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A Study On Efficacy And Safety Of Nabumetone And Aceclofenac In Osteoarthritis Patients Using Visual Analogue Scale

Dr. P. Jagadeesh[*1], Dr. B. Vasundhara Devi [2], Dr. P. Vijayalakshmi [3]
[*1]*Associate professor, Department of Pharmacology*
[3] *Tutor, Department of Microbiology*
GITAM institute of medical sciences and research,
GITAM University, Visakhapatnam-530045 (A.P), India, Website: www.gitam.edu
[2] *Professor and HOD, SV Medical college, Tirupathi.*
Corresponding author: Dr. P. Jagadeesh

Abstract: ***Background:*** *Osteoarthritis (OA) is the most prevalent musculoskeletal disorder and the most common form among various types of arthritis, affecting worldwide population. The prevalence of this condition increases with increasing age and functional disability due to pain in OA is one of the most common disabilities in the elderly population and accounts for approximately half of all chronic conditions in persons older than 65 years.*
Aim and objectives: *the present study was done 1) To compare the efficacy of nabumetone and aceclofenac in patients with moderate to severe osteoarthritis of the knee. 2) To compare the safety of nabumetone and aceclofenac in patients with moderate to severe osteoarthritis of the knee.* ***Materials and methods:*** *This is a randomized, parallel group, open label, comparative clinical study. Informed consent was taken from 72 patients out of which 4 patients were excluded as they did not meet inclusion criteria. 68 patients were then randomized into 2 treatment groups. 34 patients were given nabumetone1000 mg tablet once a day orally and the other 34 patients were given aceclofenac 100 mg twice a day orally. Patients were instructed not to take any other drugs during the study period and the duration of the treatment is 12 weeks. Evaluation of of efficacy was done based on pain at the knee joint assessed by Visual analogue scale (VAS) at 0 and at 12 weeks and safety assessment was done based on adverse effects caused by the individual drugs during the study period.* ***Results:*** *The overall incidence of adverse events with nabumetone 1000 mg once daily and aceclofenac 100 mg twice daily was 18.75% and 21.875% respectively. P > 0.05, the result is statistically not significant. The incidence of GI side effects was more or less similar for nabumetone 12.5% (reported by 4 patients) when compared with aceclofenac 15.625% (reported by 5 patients). But withdrawal rates because of these GI events was higher with aceclofenac (9.375%) compared to nabumetone (3.125%). P < 0.01, the result is statistically highly significant.*
Conclusion: *The efficacy and safety of nabumetone is similar to that of aceclofenac in patients with moderate to severe osteoarthritis of knee. However, Nabumetone is more gastro friendly NSAID than aceclofenac as the patient withdrawal rates are lesser for nabumetone than for aceclofenac.*

Keywords: *Osteoarthritis, nabumetone, aceclofenac, visual analogue scale*

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I. Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder worldwide with huge economic and social consequences. It is also the most common form among 100 different types of arthritis, affecting 100 million Indians, 21 million Americans and 2 million British people. The prevalence of this condition in the 75 to 90 year old population is about 85% [1]. Functional disability due to pain in OA is one of the most common disabilities in the elderly population and accounts for approximately half of all chronic conditions in persons older than 65 years [2]. OA is projected to be the 4th leading cause of disability by 2020 worldwide, due to steady increase in the obese and aged population [3]. Paracetamol is generally recommended as first line pharmacotherapy in majority of patients with OA. Non-steroidal anti-inflammatory drugs (NSAIDS) are widely used in the treatment of pain and inflammation associated with osteoarthritis and rheumatoid arthritis. However, concern persists over the potential for serious gastrointestinal side-effects associated with NSAID use. NSAIDs should be considered only in those cases with poor response to paracetamol as is the case with moderate to severe OA with severe pain, swelling and restricted mobility of the affected joints. The NSAIDs act by inhibition of COX-2, a key enzyme involved in pain and inflammation associated with OA and effectively

modifies the pain and other symptoms of OA. But conventional NSAIDs also inhibit COX-1, a gastro protective enzyme and are associated with significant gastro intestinal adverse effects ranging from dyspepsia to serious life threatening complications like ulcers, hemorrhages and perforations [4]. The incidence of ulcers induced by conventional NSAIDs in randomized, controlled trials has been reported to be as high as 45% at 6 months. Any patient taking NSAIDs has approximately 2.5 to 5.0 fold increased risk of developing GI complications [5]. Selective COX-2 inhibitors like celecoxib, valdecoxib are gastro friendly NSAIDs but their COX-2 selectivity is a cause of concern for their cardiovascular safety. Since they do not inhibit COX-1 enzyme, which plays a key role in thrombosis and vasoconstriction they do not possess the anti thrombotic property of aspirin. The concept of preferential COX-2 inhibition came into force to overcome the GI and renal side effects associated with COX-1 inhibition by traditional NSAIDs and cardiovascular side effects associated with selective COX-2 inhibitors. Nabumetone is a novel NSAID and is a preferential COX-2 inhibitor. The drug has good clinical efficacy while showing reduced potential to cause GI and cardiovascular side effects. Aceclofenac on the other hand is an inducible COX-2 inhibitor at the site of inflammation and has potent anti-inflammatory action. A clinical study was conducted to compare the efficacy of nabumetone and aceclofenac after treatment for 12 Weeks in patients with moderate to severe osteoarthritis of the knee [5].

II. Materials And Methods

This study was conducted in the department of Pharmacology in collaboration with the department of Orthopedics, Government General Hospital, Kurnool. Subjects included in the study were Osteoarthritis patients aged between 40 to 65 years. Half of the patients were given nabumetone and the other half were given aceclofenac. They were monitored as out patients in the department of Orthopedics, Government General Hospital, Kurnool.

***Study population*:** The patient population of osteoarthritis was recruited by using the following inclusion and exclusion criteria.

Inclusion criteria: Men and women aged 40 to 65 years with moderate to severe OA of one or both knees having symptoms for at least 6 months with grade 3 or 4 radiological findings of OA

Exclusion criteria:

Patients unwilling to give informed consent
Patients with mild OA of one or both knees
Patients with significant renal impairment with creatinine levels > 1.6mg and proteinuria 1+
Patients with hypertension and with H/o hypertensive encephalopathy
Patients with diabetes mellitus (Type – I and Type – II)
Patients with H/o cerebrovascular accidents and MI
Patients with abnormal liver function tests
Patients with bronchial asthma
Patients with neoplasia or acute meniscus injury or arthroscopy in the knee joint with in the last 6 months
Patients with peptic ulcer and history of active GI bleeding
Patients with H/o known drug allergy to NSAIDs
Obese patients with body weight >100 kgs.
Patients who required systemic steroids, warfarin, lithium, low dose aspirin, anti ulcer drugs or intra articular steroids within last 2 months.

***Sample size and administration of drugs*:** Informed consent was taken from 72 patients. 4 patients were excluded as they did not meet inclusion criteria. 68 patients were then randomized into 2 treatment groups. 34 patients were given nabumetone and the other 34 patients were given aceclofenac. 2 patients in each group did not attend for follow up. Three patients from nabumetone group and 5 patients from aceclofenac group discontinued from the trial because of adverse effects. Thus the final sample size is 29 in nabumetone and 27 in aceclofenac group. The patients in nabumetone group were started with nabumetone 1000 mg tablet once a day orally. The patients in aceclofenac group were started with aceclofenac 100 mg twice a day orally. Patients were instructed not to take any other drugs during the study period and the duration of the treatment is 12 weeks.

***Trial design and clinical assessment of patients*:** This is a randomized, parallel group, open label, comparative controlled trial. Four visits were scheduled. At the first visit patients were selected. At the second visit patients were allotted drugs. Third visit was scheduled at 6 weeks and the fourth visit at 12 weeks. During the first visit informed consent was taken from all participants (72 patients). Symptoms of OA of knee like pain, swelling and restricted mobility of the knee joint were questioned. Demographic data, physical, general and systemic examination was done. X-ray of the affected knee joints is taken. In the second visit, (0 weeks) four patients were excluded as they did not meet inclusion criteria. 68 patients were then randomized into 2 treatment groups. 34 patients were given nabumetone 1000 mg once a day and the other 34 patients were given aceclofenac 100 mg twice a day. Physical, general and systemic examination was done and the pain at the knee joint is measured by Visual analogue scale (VAS). Patients were given a telephone number to which they have to dial if they

experience any adverse event. Patients were advised to return back after 6 weeks. In the third week (6 weeks) patients were enquired for any adverse effects like GI distress, ankle edema, vertigo, rash etc that warranted the end of the trial. 2 patients from both the groups did not attend for follow up. 3 patients from nabumetone group and 5 patients from aceclofenac group discontinued from the trial because of adverse effects. Drug compliance of the patients was assessed by counting the number of remaining tablets. In the final fourth visit (12 Weeks), 29 patients from nabumetone group and 27 patients from aceclofenac group completed the trial. Drug compliance of the patients was assessed by counting the number of remaining tablets. Pain at the knee joint was assessed by Visual analogue scale (VAS). Visual analogue scale is one of the most frequently used measurement scale for pain. It is a valid and reliable measure of chronic pain intensity [6]. A patient is asked to indicate his/her perceived pain intensity (most commonly) along a 100 mm horizontal line, and this rating is then measured from the left edge. VAS value 0 mm suggests no pain while 100 mm suggests worst possible pain.

***Evaluation of adverse effects and safety*:** All patients were questioned about adverse effects at each visit using questionnaire. Both serious and non-serious mild adverse effects were recorded and data reviewed. The participants may discontinue the study drug at any time during the trial at their own discretion in case of any serious adverse effects.

***Statistical methods*:** Degree of clinical improvement and incidence of adverse effects were studied in both groups taking nabumetone and aceclofenac. Individual assessment of pain at the knee joint was done by VAS and the difference in treatment outcome was recorded in each group. The significance of difference between treatment outcomes was analyzed by student's t-test. Statistical analysis was done with the help of statistical unit of the department of social and preventive medicine. All statistical tests are two tailed and p value rounded to two decimal places. $p < 0.05$ was considered statistically significant.

III. Results

Efficacy: The results of efficacy and safety were analyzed and compared after 12 weeks of drug treatment with both nabumetone and aceclofenac. Baseline characteristics were similar and identical between both nabumetone and aceclofenac groups. 68 patients, out of 72 patients were randomized into nabumetone and aceclofenac groups, with 34 patients in each group. 2 patients in each group didn't attend for follow up. 8 patients discontinued the trial because of adverse effects. As a result 56 patients completed the trial and were subjected to final analysis. Evaluation of efficacy is done by the assessment of pain at the knee joint using VAS. The mean visual analogue scale in Osteoarthritis patients before taking nabumetone is 5.89 ± 0.12 (Figure-1). The mean visual analogue scale after taking nabumetone was 2.34 ± 0.11. The mean visual analogue scale in osteoarthritis patients before taking aceclofenac is 5.74 ± 0.11 (Figure-1). The mean visual analogue scale after taking aceclofenac was 2.37 ± 0.13. $p > 0.05$, the result is statistically not significant. The mean reduction in VAS is 3.55 with nabumetone while with aceclofenac it is 3.37 (Figure-2). Although the mean reduction in VAS is slightly more with nabumetone then with aceclofenac the result is statistically not significant.

Figure 1: Comparison of Visual Analogue Scale in Osteoarthrit patients taking Nabumetone and Aceclofenac

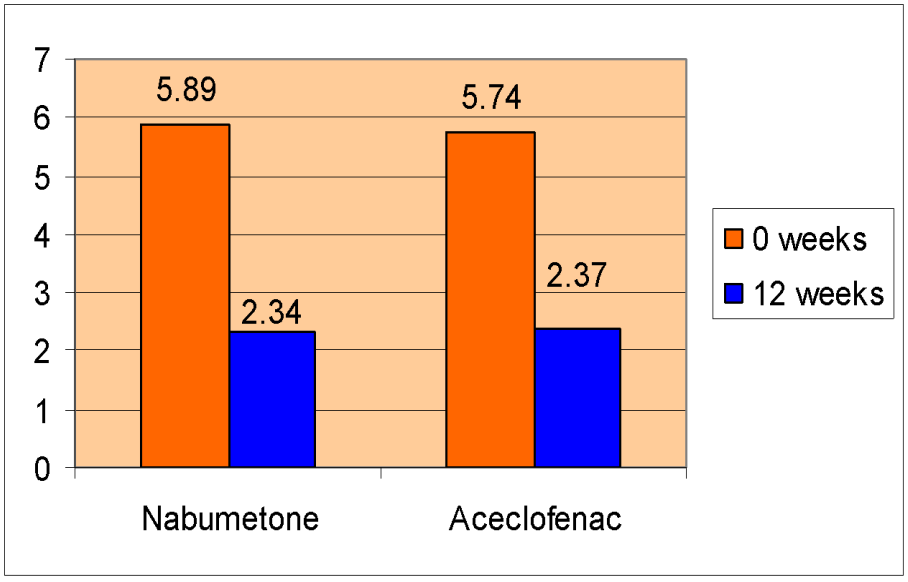
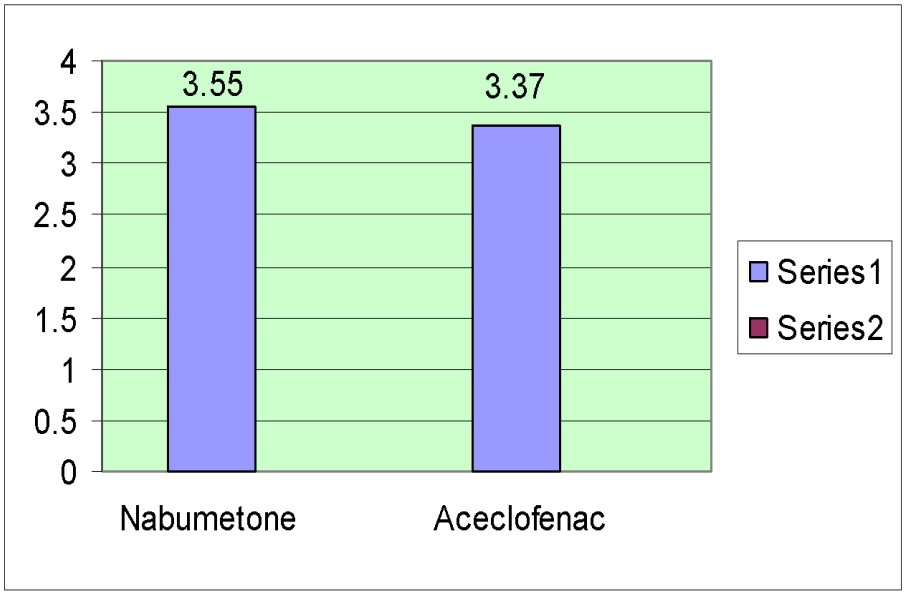


Figure 2: Mean reduction in Visual Analogue Scale in Osteoarthritis patients taking Nabumetone and Aceclofenac

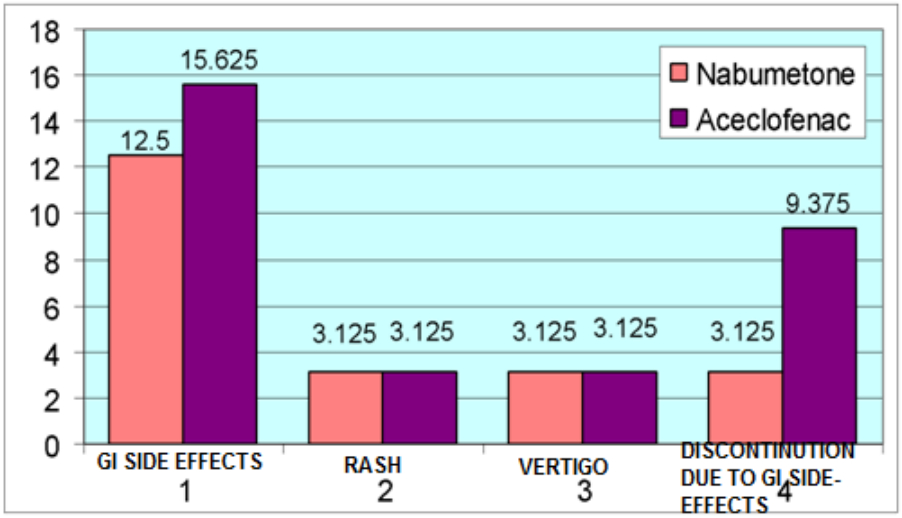


***Safety*:** Table-1 shows the adverse effects of both the analgesic drugs and discontinuity of treatment. In the nabumetone group 3 patients discontinued the trial due to development of intolerable adverse effects. 4 patients complained of GI side effects like dyspepsia, abdominal pain at the end of 4 weeks. Among them one patient discontinued from therapy due to development of gastritis which subsided after two weeks of stopping the drug. One patient discontinued therapy due to development of rash on forearms, neck after one week of drug in take, which completely subsided one week after stopping the drug. One patient discontinued the trial after a period of six weeks due to development of vertigo which completely subsided after one week of stopping the drug. In the aceclofenac group 5 patients discontinued the trial due to development of intolerable adverse effects. 5 patients reported GI side effects after a period of 3 weeks of drug in take. Among them 3 patients discontinued therapy after a period of 4 weeks due to development of gastritis which subsided two weeks after stopping the drug. One patient had to stop further drug therapy due to development of rash on upper chest associated with itching after a period of one week which resolved completely after one week of stopping the drug. One patient complained of vertigo after a period of 4 weeks and discontinued the trial after which the vertigo subsided completely in one week. There were no other adverse events reported in the study. Also there was no change in bio-chemical, hematological and hepatological parameters that were evaluated in patients with adverse effects. The overall incidence of adverse events with nabumetone 1000 mg once daily and aceclofenac 100 mg twice daily was 18.75% and 21.875% respectively (Figure-3). $P > 0.05$, the result is statistically not significant. Adverse events were most commonly associated with GI system. The incidence of GI side effects was more or less similar for nabumetone and aceclofenac (reported by 4 (12.5%) and 5 (15.625%) patients respectively). But withdrawal rates because of these GI events was higher with aceclofenac (9.375%) compared to nabumetone (3.125%). $P < 0.01$, the result is statistically highly significant. No significant differences were observed in incidences of non-GI adverse effects. Adverse events with both the drugs were more common in older patients (53 to 65 years) and in females (events reported by 8 (12.5%) women and 5 (7.81%) men).

Table 1: Group-wise distribution of cases with adverse event for discontinuation of therapy

Adverse Event			
Group	GI-side effects	Rash	Vertigo
Nabumetone	1	1	1
Aceclofenac	3	1	1

Figure 4: Percentage of patients with adverse events



IV. Discussion

The present study compared the degree of efficacy and safety of nabumetone and aceclofenac in patients with moderate to severe OA. After 12 weeks of study period efficacy of both the drugs was compared by assessing the degree of analgesia using VAS. The mean reduction in VAS is 3.55 with nabumetone while with aceclofenac it is 3.37. Although the mean reduction in VAS is slightly more with nabumetone than with aceclofenac the result is statistically not significant. Safety of both the drugs was compared after 12 weeks of study period by observing the incidence of adverse events. Out of 32 patients in the nabumetone group 4 patients complained of GI side effects and one among them has withdrawn from study treatment due to development of gastritis. One patient has withdrawn from the trial due to development of rash and another patient discontinued due to development of vertigo. Out of 32 patients in aceclofenac group 5 patients complained of GI side effects and among them 3 patients discontinued during the trial due to development of gastritis. One patient has withdrawn from the trial due to development of rash and another patient due to vertigo respectively. Overall the trial was very tolerated in both the groups. The overall incidence of adverse events with nabumetone did not differ significantly from that with aceclofenac (18.75% Vs 21.87%) respectively. The incidence of GI adverse events was more or less similar for nabumetone (12.5%) and aceclofenac (15.625%) as reported by 4 and 5 patients respectively. However withdrawal rates because of GI adverse events was higher with aceclofenac 9.375% (3 patients) than with nabumetone 3.125% (1 patient). No significant differences were observed in incidences of non-GI adverse effects with both the drugs. Previous studies comparing the efficacy of nabumetone and diclofenac have shown no significant differences between these two treatments [7], [8], [9], [10]. Although all NSAIDs can cause GI complications, differences in the relative risk for developing GI complications between NSAIDs have been observed [11], [12].

V. Conclusion

Comparative study of efficacy and safety of nabumetone and aceclofenac in patients with moderate to severe OA was done. There were two study groups one consisting of 34 patients who were given nabumetone 1000 mg once daily and the other group consisting of 34 patients who were given aceclofenac 100 mg twice daily. Efficacy of both the drugs was compared by assessing the degree of analgesia using visual analogue scale and it is found that the efficacy of nabumetone 1000 mg once a day was similar to that of aceclofenac 100 mg twice daily. Safety of both the drugs was compared by observing the incidence of adverse events and it is found that the overall incidence of adverse events with nabumetone did not differ significantly from that with aceclofenac. However the withdrawal rates of patients because of GI adverse effects was more for aceclofenac than for nabumetone. The present study concludes that the efficacy and safety of nabumetone is similar to that of aceclofenac in patients with moderate to severe osteoarthritis of knee. However, Nabumetone is more gastro friendly NSAID than aceclofenac as the patient withdrawal rates are lesser for nabumetone than for aceclofenac.

The authors declared “No conflict of interest”

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