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Efficacy and Safety of Aceclofenac-CR and Aceclofenac in the Treatment of Knee Osteoarthritis: A 6-Week, Comparative, Randomized, Multicentric, Double-Blind Study

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Abstract: The efficacy and safety of aceclofenac control release (CR) tablets was compared with conventional aceclofenac tablets in patients with knee osteoarthritis (OA). This was a double-blind, double-dummy, randomized, parallel group multicentric study conducted at 6 centers. Two hundred and eighty five patients were randomized to either aceclofenac-CR (n = 143) once daily or conventional aceclofenac tablet (n = 142) twice daily and were followed for 6 weeks. The efficacy parameters were pain intensity score on visual analogue scale, Western Ontario and McMaster (WOMAC) score, patients and investigator's overall study drug assessment and total consumption of acetaminophen and ranitidine tablets. Both treatments showed significant improvement in their efficacy parameters from baseline at the end of therapy. Aceclofenac-CR was comparable to conventional aceclofenac with respect to change in pain intensity and WOMAC score ($P > .05$) There was no statistically significant difference between the treatment groups in patient's and investigator's overall study drug assessment at the end of therapy ($P > .05$). Aceclofenac-CR treated patients took fewer acetaminophen and ranitidine tablets during the treatment period as compared to conventional aceclofenac treated patients. Both the study medications were well tolerated with no incidence of serious adverse event (SAE). In conclusion, the new aceclofenac-CR formulation was found to be effective and safe while offering practical advantage of once daily administration.

***Perspective:** This article represents the advantages of control release aceclofenac over the conventional aceclofenac tablets. Aceclofenac-CR was found to be similar in terms of efficacy as conventional aceclofenac in knee OA patients with fewer adverse events.*

***Key words:** Aceclofenac, control release, knee osteoarthritis, NSAIDs.*

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Osteoarthritis (OA) is characterized by joint pain, tenderness, stiffness, crepitus, and local inflammation.[8] OA is a major cause of impaired mobility that has a serious detrimental impact on a patient's quality of life and their ability to perform normal daily activities.[8,12] OA is the most common arthritis in adults with an estimated worldwide prevalence of 9.6% for men and 18.0% for women aged at least 60 years.[15] As a consequence of an increasingly aging population together with an elevated risk with advancing age, OA will become an even greater burden in the coming years.[7]

The goals of the contemporary management of the patient with OA include control of pain and improvement in function and health-related quality of life, with avoidance, if possible, of toxic effects of therapy. The recommended approach to the medical management of knee OA includes nonpharmacologic modalities and drug therapy.[1]

Aceclofenac is effective in the treatment of painful inflammatory diseases and has been used to treat more than 75 million patient's worldwide.[9] The inhibitory effects of aceclofenac on synovial levels of Prostaglandin E_2 have been confirmed in patients with acute knee pain and synovial effusions.[5] Controlled clinical trials have demonstrated that aceclofenac is effective and well tolerated in patients with OA, rheumatoid arthritis, and ankylosing spondylitis.[10]

During the treatment of OA, nearly 10% of patients withdraw from NSAID treatment because of side effects;[13] the compliance with the therapy constitutes another fundamental aspect of the matter. Rheumatic patients often need to take several other drugs to control other concurrent diseases. In order to maintain a high compliance with the therapy, NSAIDs should be administered once daily and their therapeutic action should last for 24 hours even with a daily single-dose administration.[11] Controlled release (CR) preparations not only provide an extended duration of action and reduced dosing frequency, but because of reduced fluctuations in plasma concentrations, they may provide a favorable efficacy and side effect profile, as well as improved compliance.[2] These considerations led us to evaluate efficacy and safety of controlled release formulation of aceclofenac against conventional aceclofenac formulation in Indian patients with knee OA.

Methods

Trial Design

This was a randomized, parallel group, multicentric, double-blind, double-dummy study conducted at outpatient department of 6 centers comparing aceclofenac-CR 200 mg once daily and aceclofenac 100 mg twice daily.

The study was carried out according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by hospital ethics committee of each center. All patients gave their written informed consent to participate in the study. The primary objective of this study was to evaluate the efficacy of aceclofenac-CR once daily in comparison with conventional aceclofenac tablet twice daily in patients with knee OA. The secondary objective was to assess the safety of the study medications.

Subject Selection Criteria

Patients of either sex aged between 40 and 65 years with confirmed symptomatic primary knee OA for at least 3 months were included in the study. OA was diagnosed on combined radiological (characterized by joint space narrowing, osteophytes and subchondral sclerosis) and clinical grounds as per ACR diagnostic criteria for OA and ACR criteria for classification of functional status from class I, II or III. Moreover, patients were required to have a pain intensity of at least 4 on an 11-point visual analog scale (VAS) and Western Ontario and McMaster Universities (WOMAC) score of minimum 25 during physical activities for inclusion in the study.

Patients were excluded from the study if they had secondary OA or had undergone joint replacement surgery within past 1 year or had received ancillary physiotherapy, massage or physical therapy within 48 hours prior to study entry. Patients with recent cardiovascular problem in the past 6 months were also excluded from the study. Patients with abnormal renal and liver functions, uncontrolled/severe hypertension, diabetic ketoacidosis, alcoholism, asthma, urticaria and history of peptic ulcers, duodenal ulcers, GI bleeding, or other hematopoetic disorders were not included in this study.

Furthermore, patients with history or diagnosis of fibromyalgia, rheumatoid arthritis, ankylosing spondylitis, active gout, active pseudogout, anserine bursitis or other inflammatory arthritic disorder; patients requiring drugs affecting platelet functions and coagulation were excluded from the study. Patients with history of hypersensitivity to aceclofenac, acetaminophen or any other NSAIDs and patients receiving any concomitant medication that may interact with the action of study drug were also excluded. Women who were pregnant, lactating or of child bearing potential not using a medically accepted means of birth control were not eligible for the study.

Treatment Procedures

Patients who satisfied the inclusion and exclusion criteria were subjected to 7 days placebo washout. These patients were then randomized to either aceclofenac-CR 200 mg once daily or conventional aceclofenac tablet 100 mg twice daily for 6 weeks. Patients were evaluated for efficacy and safety parameters at baseline and at the end of week 1, week 2, week 4, and week 6. Acetaminophen (500-mg tablets, maximum 4 tablets/day) was allowed as a rescue medication during washout as well as treatment phase of the study. Patients were asked to refrain from usage of rescue medication 48 hours before the baseline visit. Usage of rescue medication on both the treatment was recorded by performing drug accountability at each study visit. In addition, ranitidine tablets were allowed to be prescribed to patients who were presenting gastrointestinal adverse events during the treatment phase of study.

Blinding/Randomization Techniques

Patients were randomized to either treatment as per the computer-generated block randomization. Randomization chart was provided to each site by the sponsor. The double-blind, double-dummy study design was adapted to mask the identity of both the products to eliminate bias. Dummy placebos of both the products were prepared and during the treatment phase, each patient received an active medicine along with the dummy placebo of other product.