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COMPARISON OF EFFICACY OF INDOMETHACIN AND TIZANIDINE IN EXPERIMENTAL MODEL OF ARTHRITIS IN ALBINO WISTAR RATS

Pharma

Ragini Mishra PhD Scholar, Department of Pharmacology, Index Medical College, Malwanchal University, Indore MP, India

Abhay John Associate Professor, Department of Pharmacology, Index Medical College, Malwanchal University, Indore MP, India.

Vikash K. Tiwari* Assistant Professor, Department of Physiology, Autonomous state Medical College, Hardoi, UP, India *Corresponding Author

ABSTRACT

Background: Rheumatoid arthritis is an autoimmune disease primarily affecting small peripheral join. It is characterised by joint inflammation and pain. **Methods:** There were 3 groups with 6 albino wistar rats in each. Each group was injected with CFA in one of hind paw on a day before (day 0) treatment with Indomethacin (3mg/Kg), Tizanidine (1mg/Kg), & Tizanidine (2mg/Kg). Each drug was given PO in their respective group. Joint size was measured on day 0, 3, 7, 14, and 21. Difference in joint size with day 0 was calculated. **Results:** Difference in joint size on different days of measurement was minimum for indomethacin & maximum for tizanidine (1mg/Kg). Difference of joint size for tizanidine (2mg/Kg) was in between two. Data was analysed using one way ANOVA. There was no significant difference between the groups. **Conclusions:** Tizanidine has an anti-inflammatory property in CFA induced rheumatoid arthritis experimental model. This property of tizanidine was more at dose of 2 mg/ Kg as compared to 1 mg/Kg. As tizanidine has gastro-protective effect so it can be a promising treatment along with NSAIDs.

KEYWORDS

Rheumatoid arthritis (RA), Indomethacin, Tizanidine (TZD), and Joint size.

INTRODUCTION

Rheumatoid arthritis (RA) is defined as systemic disorder associated with chronic joint inflammation that most commonly affect peripheral joints. Occurs more often in women 30 to 50 years of age.[1] There is painful inflammation and stiffness of joints. There are several types of arthritis like crystal-induced arthritis, osteoarthritis, ankylosing spondylitis, rheumatoid arthritis, etc.[2] Crystal induced arthritis is caused by the deposition of uric acid crystals in joints. Osteoarthritis is a degenerative disease caused by advancing age. Large weight-bearing joints are mainly involved in osteoarthritis. Ankylosing spondylitis is a disease of the axial skeleton characterized by sacroilitis and progressive stiffening of the spine. Rheumatoid arthritis is a chronic inflammation of the synovial membrane of many peripheral joints.[3]

Treatment of rheumatoid arthritis involves non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying anti-rheumatoid drugs (DMARDs). DMARDs include non-biologic and biologic agents. Non-biologic agents include methotrexate, azathioprine, sulfasalazine, and hydroxychloroquine. Whereas biologic agent includes TNFα inhibitors (etanercept, and infliximab), anakinra, abatacept, etc. As rheumatoid arthritis is a chronic condition so long-term treatment is required, which put the patient at higher risk of side effects of above drugs.[3]

Tizanidine is a α2-selective adrenergic agonist drug. It is useful for the treatment of spasticity associated with cerebral and spinal disorders.[4,5] It also shows some property similar to those of clonidine.[6] Along with its conventional activity Tizanidine show anti-inflammatory activity in various study conducted over last several years. These studies also show that TZD has not only anti-inflammatory but analgesic effect too. Thus it is very reasonable to think of the effectiveness of tizanidine in rheumatoid arthritis.[7,8] So this study was conducted to find out the effect of tizanidine in an experimental model of arthritis (RA) in albino Wistar rats.

MATERIALS AND METHODS

01-STUDY SETTING

This study was conducted in the Department of Pharmacology, Index Medical College, Malwanchal University, Indore, M.P. after getting the approval.

02-DRUGS & CHEMICALS

A-Complete Freuds Adjuvant 0.1ml (CFA: 0.05% w/v Mycobacterium butyricum mineral oil)[9-11]
B-Indomethacin (3mg/kg)[5]
C-Tizanidine/ TZD (1mg/kg, and 2mg/kg)[5]

03-ANIMALS

Male Wistar albino rats weighing 150 – 200 gm and 8 to 10 weeks of age were kept in polypropylene cages with stainless steel grill tops and bedding of clean paddy husk. The animals were housed in 3 groups under normal laboratory conditions with a normal light-dark cycle. The animals were acclimatized to the lab environment for a week before experimentation with free access to water and a standard pellet diet for laboratory animals. Then animals were weight matched and divided into 3 groups with 6 animals in each.

04-IN-VIVO SCREENING OF THE ANTI-ARTHRITIC ACTIVITY OF THE LAMOTRIGINE

Two doses of tizanidine were evaluated for anti-arthritic activity in comparison to the standard drug indomethacin. Doses of TZD evaluated as per table number-01.

The size of the joint was measured a day before starting the experimentation (day-0, baseline joint size) in millimeters using the micrometer screwgauge. Arthritis was induced by using a single dose injection of 0.1 ml of 1% Complete Freund's Adjuvant (CFA) into the plantar surface of one of the hind paws of the rat.9-10, (Newbold; 1963, Vogel; 2002). The day of the administration of CFA was designated as Day 1. All the animals were maintained for 21 days with daily administration of indomethacin and the test drug (tizanidine) in their respective doses. The joint size was measured again on day 3, 7, 14, and 21.

TABLE-01. GROUP WISE DRUG DOSES (mg/Kg)		
SN	**GROUP**	**TREATMENT GIVEN**
1	GROUP I	INDOMETHACIN (3mg/kg)
2	GROUP II	TIZANIDINE (1mg/kg)
3	GROUP III	TIZANIDINE(2mg/kg)

RESULTS

Table-02 and figure-01 show the difference in the size of the joint on different days in comparison to day 0 for indomethacin 3mg/Kg, TZD 1mg/Kg, and TZD 2mg/Kg. The difference was calculated from the mean of the individual groups of animals. Data were represented as mean ± SEM. For Indomethacin, the difference in joint size on Day 3 was 1.47 ± 0.15, Day 7 was 1.80 ± 0.19, Day 14 was 0.88 ± 0.09 and Day 21 was 0.71 ± 0.07. Similarly for TZD (1mg/Kg) difference in joint size on day 3 was 2.03 ± 0.17, day 7 was 1.94 ± 0.15, day 14 was 1.73 ± 0.20, and on day 21 it was 1.42 ± 0.14. For TZD (2mg/Kg) difference in joint size on day 3 was 1.92 ± 0.13, day 7 was 1.90 ± 0.09, day 14 was 1.39 ± 0.11, and on day 21 it was 1.12±0.08 mm.

Table-02. Difference In Size Of Joint In Comparison To Day-0 (mean ± Sem (in Mm)				
DRUG	**Day-3**	**Day-7**	**Day-14**	**Day-21**
Indomethacin-3mg/kg	1.47 ± 0.15	1.80 ± 0.19	0.88 ±. 0.09	0.71 ± 0.07

Tizanidine-1mg/kg	2.03 ± 0.17	1.94 ± 0.15	1.73 ± 0.20	1.42 ± 0.14
Tizanidine-2mg/kg	1.92 ± 0.13	1.90 ± 0.09	1.39 ± 0.11	1.12 ± 0.08

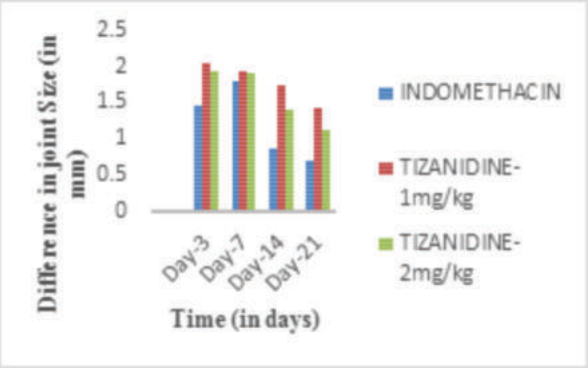

Figure 1, Difference In Size Of Joints In Comparision To Day-0 (mm)

Statistical analysis of the data was performed by one-way ANOVA, the p-value came to be insignificant (p = 0.1876). Thus there is no significant difference in changes in joint size by tizanidine as compared to the standard drug indomethacin.

Difference in size of joints of experimental albino wistar rats getting daily treatment of TZD (1mg/Kg) and TZD (2mg/Kg) were compared with Indomethacin (3mg/Kg). This difference was measured on 3, 7, 14, and 21 day of experiment. The difference in joint size was more for TZD (1mg/Kg), than TZD (2mg/Kg) on each day of measurement as compared to indomethacin..

So we can derive from this study that both doses show anti-inflammatory activity, but the dose of 2 mg/kg of TZD is more effective. Indomethacin was superior on each day of experiment in comparison to both doses of TZD. So we can say that TZD shows higher anti-inflammatory activity at 2 mg/kg, but this activity is lower than indomethacin.

DISCUSSION

Patiño-Camacho SI et al (2017)[8] demonstrated in their study that tizanidine increases the anti-inflammatory and anti-nociceptive effects of naproxen and ketorolac, TZD also increases gastric tolerability so tizanidine could provide therapeutic advantages in the clinical treatment of inflammation with pain.

Patiño-Camacho SI et al (2013)[12] in his experimental study in rats suggested that systemic tizanidine can increase the naproxen-induced anti-inflammatory effect in rats and this effect was not due to any modification in the bioavailability of naproxen. Thus synergistic anti-inflammatory activity was proved by their study.

Jain NK et al (2002)[7] speculated in their study that tizanidine and NSAID combination therapy can be a novel approach to treat pain and inflammation involving conditions with improved gastric tolerability of NSAIDs.

Pei w et al (2018)[13] demonstrated that tizanidine has anti-nociceptive effects on neuropathic pain via inhibiting the production of pro-inflammatory cytokines by suppressing the activation of TLR4/NF-κB p65 signaling pathway.

Talakoub R et al (2016)[14] concluded in their study that oral administration of 4 mg tizanidine before laparoscopic cholecystectomy reduces postoperative pain. Another analgesic like opioid consumption was also reduced. Thus this study shows the analgesic action of TZD.

Analgesic activity of TZD was proved by Kameyama T et al (1985)[15] in their study. They also proved that the analgesic action of TZD was more as compared to morphine. The analgesic action of TZD was unaffected by treatment with naloxone, so this effect of TZD involves a mechanism of action other than morphine.

From the above studies, it can be concluded that TZD has both anti-inflammatory & anti-nociceptive action. As RA is an inflammatory autoimmune disease involving mainly metacarpophalangeal and proximal interphalangeal joints. Affected joints have both swelling and pain. In our study, we found reduction in joint swelling in the experimental model. This reduction in joint size can be due to the inhibition of the formation of pro-inflammatory mediators and cytokines. Thus TZD can be a promising treatment option along with conventional NSAIDs in RA.

CONCLUSION

Tizanidine has an anti-inflammatory property. This property of tizanidine was more at dose of 2 mg/ Kg as compared to 1 mg/Kg. As tizanidine has gastro-protective effect too, so it can be a promising treatment along with NSAIDs.

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