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A RANDOMIZED CLINICAL STUDY TO DETERMINE THE EFFICACY OF NABUMETONE AND ACECLOFENAC IN OSTEOARTHRITIS PATIENTS USING IGADS

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ABSTRACT

Background: Osteoarthritis (OA) is a common degenerative form of joint disease predominantly affecting the weight bearing joints of the body. It is also the most common among all other types of arthritis and its treatment poses a huge financial burden to the society. It is caused by the breakdown and eventual loss of cartilage of one or more joints. OA frequently leads to chronic pain and disability and the chances of its occurrence increases with increasing age.

Aim and objectives: the present study was done 1) To study the efficacy of nabumetone and aceclofenac in patients with moderate to severe osteoarthritis of the knee. 2) To compare the efficacy of nabumetone and aceclofenac in patients with moderate to severe osteoarthritis of the knee. Materials and methods: A total of 68 patients were randomized into 2 treatment groups of which 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. The duration of treatment is 12 weeks during which the patients were instructed not to take any other drugs. Evaluation of of efficacy was done based on the assessment of clinical improvement in terms of pain intensity, joint swelling and tenderness, functional capacity and ability to flex the knee by Investigator Global Assessment of Disease Status (IGADS) scale at 12 weeks.

Results: Nabumetone as well as aceclofenac markedly, improved the clinical condition in the study population with 82.75% of patients showing fair to very well improvement in clinical outcome in the case of nabumetone. In the case of aceclofenac the improvement was 81.47%. $p > 0.05$, the result is statistically not significant.

Conclusion: The efficacy of nabumetone is similar to that of aceclofenac in patients with moderate to severe osteoarthritis of knee.

KEYWORDS : Osteoarthritis, Pain, nabumetone, aceclofenac, Investigator Global Assessment of Disease Status scale.

INTRODUCTION:

Osteoarthritis (OA) is a common degenerative form of joint disease predominantly affecting the weight bearing joints of the body. It is caused by the breakdown and eventual loss of cartilage of one or more joints. OA frequently leads to chronic pain and disability and its treatment poses a huge financial burden to the society. Pain is the most common symptom that brings the patient to the doctor and tends to be more severe in the evenings, on weekends and early in the work week [1]. Pain in the affected joint is typically worse after use and is relieved by taking rest. Presence of rest pain is seen in advanced cases of OA and reflects inflammation. Among the various types of arthritis, osteoarthritis usually affects 100 million Indians, 21 million Americans and 2 million British people. The occurrence of this condition in the 75 to 90 year old population is about 85% [2]. Osteoarthritis 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) should be considered in those patients who show poor response to paracetamol. Orally administered NSAIDs play an important role in the symptomatic management of OA. However, concern persists over the potential for serious gastrointestinal side-effects associated with NSAID use. Generally they produce their anti-inflammatory and analgesic effects by inhibiting cyclooxegenase (COX) and thus preventing the production of prostaglandins from arachidonic acid. 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]. Patient education has a significant impact on pain management in OA. Studies suggest that patient education is around 20% as effective as NSAIDs and can have a synergistic effect with other treatments [5]. Self management strategies and patient education can empower patients to take control of their arthritis. The patient education techniques include individualized education packs, regular telephone calls, group education, patient coping skills and spouse assisted coping skills training [6]. Any patient taking NSAIDs has approximately 2.5 to 5.0 fold increased risk of developing GI complications [7]. 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. NICE guidance recommends that COX-2 selective inhibitors should be considered only in patients who may be at 'high risk' of developing serious gastro-intestinal (GI) adverse events [8]. In the year 2005, European Medicines Agency advised clinicians that Cox-2 selective inhibitors should only be prescribed to people with arthritis at 'the lowest effective dose for the shortest possible duration. 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 naphthylalkanone compound designated chemically as 4-(6-methoxy-2-naphthalenyl)-2-butanone. Nabumetone is a novel NSAID that exhibits anti-inflammatory, analgesic and antipyretic properties. It is a preferential COX-2 inhibitor, preferentially inhibits COX-2 over COX-1 enzyme [9]. The drug has good clinical efficacy while showing reduced potential to cause GI and cardiovascular side effects. Aceclofenac is a non-steroidal anti-inflammatory drug indicated for the symptomatic treatment of pain and inflammation in various musculo-skeletal conditions including osteoarthritis. Chemically aceclofenac is a phenyl acetic acid derivative (2-(2,6– dichlorophenyl) amino phenyl acetoxyacetic acid), related to diclofenac. Aceclofenac is an inflammatory site specific NSAID and has been shown to have potent anti inflammatory, analgesic and antipyretic properties. Aceclofenac inhibits the inducible form of COX-2 enzyme which is synthesized at the site of inflammation by various inflammatory mediators. A clinical randomized controlled 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 [7].

MATERIALS AND METHODS:

Initially seventy two out patients (OP) of either sex aged 40 to 65 years with osteoarthritis of knee joint were randomly allocated into two groups based on the type of drug given to them. Half of the patients were given nabumetone and the other half was given aceclofenac. However the individuals who do not obey the following conditions were excluded from the study. The study was performed in the department of Pharmacology in collaboration with the department of Orthopedics, Government General Hospital, Kurnool. 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:

Informed consent was taken from 72 patients. 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 and the other 34 patients were given aceclofenac. 2 patients in each group 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. Thus the final sample size is 29 in nabumetone and 27 in aceclofenac group.

Administration of drugs:

The patients with 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 is12 weeks.

Trial Design:

This is a randomized, parallel group, open label, comparative clinical study.

Clinical assessment of patients:

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 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. The degree of clinical improvement at 12 weeks was assessed in terms of pain intensity, joint swelling and tenderness, functional capacity and ability to flex the knee by an established Investigator Global Assessment of Disease Status (IGADS) (0 – 4 point) scale, where 0 = very well, 1=moderately well, 2=fair, 3= poor, 4 = very poor. X-ray of the affected knee joints was taken. Patients were enquired for any adverse effects.

Statistical methods:

The assessment of clinical improvement by IGADS scale was analyzed. 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.

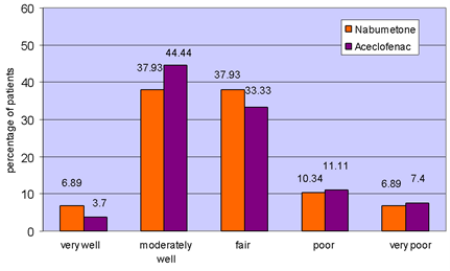
RESULTS:

The results of efficacy 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. Sixty-eight 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. Eight patients discontinued the trial because of adverse effects. As a result 56 patients completed the trial and were subjected to final analysis. The assessment of clinical improvement at the end of 12 weeks was done by IGADS scale [10]. Assessment of pain intensity, joint swelling and tenderness, functional capacity and ability to flex the knee were made by IGADS (0 – 4) point scale in which 0 = very well, 1=moderately well, 2=fair, 3= poor, 4 = very poor (Table-1) (Figure-1). Lower scores in IGADS scale indicate fewer symptoms. Nabumetone as well as aceclofenac markedly, improved the clinical condition in the study population with 82.75% of patients showing fair to very well improvement in clinical outcome in the case of nabumetone. In the case of aceclofenac the improvement was 81.47%. $p > 0.05$, the result is statistically not significant although the clinical outcome was slightly better with nabumetone than with aceclofenac.

Table 1: Distribution of Cases (%) with Clinical Outcome as per Investigator Global Assessment 0 – 4 Point Scale

Investigator Global Assessment 0 – 4 Point Scale					
Group	'0'	'1'	'2'	'3'	'4'
Nabumetone (n=29)	2 (6.89%)	11(37.93%)	11(37.93%)	3(10.34%)	2 (6.89%)
Aceclofenac (n=27)	1 (3.7%)	12(44.44%)	9 (33.33%)	3 (11.11%)	2 (7.4%)

Figure 1: Global assessment of efficacy using IGADS scale



DISCUSSION:

Until recently the new COX-2 selective inhibitors have been increasingly used. They have equal efficacy to standard NSAIDs. However the cardiovascular safety of these drugs was found to be controversial. Nabumetone and Aceclofenac has been evaluated in international studies and is indicated for the relief of pain and inflammation associated with rheumatoid arthritis, osteoarthritis or Ankylosing spondylitis. The present study compared the degree of efficacy 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 clinical improvement in terms of Assessment of pain intensity, joint swelling and tenderness, functional capacity and ability to flex the knee using IGADS scale. Nabumetone as well as aceclofenac markedly improved the clinical condition in study population with 82.75% of patients showing fair to very well response on IGADS scale in the case of nabumetone. In the case of aceclofenac the response was 81.47%. The result is statistically not significant although the clinical outcome was slightly better with nabumetone than with aceclofenac. Paul et al. (2009) used the IGADS scale to study the efficacy of placebo, aceclofenac and nabumetone on osteoarthritis. They found that among the 423 subjects, 108 (76.6%) participants could take the full course of treatment with aceclofenac, 118 (83.7%) of the nabumetone group completed the study. Drop outs were highest in the placebo group (33.9%) followed by the aceclofenac group (12.1%) and nabumetone group (8.5%). Discontinuation due to G.I. intolerance was least in the placebo group (2.1%) followed by the

nabumetone group (5%) and aceclofenac group (7.8%). They concluded that preferential inhibition of cyclo-oxygenase 2 by nabumetone was postulated to afford better clinical efficacy and gastrointestinal tolerability in osteoarthritis as compared to aceclofenac[11].

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 IGADS 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.

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