ORIGINAL ARTICLE

Efficacy and Safety of Etoricoxib , A Cox2 Specific Inhibitor in Patients with Osteoarthritis of Knee Joint In Comparison With Aceclofenac

Farid H Malik*, Brij Mohan Gupta, Nusrat Kreem Bhat, Seema Gupta , Rashmi Sharma

Abstract

Osteoarthritis is the most common degenerative disorder of the articular cartilage associated with hypertrophic bone changes, presenting with pain and stiffness of the affected joints, feeling of instabilities, deformities and severe loss of function of the involved joint affecting activities of daily livings as well as economic burden, most common involved being knee join. The present study evaluates the efficacy and safety of aceclofenac a non selective cox inhibitor with a selective cox2 inhibitor etoricoxib in bilateral osteoarthritis of knee joints . Both aceclofenac and etoricoxib showed statistically significant results from the base line to 6 wks of therapy within the group but the results were statistically insignificant on comparison between two groups. The adverse effects were mild in both the groups and they were not statistically significant.

Key Words

Non steroidal anti-inflammatory drugs , Osteoarthritis, Etorocoxib , WOMAC, Aceclofenac

Introduction

Osteoarthritis is the most prevalent chronic joint disease in the elderly age group and is a leading cause of disability and economic strain .It presents a challenge to the treating physician. The incidence of osteoarthritis is rising because of the ageing population and the epidemic of obesity. Osteoarthritis mainly involves weight bearing joints leading to erosions, loss of joint space, thinning of cartilage, cartilage fibrillation and new bone formation on the joint surface. Prevalence of osteoarthritis increases with age, the disease effects 10% of males and 18 % of females over the age of 45 years and it effects 35 % of adults over 65 years of age or older. (1)The overall prevalence of osteoarthritis is 24.9% in India.(2) The studies estimates that 80 % of patients having osteoarthritis show radiographic changes but symptoms are seen only in 60% of the patients(3) .The clinical manifestation of osteoarthritis are jointpain, swelling, stiffness and loss of motion.Therefore, attention is being focussed on the aggressive prevention and treatment of pain to reduce complications and progression to chronic pain states. The non pharmacological therapies includes various types of exercises like isometric, dynamics , stretching , joint loading ,aerobic and underwater exercises (4).The physiotherapy forms include therapeutic heat, hydrotherapy,spa treatment, electrotherapy and acupuncture etc. The pharmacological treatment of osteoarthritis is symptomatic and the major goal of treatment is to decrease the pain, stiffness, loss of function of affected joint to prevent further damage to the joint and to improve patients quality of life with the analgesics. Drugs for the treatment of osteoarthritis are disease modifying osteoarthritis drugs (DMOADs) and symptom modifying osteoarthritis drugs (SMOADs).(5,6) DMOADs are also known as chondroprotective drugs and include glucosamine, chondritin sulphate and hyaluronic acid. These cells stimulate cartilage cells to produce glycosaminoglycans with proteoglycans which are building blocks of cartilage and they stop the progression of osteoarthritis.(7)

In SMOADs the mainstay of treatment for mild osteoarthritis is acetaminophen. It is inexpensive, safe and effective with fewer gastrointestinal side effects(8).It is given in the dose of 650 mg -1000mg four times a day to relieve mildosteoarthritis. NSAIDS are recommended inpatients with moderate to severe osteoarthritis. This class is superior to acatamiophen but carries the risk of gastrointestinal adverse effects . Conventional NSAIDs are non-specificinhibitors of both isoforms of the enzyme

From the Dept. of *Orthopedics and Pharmacology, Govt. Medical College Hospital, Jammu (J&K), India
Correspondence to : Dr. Nusrat Kareem Bhat, Lecturer, Department of Pharmacology, GMC Jammu (J&K), India

cyclo-oxygenase (COX-1 and COX-2), which catalyze two key steps in the biosynthesis of prostaglandins from arachidonic acid. All conventional NSAIDs produce mechanism-based gastrointestinal (GI) toxicity and platelet inhibition via COX-1inhibition. (9) .Etoricoxib is a NSAID and a selective COX2inhibitor. It is chemically designated as 5-chloro 6-methyl-3(p-(methyl Sulfonyl)phenyl)2-3 bipyridine. Its empirical formula is C(18)H(15)CIN(2)O(2)S. Its molecular weight is 358.8 It is aneffective analgesic, associated with a reduced risk of bleeding due to platelet dysfunctiongastrointestinal bleeds and ulcers but are costly and offer an increase cardiovascular risk.(10,11)

Aceclofenac a phenyl acetic derivative(2-(2,6-dichlorophenyl)amino derivative),is a nonselective inhibitor of Cox enzyme Indicated for treatment of pain and inflammation (12). It's molecular formula is 3C16H13C12NO4 and molecular weight is 354.2 Daltons. It is a white crystalline powder with 99.2 to 101% purity and melting point is 149-153°C. The concentration in synovial fluid is about 60% of the plasma concentration. It is metabolized by CYP2C9 and main metabolitesare 4 hydroxyaceclofenac, diclofenac and 4hydroxy diclofenac. Aceclofenac inhibits increase of inflammatory tissue in the synovial layer.Itinhibits IL-1(interleukin) and Matrix metallo protease(MMP)It ensures proteoglycan production. It blocks suppression of Gag gene and stimulates growth factor mediated synthesis of collegan. (13) Adverse effects are mild which include epigastric pain, nausea, headache, dizziness and rashes. Doasge is 100mg tablet twice daily. It can be taken before or after food.

Material and Method

This randomized prospective parallel study was conducted on 60 patients in the department of pharmacology in collaborationwith the department of orthopaedics in a tertiary care teaching hospital. The study compared the efficacy& safety of etoricoxib 90mg BD and aceclofenac 100 mg BD for 6 weeks in patients of osteoarthritis of knee joint. Eligible patients were enrolled into the study and discontinued regular pain medication at least 2 days before the baseline assessment. The use of aspirin and other analgesics were discontinued at least 4 days before the baseline arthritis.

Patients with a diagnosis of bilateral symptomatic osteoarthritis of the knee joint were included in the study. Diagnosis of osteoarthritis was based on American college of rheumatology (ACR). The study was conducted in outdoor patients and the Patients with arthritis other than the osteoarthritis, chronic pain syndrome, active gastrointestinal disease, significant bleeding disorders, renal disease and cardiovascular disease were excluded from the study. The pregnant and lactating females and patients having hypersensitivity reaction to cox1 and 2 inhibitors and other drugs were also excluded from the study. Patients with active GI disease, GI tract ulceration within 30 days of study medication, or significantbleeding disorder were also excluded .Efficacy assessments were made at out patientvisits at 0, 2 &6 wks. Patient's and physician's Global Assessment of Arthritis were measured on a 5-point categorical scale;1=very good, 2=good, 3=fair, 4=poor and 5=very poor. Patient's Assessment of Arthritis for Pain-VAS was measured on a scale of 0-100 mm,

Table.1. Efficacy of an Individual Drug and Comparative Efficacy of Etoricoxib and Aceclofenac in Patients of Osteoarthritis of Knee Joint.

	Parameters	Baseline	2wks	6wks
Physician Global Assessment Of Osteoarthritis	**Etoricoxib(30)**	4.1+_0.07	2.1+_0.15**	1.23+_0.O7**
	Aceclofenac(30)	4.1+-0.01	2.03+_0.12**	1.0+_0.05**
Womac OA Index	**(Etoricoxib)**	10.66+_0.33	4.83+_0.37**	2.06+_0.36**
	Mean Pain Index (Aceclofenac)	10.73+_0.32	4.73+_0.37**	2.05+_0.32**
		4.46+_0.15	3.0+_1.51**	1.23+_0.19**
	(Etoricoxib Mean Stiffness Index	4.56+_0.22	2.61+_0.14**	1.73+_0.22**
	(Etoricoxib Mean Physical Function Index (Aceclofenac)	23.6+_1.38	12.93+_0.47**	4.06+_0.48**
		23.2+_1.06	12.56 +_0.41**	4.06+_0.44**

***p value<0.001 in the same group as compared to baseline: P value>0.05 on comparison between two groups.*

Fig.1 Effect of Etoricoxib and Aceclofenac on the patients Global Assessment of Arthritis

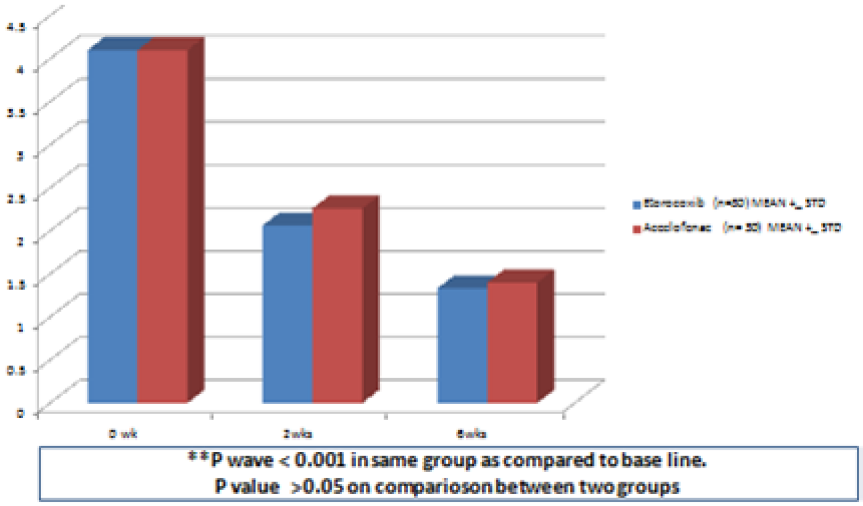


Fig.2 Effect of Etoricoxib and Aceclofenac on the VAS

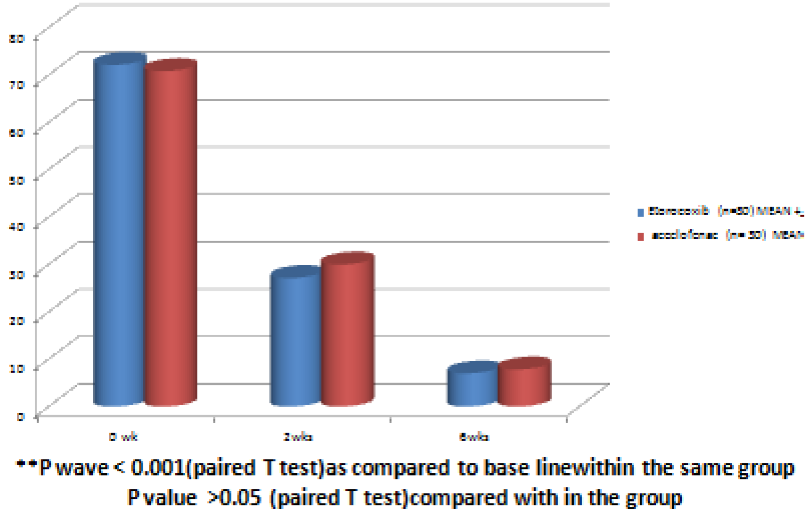
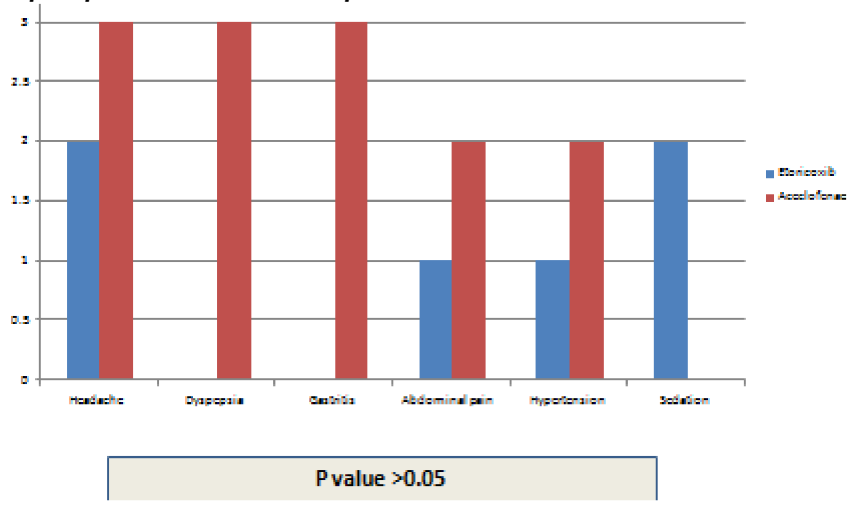


Fig.3 Adverse Drug Effect profile of Etoricoxib and Aceclofenac on the VAS



where0=no pain and 100=most severe pain). and the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis (OA) Index.WOMAC OA index, is a patient-administered questionnaire consisting of 24 questions, five regarding pain, two regardingstiffness and 17 regarding physical function .

The clinical safety was monitored by the incidence of treatment-emergent adverse events, physical examinationincluding vital signs, recording of blood pressure and changes in clinical laboratoryvariables. Adverse events were monitored at baseline andthroughout the study. Upper gastrointestinal endoscopy was done in patients with gastrointestinal related symptoms. Adverse events that occurred with study medication dose and serious adverse events were included in the safety analysis.

Effect of individual drug on patients and physician global assessment of arthritis, VAS and WOMAC OA index were analysed using paired T test and comparative efficacy between two drugs was done by unpaired t test. Safety profile was assessed and compared using bar graph.The disposition of patients is summarized in table 1. Out of 85 total of 60 patients were randomized to receive study medication. Patients demographics, baseline arthritis assessments, and other baseline characteristics were comparable between all the treatment groups.

Results

Among sixty patients satisfying the incusion criteria , 30 patients received etoricoxib 90 mg bd and 30 received aceclofenac therapy100 mg bd. The mean age of the patients taking etorocoxib was 56.93+-6.41 while that patients in the aceclofenac was 57.46+-5.61.out of 60, 68.33% were females and 31.66% were males.

Patients of both the groups showed greater improvement in their osteoarthritis symptoms. There was significant reduction of intensity of pain on patients and physician global assessment of osteoarthritis scale in both the groups. Both these effects were statistically signicant with p value <0.001 and no statistically difference was found among two drugs after 2weeks and 6 weeks of therapy with p value>0.05(*Fig1,Table 1*). The intensity of pain reduction was also excellent on Visual analogue scale. In both the groups the effects were statically significant with p value <0.001. There was no significant difference between two drugs after 2 weeks and 6 weeks of therapy on comparison with pvalue >0.05>(*Fig2*). There WOMAC SCALE from baseline to 2 wks than to 4 wks and 6 wks. There was great reduction in pain, stiffness and physical function index within both the group with p value <0.001 on WOMAC OA index but but there was no statistical significant difference between two groups after 2weeks and 6 weeks of therapy with p value >0.05.(Table 3).Both etoricoxib (90 mgbd and aceclofenac 100mg bd) were comparable (P>0.05) for all OA assessments throughout the study period .

Similarly both the groups experienced great reduction in pain from base line to 6 wks which was statistically significant in both the group sp value <0.001 but on comparison the effects in both the groups were statistically not significant p value >0.05 (*Fig 1&2*) The total number of side effects reported were 19 among which 13 were in the aceclofenac group and 6 were in the etorocoxib group . In the etoricoxib group 2 patients reported headache,2 reported sedation, 1 patient had abdominal pain and 1 patient had hypertension wheras in aceclofenac group 3 patients reported headache, 3 reported gastritis , 3 dyspeppsia, 2 hypertension ,2 sedation. All the adverse effects were statistically non significant (pvalue >0.05).(*Fig.3*)

Discussion

Clinical studies have shown that etoricoxib is more effective than placebo, and of similar efficacy to traditional NSAIDs patients with hip, knee, hand, or spine OA, showed sustained and comparable improvements in Patient's Global Assessment of Disease Status (PGADS) with etoricoxib 90 mg QD or diclofenac 50 mg TID at 12 months (14). Two randomized, double-blind, 12-week studies in a total of 997 patients with hip or knee OA showed that etoricoxib 60 mg QD and naproxen 500 mg TID were of comparable efficacy, and superior to placebo, as measured by WOMAC pain and physical function subscales and PGADS (15,16). A recent randomized trial in 528 patients with hip or knee OA demonstrated that the efficacy of etoricoxib 30 mg QD was comparable with that of ibuprofen 800 mg TID over 12 weeks on the WOMAC pain and physical functioning scales ($p < 0.001$ versus placebo for all comparisons)(17). A multicentre, double-blind, randomised, parallel group study was undertaken to investigate the efficacy and safety of aceclofenac (123 patients, 100 mg twice daily) in comparison to piroxicam (117 patients, 20 mg once daily and placebo once daily) in patients with osteoarthritis of the knee this study confirms the therapeutic efficacy of aceclofenac and suggests that it is a well-tolerated alternative NSAID to piroxicam in the treatment of osteoarthritis (18). Similarly A multicentre randomised, double-blind, parallel group, general practice study was undertaken to investigate the efficacy and safety of aceclofenac (200 patients, 100 mg twice daily and placebo once daily) in comparison with diclofenac (197 patients, 50mg three times daily) in patients with osteoarthritis of the knee. (19). This study supports a therapeutic role for aceclofenac in arthritis and suggests that it is an alternative NSAID to diclofenac in the treatment of osteoarthritis.in a randomized double blindparallel group study which incuded 60 patients of osteoarthritis 30 patients were give

n aceclofena c and 30 were given diclofenacfor 8 weeks. The patients were evaluated and compared statistically for pain intensity on VAS sore,jointtenderness,swelling ,erythema,pain on movement,functional capacity and overall assessment on LIKERT scale.bothe the drugs caused marked improvementin all the parametreson movement of knee joint but there was increased movement with aceclofenac.(20) Etorocoxib has better gastrointestinal tolerability profile than aceclofenac . An analysis of 5441 patients with OA from 10 clinical trials, showed that etoricoxib 60 to 120 mg QD was associated with a lower incidence of gastrointestinal side effects than traditional NSAIDs (ibuprofen 800 mg TID, diclofenac 50 mg TID, naproxen 500 mg BID) (21) . In our study three patients in the aceclofenac group developed dyspepsia ,gastritis and abdominal pain but upper gastrointestinal endoscopy of all the 3 patients was normal .The side effects in both the groups were statistically non significant.The present study has some limitations .The study was of very short duration.sample size was also small.The patients who completed the study were included in the efficacy and safety analysis only .Our study suggest that etorocxib 120 mg bd is equally effective to aceclofenac 100 mg bd in osteoarthritis patients.

References

1. Mobashri AI. The future of osteoarthritis therapeutics:Targetted pharmacological therapy.*Curr Rep* 2013;15(364):1-13.
2. Aggarwal V. Prevalence of Rheumatic Diseases in india.*JK Science* 2003;5(2) 48-49.
3. Dilip K, Shobana M, Jagdiswar R.Evaluation of Efficacy and safety of Diacerein in osteoarthritis of Knee join.*Int J Pharma & Bioscience* 2010;1(3)1-12.
4. Balint Gandandszebenyl, B.Nonpharmacological Therapy In Osteoarthritis.*Clinical Rheumatol* 1997;11(4):795-815.
5. Brady SJ, BooksP, ConaghanKenyon LM. Pharmacotherapy and osteoarthritis. *Clinical Rheumatol* 1997;11:749-68.
6. Amadio PJR Cummings DM. Evaluation of acetaminophenin the management of osteoarthritis of the knee joint. *Curr Ther Resp* 1983;34:59-66.
7. Malhotra R, Ghani A. New therapeutic option for effectivemanagement of osteoarthritis.*Orthopaedc Today* 2002;6(4)193-95.
8. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006;(1):CD004257.
9. Machlis BK, Klostomeyeres BS.COX2 inhibitors safety and effectiveness. *Ann Pharmacotherapy*1999:33:979-88
10. Bombardier C, Laine L, Reicin A, *et al*. "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis". *NEJM*; 2010; 343 (21): 1520.
11. Vardeny O, Solomon SD. Cyclooxygenase-2 inhibitors, nonsteroidal anti-inflammatory drugs, and cardiovascular risk. *Cardiol Clin* 2008; 26(4):589-601.
12. DooleyMSpencer CM, Dunn CJ. Aceclofenac :a reappraisal of its use in the management of pain and rheumatidisease. *Drugs* 2001:61:1351-78.
13. Saraf S. Aceclofenac :Apotent nonsteroidal anti-inflammatory drug. Pharmaceutical Information Snet 2006 45;12: 23.
14. Baraf HSB, Fuentealba C, Greenwald M, *et al*. 2004. Tolerability and effectiveness of etoricoxib compared with diclofenac sodium in patients with osteoarthritis: a randomized controlled study (EDGEtrial) [abstract]. American College of Rheumatology 68th Annual Scientific Meeting, 16-21 October 2004, San Antonio, TX, USA. 832.
15. Fisher CA, Curtis SP, Resnick H, *et al.* Treatment with etoricoxib, a COX-2 selective inhibitor, resulted in clinical improvement in knee and hip osteoarthritis (OA) over 52 weeks [abstract]. *Arthritis Rheum2001;* 44(Suppl 9):S135, 495.
16. Leung AT, Malmstrom K, Gallacher AE, *et al*. Efficacy and tolerability profile of etoricoxib in patients with osteoarthritis: Arandomized, double-blind, placebo and active-comparator controlled 12-week efficacy trial.*Curr Med Res Opin* 2002;18:49-58.
17. Wiesenhutter CW, Boice JA, Ko A, *et al.* Evaluation of the comparative efficacy of etoricoxib and ibuprofen for treatment of patients with osteoarthritis: A randomized, double-blind, placebocontrolledtrial. *Mayo Clin Proc* 2002; 80:470-9.
18. PerézBusquier M, Calero E, Rodríguez MC, *et al*. Comparison of aceclofenac with piroxicam in the treatment of osteoarthritis.*Clin Rheumatol* 1997 ; 16(2):154-59
19. Pareek A, Chandanwale AS, Oak J, Jain UK, Kapoor S.Efficacy and safety of aceclofenac in the treatment of osteoarthritis: a randomized double-blind comparative clinical trial versus diclofenac - an Indian experience.*Curr Med Res Opin* 2006;22(5):977-88.
20. Sehgal A, Sehgal VK, Singh. Comparison of efficacy and tolerability of aceclofenac and diclofenac in osteoarthritis of knee joint. *IJMDS* 2015; 4(2)
21. Ramey DR, Watson DJ, Yu C, *et al*. The incidence of upper gastrointestinal adverse events in clinical trials of etoricoxibversus.non-selective NSAIDs: an updated combined analysis. *Curr Med Res Opin* 2005; 21:715-22.