, nifedipine alone was a better anti-inflammatory drug compared to aspirin alone and aspirin - nifedipine combination. On the other hand as an analgesic nifedipine alone was not found to be as effective as aspirin. But when nifedipine was combined with aspirin it was found to potentiate the anti-nociceptive action of aspirin. Therefore, it is concluded that the CCBs may to be used as an analgesic in

combination with NSAIDS where the required doses of NSAIDS can be reduced and there by minimize the various adverse effects which are so common with NSAIDS group of drugs.

References

1. Aditya G.N et al (1997): Possible mechanism of anti - inflammatory activity of calcium channel blockers. Indian Journal of Pharmacology, 29; 325-326.
2. Aditya G.N et al (1997): Preliminary study on anti - inflammatory effects of calcium channel blockers in albino rats. Indian Journal of Pharmacology, 29; 130-134.
3. Aditya G.N et al (1999): Calcium channel blockers and Non steroidal anti - inflammatory drugs. A possible synergistic anti - inflammatory combination. Indian Journal of Pharmacology, letters to the editor, 31; 36-37.
4. Ghosh M.N. (1984): Fundamentals of Experimental Pharmacology, 2nd edition, pages 144-147.
5. Janssen and Jageneau (1957): Hot plate method. Quoted by Taylor, R.A. (1965) in screening method in Pharmacology. New York Academic Press, New York.
6. Del Pogo et al (1947): Analgesic effects of several calcium channel blockers in Mice. European J. Pharmacology, 137; 155-160.
7. Al - Umayyad, M.S. (1991): Effect of diltiazem, nifedipine & verapamil on the anti - nociceptive action of acetyl salicylic acid. Gen. Pharmacol. 22(1)