INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 6; Issue 06(A); June 2020; Page No. 5197-5201
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr202006891

Research Article

IMPROVED TOLERABILITY WITH ACECLOFENAC-HPBCD INCLUSION COMPLEX COMPARED TO ACECLOFENAC IN PATIENTS WITH KNEE OSTEOARTHRITIS

[1]Gagan A. Sharma, [2]Santoshi B. Kadam and [3]Dr. Prashant J. Palkar

[1]Sr. Executive- Medical Services, Akumentis Healthcare Ltd. G.Corp Tech Park, Thane – 400615, Maharashtra, India
[2]AGM- Medical Services, Akumentis Healthcare Ltd. G.Corp TechPark, Thane – 400615, Maharashtra, India
[3]General Manager Medical, Business Development & Strategy, Akumentis Healthcare Ltd. G.Corp TechPark, Thane – 400615, Maharashtra, India

ARTICLE INFO

Article History:
Received 13th March, 2020
Received in revised form 11th April, 2020
Accepted 8th May, 2020
Published online 28th June, 2020

Key words:
HPβCD- Hydroxypropyl Beta-cyclodextrin, WOMAC - The Western Ontario and McMaster Universities Osteoarthritis Index, BCS- Biopharmaceutical classification system, PPIs- Proton-pump inhibitors, NSAID- Non-steroidal anti-inflammatory drug

ABSTRACT

Background: Aceclofenac is a NSAID which possesses anti-inflammatory and analgesic properties. However, it has low aqueous solubility, leading to poor dissolution, insufficient oral bioavailability and more gastrointestinal (GI) adverse effects. The aim of the study was to evaluate the efficacy, safety and tolerability of Aceclofenac-HPβCD complex tablets compared with Aceclofenac tablets in patients with knee osteoarthritis (OA).

Materials and Methods: This was a prospective, randomized, multi-centric study. A total of 240 subjects with OA were randomized into two groups: Group A (n=120) were administered Aceclofenac-HPβCD tablets, twice daily and Group B (n=120) were administered Aceclofenac tablets twice daily day for 6 weeks. The primary outcome was to assess and compare GI tolerability and safety between two treatments groups. A visual analogue scale (VAS), WOMAC index, pain relief score and patients and investigators overall assessment of response to study were also noted.

Results: The results of the study showed a trend towards significantly lower incidence of GI adverse effects with group A compared to group B. The change in VAS score and WOMAC score showed significant improvement in group A compared to group B. The patients and investigators overall assessment of response to study drugs was better in Aceclofenac-HPβCD complex tablets group as compared to Aceclofenac tablets. The consumption of gastro-protective agents was also significantly lower in group A compared to group B.

Conclusion: Aceclofenac-HPβCD tablets was found to safe and effective in improving pain, stiffness, and physical performance in knee OA patients. Aceclofenac-HPβCD tablets were associated with significantly better GI tolerability compared to Aceclofenac tablets.

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INTRODUCTION

Osteoarthritis (OA) is the most general type of arthritis. It is also the main cause in elderly people. Reducing pain and improving functions are the key goals in the treatment of OA [1]. Aceclofenac, the most well tolerated non-steroidal anti-inflammatory drug (NSAID) shows noteworthy analgesic, anti-inflammatory and anti-pyretic properties[2] and it is a phenylacetic acid derivative, preferential COX-2 inhibitor and an analogue of diclofenac. It has additional properties to inhibit the synthesis of inflammatory cytokines such as TNF, interleukin-1, and Prostaglandin E2[3]. Belonging to BCS class II category (low solubility and high permeability), aceclofenac is plagued with the issue of low aqueous solubility which limits its dissolution and thus absorption[2]. The main side effects of aceclofenac include gastrointestinal (GI) disturbance, peptic ulceration, and gastric bleeding. These gastroenteropathies which can be attributed to the combination of local irritation produced by blocking it prostaglanding biosynthesis in GI tract and by the free carboxylic group present in the molecular.[4].

Hydroxypropyl Beta-Cyclodextrin (HPβCD), a highly soluble derivative of beta-cyclodextrin[5], can enhance the aqueous solubility of lipophilic drugs without changing their intrinsic ability to permeate biological membranes[6]. A recent pharmacokinetic study showed higher C_{max} and AUC for Aceclofenac-HPβCD complexation compared to uncomplexed Aceclofenac formulation[2]. The aim of the present study was to compare the safety and efficacy of Aceclofenac-HPβCD complexed formulation with conventional uncomplexed Aceclofenac formulation in knee OA patients.

*Corresponding author: **Gagan A. Sharma**
Sr. Executive- Medical Services, Akumentis Healthcare Ltd. G.Corp Tech Park,Thane – 400615,Maharashtra, India

MATERIAL AND METHODS

This was a prospective, randomized, multi-centre, single-blind study in patients with knee osteoarthritis. The study protocol and informed consent form was approved by Ethics Committee and study was conducted at 2 centers, Royal Hospital and Sai Sneh hospital & Diagnostic Centre, Pune, India and the duration of the study was from 15th January 2019 to 11th June 2019.

Inclusion criteria were: Patients with 45-65 years of age of either sex with pain intensity score of at least 4 on a 10 cm visual analogue scale (VAS) and a minimum WOMAC score of 25 during physical activities at the screening and the randomization visit, radiographic diagnosis of osteoarthritis of the knee (characterized by joint space narrowing, osteophytes, and subchondral sclerosis), patients with mild to moderate documented diagnosis of knee osteoarthritis that fulfill the ACR (American College of Rheumatology) criteria, patients willing to avoid NSAIDs use during the study and also to avoid other anti-inflammatory medications, patients who agree to stay weight stable during this 6-weeks study and willing to follow all study procedures, including randomization to one of two groups and female patients with negative urine or serum pregnancy test within 7 days prior to baseline visit.

Exclusion criteria were:

Patients suffering from secondary osteoarthritis or a history of any disease like septic arthritis, inflammatory joint disease, and gout, recurrent episodes of pseudogout, Paget's disease, articular fracture, ochronosis, acromegaly, Wilson's disease, hemochromatosis, primary osteochondromatosis, or heritable disorders (e.g. hypermobility) in the target joint.

Patients having a history of peptic ulcers, duodenal ulcer, GI bleeding or bleeding disorders, active hepatitis or hepatic diseases, bleeding diathesis and inflammatory bowel disease, malignancy, diabetic ketoacidosis, hypersensitivity or allergy to aspirin, other traditional NSAIDs or coxibs.

Patients with GI malabsorption, morbid obesity, abnormal liver, uncontrolled/severe hypertension, renal or heart function, or diseases of the blood.

Patients who were on therapy with anticoagulants, aspirin, non-study NSAIDs or coxibs, or combination of ticlopidine or clopidogrel, or had received H_2-receptor antagonist, or PPIs for more than four consecutive days within 1 month prior to screening, or sucralfate or misoprostol within 3 days prior to screening.

Product Information: Test Product contained Equidol Tablets (Aceclofenac with Hydroxy-propyl-Beta-cyclodextrin, USP 100 mg film-coated tablets) in 1:1 ratio manufactured by Akumentis Healthcare Limited, Thane compared with reference product containing Zerodol Tablets (Aceclofenac, USP 100 mg film-coated tablets) manufactured by IPCA Laboratories Limited, India. Patients were randomly assigned to one of these groups in a 1:1 manner and products were administered twice daily for 6 weeks. Group A (n=120) were administered Aceclofenac-HPβCD tablets, twice a daily and Group B (n=120) were administered Aceclofenac tablets twice a day for 6 weeks.

Changes in the laboratory parameters were assessed by obtaining blood samples at baseline and at the end of therapy and to perform routine hematology and biochemistry. A routine urine test also performed at baseline and at end of therapy. At the baseline visit, after signing the consent form, each patient had undergone physical examination and vital signs evaluation. After the tests were performed, each patient was screened against the inclusion and exclusion criteria of the study. The patients was randomized for 6 weeks and were given patient diary to fill the information. Subjects were prescribed to take 2 tablets per day. The Investigator instructed the patients for administration of study drug and filling of information in the patient diary and collected the information for VAS score, WOMAC index score and Likert scale score.

The primary endpoint was to assess and compare gastrointestinal tolerability and safety between two treatments based on the incidence and severity of predefined GI adverse events (AEs) (abdominal pain, dyspepsia, dysphagia, nausea, constipation, diarrhea, and vomiting) in both treatment groups, number of GPAs (gastro-protective agents) consumed – PPIs (omeprazole) and H_2-receptor antagonists (ranitidine) to manage any GI AE, discontinuation from the study due to GI AEs and number of (GPAs) consumed by patients. Pain intensity was captured on a VAS, from '0 to 10' where score of '0'represented 'no pain' and '10' represented 'worst possible pain' at baseline, Week 1, Week 2, Week 4, and Week 6 (end of therapy). WOMAC index was also assessed at baseline and Week 6. Secondary Objective was to assess and compare efficacy between two treatments based on pain relief score, and investigators and patients overall assessment of response to study drug. Pain relief score was captured on a 5 point Likert scale (0.none, 1.slight, 2.moderate, 3.a lot, and 4.complete) at Week 1, Week 2, Week 4, and Week 6. Patients' and investigators' overall assessment response to study drug was recorded at the end of therapy visit (Week 6) on a 5-point scale.

The study consisted a screening visit (Visit 1), four on-treatment visits (Visits 2-5), and end of therapy visit (Visit 6) for all patients. The patients were followed-up at 1 week, 2 week, 4 week and 6 weeks to collect information for safety, concomitant medications, rescue medications, and patient diary (Figure 1). The patients were reminded to take study medication on time and note the same in patient diary. At week 6 or end of treatment visit, the investigator collected the information for safety, concomitant medications, rescue medications, and patient diary for study drug administration. Also the information was collected for WOMAC score, VAS score questionnaire and Likert scale score. The patient had undergone weight measurement and blood collection for laboratory tests. The efficacy of study drugs was measured by change in VAS score, WOMAC index score and Likert scale from baseline to week 6. The safety and compliance of study patients was also evaluated.

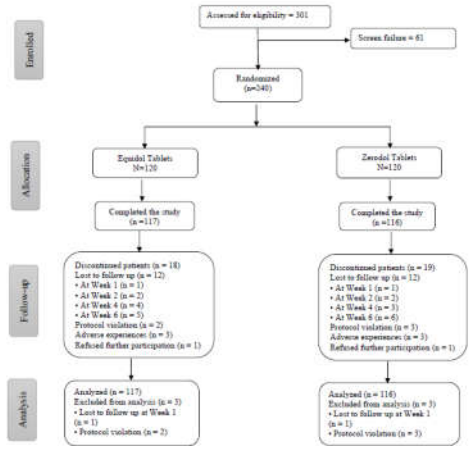

Figure 1 visible properly

Statistical analysis

Descriptive statistical methods were used to summarize demographic, baseline characteristics and all other analysis variable. Data were presented in terms of mean ± SD and median or range for continuous variables and percentage for categorical variables. All patients at baseline were compared for homogeneity using analysis of variance (ANOVA) or Kruskal Wallis test as appropriate for continuous variables and Chi square test or Fisher's exact test for categorical variables.
Safety analysis: Statistical analysis was performed on the modified intention to treat (mITT) population, which included randomized patients having records of at least one-post randomization measurements (Week 1). The last observation carried forward (LOCF) method is used to assign missing values. Chi-square or Fisher's exact test was used to compare the treatment groups .

Efficacy analysis: Overall pain intensity was assessed in the target joint, WOMAC score and pain relief score, was analyzed using ANOVA or Kruskal Wallis test as appropriate. Patient's and investigator's assessments of response to study drug was analyzed using Fisher's exact test or chi-square test as appropriate. *P* values <0.05 were considered statistically significant.

RESULTS

Primary Outcome Measure

Commonly reported GI AEs were dyspepsia and abdominal pain, and the incidence of these two common GI AEs was significantly lower in the group A compared to the group B (*p=0.0352* for dyspepsia and *p=0.0469* for abdominal pain). The number of patients reporting GI AEs increased with the duration of NSAID treatment in both groups. The incidence and severity of GI AEs occurring throughout the study are shown in Table 1.

Table 1 Incidence and severity of gastrointestinal adverse events throughout the study

GI Adverse Events	Group A, Aceclofenac-HPβCD (n=117)	Group B, Aceclofenac (n=116)	*p-value*
Dyspepsia	34 (29.1)	45 (38.8)	*0.0352*
Abdominal pain	22 (18.8)	31 (26.8)	*0.0469*
Nausea	7 (6.0)	6 (5.2)	*0.2314*
Dysphagia	2 (1.7)	2 (1.7)	*0.3782*
Constipation	2 (1.7)	2 (1.7)	*0.3782*
Diarrhoea	0 (0)	1 (0.9)	*0.5000*
Vomiting	0 (0)	0 (0)	*0*
Total	67 (56.4)	87 (75.9)	*0.1079*

Value shown as n (%).Fisher's exact test used for comparison

The cumulative sum of GI AEs was significantly lower in the Aceclofenac- HPβCD tablets group than in the Aceclofenac tablets at all visits throughout the study (Table 2).

Table 2 Cumulative Sum of Gastrointestinal Adverse Events Reported Throughout Study

Visit	Group A, Aceclofenac-HPβCD(n=117)	Group B, Aceclofenac (n=116)
Week 1	8 (6.8)	12 (10.3)
Week 2	24 (20.5)	32 (27.6)
Week 4	44 (37.6)	58 (50.0)
Week 6	67 (57.3)	87 (75.0)

Value shown as n (%); chi square test used for comparison.

The cumulative sum of patients consuming GPAs was lower in the Aceclofenac-HPβCD group compared to the Aceclofenac group. At week 1 (p=0.03), week 2 (*p=0.0176*) and week 6 (*p=0.050*), the cumulative sum of patients consuming GPAs was significantly lower in the group A compared to the group B (Table 3).

Table 3 Cumulative Sum of Patients Consuming Gastroprotective Agents

Visit	Group A, Aceclofenac-HPβCD (n=117)	Group B, Aceclofenac (n=116)	*p-value*
Week 1	8	11	*0.030*
Week 2	26	31	*0.0176*
Week 4	44	54	*0.109*
Week 6	62	76	*0.050*

Value shown as n (%); chi square test used for comparison.

Comparison consumption of gastroproective agents

A total of 14 non-GI AEs were reported by 14 patients, 5 from the group A and 9 from the group B. A commonly reported non-GI AE in the study was edema. None of the patients were withdrawn from the study due to non-GI AEs. Laboratory evaluations were performed at baseline and end of therapy. There were no clinically significant trends observed for any of the laboratory parameters in either treatment group.

Secondary Outcome Measure

There was a significant difference between the change in VAS score among Aceclofenac-HPβCD tablets group compared to Aceclofenac group.

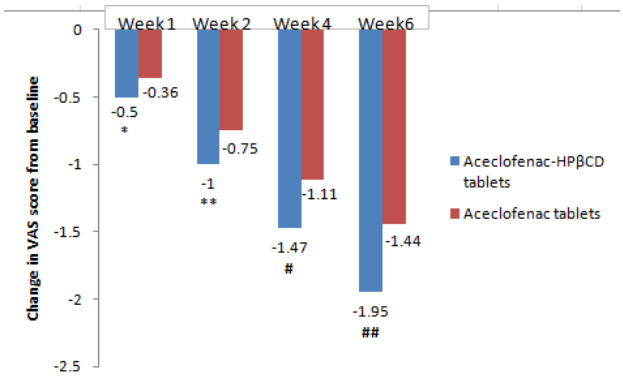

Figure 2 Change in VAS Scores for Pain in the Two Treatment Groups at Baseline and after 1, 2, 4 and 6 Weeks of Treatment (Mean)

**p= 0.0204, **p= 0.0036, #p= 0.0005, ##p= 0.0097*

At week 2 there was a significant difference in change of VAS score in Aceclofenac-HPβCD tablets group compared with Aceclofenac tablets group (p=0.0036)

And at week 6 a significant difference in change of VAS score in Aceclofenac-HPβCD tablets group compared with Aceclofenac tablets group (p= 0.0097)

Higher WOMAC scores (mean ± SD) reduction was seen in Aceclofenac-HPβCD tablets group than Aceclofenac tablets groups after 6 weeks of treatment. There was a significant difference for change in WOMAC score in Aceclofenac-HPβCD tablets group compared with Aceclofenac group (p=0.015)

Table 4 WOMAC Scores in the Two Treatment Groups at Baseline and after 6 Weeks of Treatment (Mean ± SD)

	Group A, Aceclofenac-HPβCD (n=117)	Group B, Aceclofenac (n=116)	P value
Baseline	67.0±7.126	67.87±5.013	-
Week 6	33.0±9.58	50.0±5.30	-
Difference	-33.6 (7.711)	-17.82 (5.014)	*0.0158*

A total of 26 patients from group A and 2 patients from group B experienced 'Complete' relief throughout the study. A comparison between group A and group B with respect to the mean pain relief score throughout the study is presented figure 3:

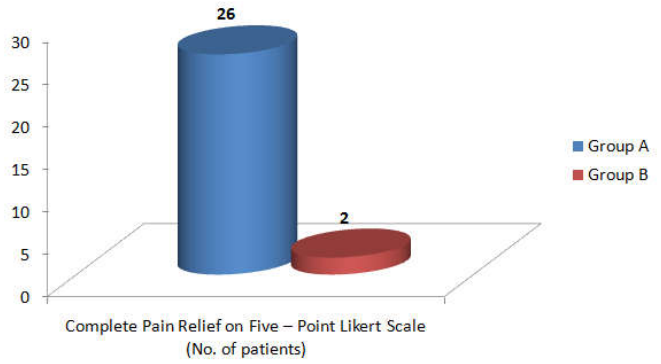

Figure 3 Mean Pain Relief Score Throughout the Study

A comparison between group A and group B with respect to the Patient's and investigator's overall efficacy assessment of study drug is presented figure 4.

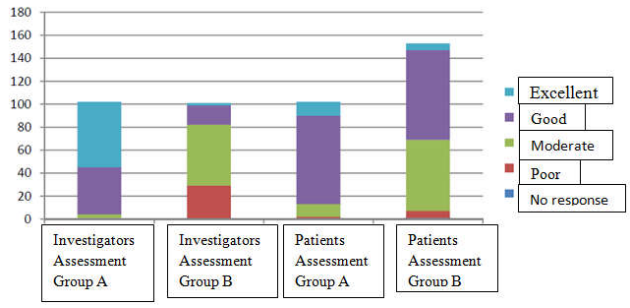

Figure 4 Patients' and Investigators' Overall Efficacy Assessment of Study Drug

DISCUSSION

Aceclofenac is a phenylacetic acid-derived NSAID that is used for chronic joint conditions, such as OA, ankylosing spondylitis and rheumatoid arthritis but also for relief of acute pain, especially following surgery[7]. It is an effective, well-tolerated, and well-accepted therapy for degenerative diseases and for both acute and chronic inflammatory diseases. The most commonly prescribed agents for patients with OA is aceclofenac in Asian and European countries. For osteoarthritis patients receiving NSAIDs, the gastrointestinal adverse events are an important safety challenge. Gastrointestinal protection is an important strategy to increase compliance during long-term NSAID use. The possibility of gastrointestinal adverse events increases with duration of treatment. For gastrointestinal adverse events and function improvement the effect of aceclofenac over other analgesics was significant [8]. Aceclofenac has been assessed in international studies and is indicated for the relief of pain and inflammation associated with rheumatoid arthritis, osteoarthritis or Ankylosing spondylitis. Aceclofenac may prevent the degradation of articular connective tissue in patients with rheumatoid arthritis and osteoarthritis, and should be classified as a unique NSAID[9]. The study of Diaz *et al* showed that there was significant improvement in pain and movement of OA patients taking aceclofenac as compare to diclofenac[10]. Aceclofenac was better than diclofenac in investigator response to therapy which is supported by previous studies done by Ward DE *et. a.l*[11].

Most of the patients taking NSAIDs common GI AEs include nausea and vomiting, dyspepsia, which can add extra cost to the treatment of OA. These AEs, though not predictive of more serious GI injury, lead to treatment interruptions and drug switching [8]. Economic analysis of the use of aceclofenac in the meta-analysis has suggested that the favorable tolerability profile of the drug is reflected in limiting the costs associated with managing adverse events comparable to other NSAIDs from a healthcare provider's perspective. However, aceclofenac which belongs to BCS Class II category is plagued with the issue of low aqueous solubility which limits its dissolution and thus absorption. As per literaure survey, complexation of different NSAIDs like phenylbutazone, indomethacin, ketorolac naproxen, etodolac with HPβCD or β-CD reported marked improvement in pharmacokinetic parameters and reduction in different gastrointestinal complications like ulceration, lesion formation etc[2]. In a recent study by Iyer *et.al.* increased solubility and improved pharmacokinetic parameters was observed after complexation of aceclofenac with HPβCD.

The main objective of this study was to establish the potential of Aceclofenac-HPβCD inclusion complex as a bioavailability enhancer for faster action, superior efficacy, superior GI protection and the real-life need of co-prescription of GPAs. The results of the study showed a trend towards significantly lower incidence of GI AEs with Aceclofenac-HPβCD tablets compared to Aceclofenac tablets. There were fewer patients reporting GI AEs in the Aceclofenac-HPβCD tablets group compared to the Aceclofenac tablets group. The incidence of each individual predefined GI AE was also lower with Aceclofenac-HPβCD tablets compared to the Aceclofenac tablets, specifically the incidences of dyspepsia (p=0.0352) and abdominal pain (p=0.0469). As the incidence of GI AEs was lower in the Aceclofenac-HPβCD tablets group, the consumption of GPAs was also significantly lower compared to the Aceclofenac tablets group. Change in VAS score and WOMAC score at 6 weeks of treatment from baseline was also checked and we observed statistically significant decrease in VAS scores from baseline which showed improvement in pain for Aceclofenac-HPβCD tablets group. Importantly, the total WOMAC index for pain, stiffness and physical function was reduced in both the groups at week 6 from baseline.

Likert scale scores were significantly increased at week 6 from baseline in Aceclofenac-HPβCD groups as compared to Aceclofenac groups. The patients and investigators overall assessment of response to study drugs was better in Aceclofenac-HPβCD group as compared to Aceclofenac group.

CONCLUSION

In conclusion, the results of the present study revealed that the treatment with Aceclofenac-HPβCD were found to safe and effective in improving pain, stiffness and physical performance of knee OA patients after 6 weeks of treatment. This appears to be the first study suggesting Aceclofenac-HPβCD to be significantly better GI tolerable compared to aceclofenac.

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