Aceclofenac: Superior treatment option for Osteoarthritis

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June 2009

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A Research paper submitted to the Department of Pharmacy, East West University in conformity with the requirements for the degree of Bachelor of Pharmacy

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Acknowledgement

First and foremost I would like to express my sincere thanks and gratitude to Mr. Zakiur Rahaman, for supervising me and for his valuable guidance and support throughout the entire work.

I am especially thankful to Razib Ahsanul Haq and ASM Farhad for their enthusiastic cooperation in this study.

I am grateful to Abdul al Raja and Iftekhar Reza for helping me by giving me the permission of using their computer. Without their help the work became more difficult.

Many thanks also to all of my friends who helped me by giving advices from their experiences.

Finally I express my sincere gratitude to my caring parents for guiding me all through my life and my love to my sisters, who always keep faith on my ability even in my very tough time.

Abstract

Osteoarthritis (OA) is the most commonly observed arthritis with no definite permanent relief and it needed life long medication. Aceclofenac is a potent NSAID effectively used to manage pain. The aim of this study is to find the effectiveness of aceclofenac to treat the OA in terms of efficacy and safety. Here various research journals and books and other reliable sources are checked and studied to compare aceclofenac with other alternative drugs included Diclofenac, Naproxen, Piroxicam, Indomethacin, Ketoprofen, which are generally used as medication of OA. In this study it is found that aceclofenac is the safest drug among the NSAIDs with good potency. It also helps to regenerate the cartilage which is not possible by other NSAIDs. So, aceclofenac is the best option for the treatment of OA among the NSAIDs.

1. Introduction

1.1 Arthritis:

Arthritis is the leading cause of disability in people older than fifty-five years. The word arthritis is derived from two Greek words, they are: arthro- means joint and –itis means inflammation.

There are various types of arthritis and each of them has different causes and sign symptom. But one common thing is that every types of arthritis contain pain and inflammation. The evidence of arthritis is found throughout the history. But the first written detail of arthritis is found in 1715 AD. In that time William Musgrave published *De arthritide symptomatica* which concerned arthritis and its effects (Cameron A, 2004).

Arthritis may be classified in following types:

- Osteoarthritis
- Rheumatoid arthritis
- Gout and pseudogout
- Septic arthritis
- Juvenile idiopathic arthritis
- Still's disease
- Ankylosing spondylitis

Treatment options vary depending on the type of arthritis and include physical and occupational therapy, lifestyle changes (including exercise and weight control), medications and dietary supplements (symptomatic or targeted at the disease process causing the arthritis). Arthroplasty (joint replacement surgery) may be required in eroding forms of arthritis.

In general, studies have shown that physical exercising of the affected joint can have noticeable improvement in terms of long-term pain relief. Furthermore, exercising of the arthritic joint is encouraged to maintain the health of the particular joint and the overall body of the person (Swash M, Glynn M, 2007).

Among the various types of arthritis, osteoarthritis, rheumatoid arthritis and gout, the most commonly observed arthritis have been discussed later.

1.2 Osteoarthritis:

Among the many forms of arthritis osteoarthritis is most commonly observed arthritis (Conaghan, P) and is responsible for a huge burden of pain and disability (Dieppe P, 1993). "Osteoarthritis" is derived from the Greek word "osteo", meaning "of the bone", "arthro", meaning "joint", and "itis", meaning inflammation. OA is a slowly progressive degenerative joint disease, with a high incidence (Dieppe PA, Lohmander LS, 2005), and is characterized by gradual loss of articular cartilage (Goldring MB, 2000) and simultaneous proliferation of new bone, cartilage, and connective tissue (Doherty M, Lanyon P, Rolston SH, 2006). Symptomatic osteoarthritis, particularly of the knee and hip, is the most common cause of musculoskeletal disability in elderly people in western countries (Walker-Bone K, Javaid K, Arden N, 2000) as well as developing countries (Brandt KD et al, 1998). In OA, a variety of potential forces - hereditary, developmental, metabolic, and mechanical - may initiate processes leading to loss of cartilage - a strong protein matrix that lubricates and cushions the joints. As the body struggles to contain ongoing damage, immune and regrowth process can accelerate damage (Brandt KD, Dieppe P, Radin E, 2008). More dangerously the area of local damage occurs in those parts of the joint subjected to maximal mechanical stretch (Chard J, Dieppe P, 2001).

Osteoarthritis rarely occurs before the age of 40, but by the age of 75, at least 85% of the population has either clinical or radiographic evidence of osteoarthritis (Sack KE, 1995). It is estimated that 80% of the population will have radiographic evidence of OA by age 65, although only 60% of those will show symptoms (Green GA, 2001). Its prevalence after the age of 65 is about 60% in men and 70% in women (Sarzi-Puttini P, Cimmino MA, Scarpa R et al, 2005).

1.2.1 Sign and symptom:

Osteoarthritis is associated with pain and inflammation of the joint capsule, impaired muscular stability, reduced range of motion and functional disability (Bjordal JM, Ljunggren AE, Klovning A et al, 2004). OA can cause a crackling noise when the affected joint is moved or touched, and patients may experience muscle spasm and contractions in the tendons.

Occasionally, the joints may also be filled with fluid. Humid and cold weather increases the pain in many patients (McAlindon T, Formica M., Schmid C.H., & Fletcher J, 2007).

1.2.2 Possible reasons of osteoarthritis:

Although it commonly arises from trauma, osteoarthritis often affects multiple members of the same family, suggesting that there is hereditary susceptibility to this condition. A number of studies have shown that there is a greater prevalence of the disease between siblings and especially identical twins, indicating a hereditary basis (Valdes AM, Spector TD, 2008).

A number of risk factors have been identified also (Felson DT et al, 1997). Mechanical factors, among others, are likely to play a very important role in the initiation of the disease process. Endogenous factors such as type II collagen mutation or dysplastic conditions are also known to be involved in initiating the OA process (Williams CJ, Jimenez SA, 1999).

There is now strong evidence that the structural changes globally observed in OA are due to a combination of factors, ranging from the mechanical to the biochemical (Pelletier JP, Martel-Pelletier J, Howell DS, 2000 & Nuki G, 1999). The disease process affects not only the cartilage, but also the entire joint structure, including the synovial membrane, subchondral bone, ligaments, and periarticular muscles. In OA synovium, the inflammatory changes that take place include synovial hypertrophy and hyperplasia with an increased number of lining cells, and also an infiltration of the sublining tissue with a mixed population of inflammatory cells. In patients with severe disease, the extent of inflammation can sometimes reach that observed in rheumatoid arthritis (RA) patients at the clinical stage (Haraoui B et al, 1991 & Farahat MN, Yanni G, Poston R, Panayi GS, 1993). Some degree of synovitis has also been reported in even the early stages of the disease (Smith MD et al, 1997). Synovial inflammation is clearly reflected in many of the signs and symptoms of OA, including joint swelling and effusion, stiffness, and sometimes redness, particularly at the level of the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints.

1.2.3 Treatment option for the Osteoarthritis:

A wide variety of treatments are available for those who suffer from osteoarthritis of the knee and self management, weight reduction, hydrotherapy, footwear and walking aids, other rehabilitation measures, physical therapy, systemic drug therapy, intra-articular drug therapy and surgery (Chard J, Dieppe P, 2001; Svarcova J, Trunavsky, Zvarov AJ, 1988; Thomas KS et al, 2002; & Williams FMK, Spector TD, 2006) . Much can be done to relief symptoms, optimize function and improve the quality of life. But no specific therapy has been proven to have efficacy in alternating the disease process in human (Altman RD, Lozada CJ, 2004).

1.2.4 Osteoarthritis in Bangladesh:

There are a few studies are done on osteoarthritis in Bangladesh. So it is not very easy to say the condition of osteoarthritis in Bangladesh. But it can be said that it is very common reason of suffering among the elders. Following information are got from the study about the osteoarthritis in Bangladesh:

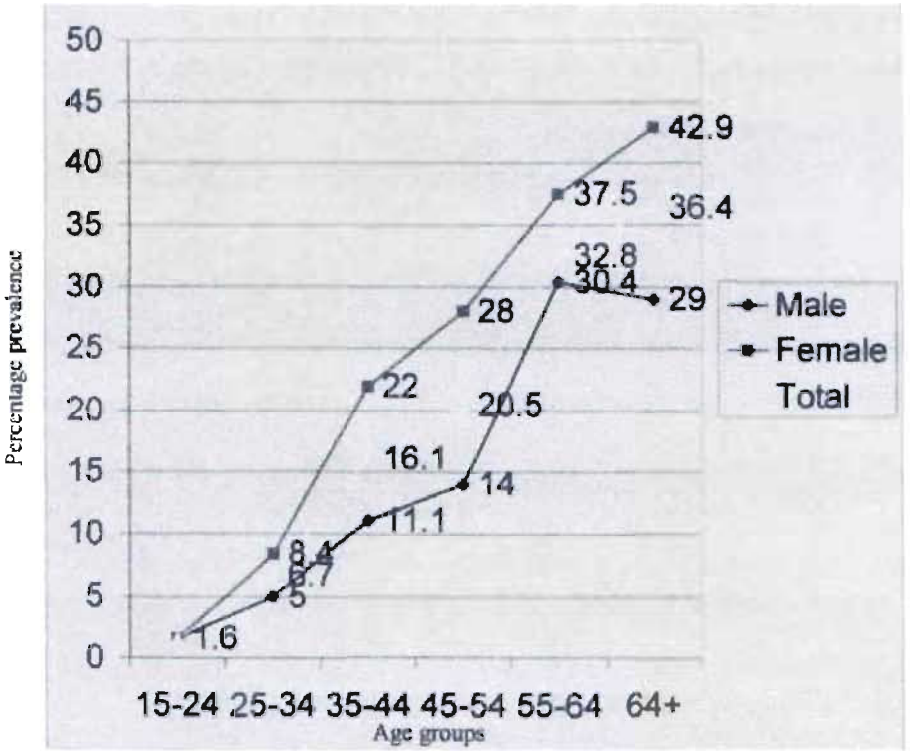


Fig.-1: Prevalence of osteoarthritis by age group and sex in the total population in Dhaka (Das et al, 2003)

In the above study we can see that OA is more common phenomena among the female than the male and more alarming information is that osteoarthritis is occurring in early 40's of Bangladeshi women in noticeable percentages. Among the elders osteoarthritis is more common than the young and it is expected.

In the following table we can see the prevalence of osteoarthritis according to the occupation. It shows the possible relationship between osteoarthritis and occupation.

Table-I

Prevalence of knee osteoarthritis by occupation in Dhaka city (Das et al, 2003)

Occupation	**No. of cases**	**Percentage**
Laborers engaged in earth digging and carrying n=123	19	15.4
Domestic servant n=193	29	15.0
Businessman n=190	26	13.7
Rickshaw pullers n=295	36	12.2
Housewife n=641	78	12.2
Service holder n=313	22	7.0
Other laborers n=129	04	3.1
Student n=310	03	0.1
Garments worker n=81	00	0.0
Others n=284	43	15.1

We can see that osteoarthritis is most commonly observed among the Laborers engaged in earth digging and carrying, Domestic servant, Rickshaw pullers, Rickshaw pullers, Housewife. Most probably the reason is that the people of these occupations have to do physical work more than other professions.

1.3 Other common Arthritis:

1.3.1 Rheumatoid Arthritis:

Rheumatic disorders are among the commonest morbidity in the world. Prevalence data for the major rheumatic diseases have been compiled in the west for several decades (Farooqi A and Gibson T, 1998). One-third of all people of physical disability have a rheumatic disease as the primary cause of their illness (Nuki G, Ralston SH and Luqmani R, 1999).

The name "rheumatoid arthritis" itself was coined in 1859 by British rheumatologist Dr Alfred Baring Garrod (Garrod AB, 1859). The name is based on the term "rheumatic fever", an illness which includes joint pain and is derived from the Greek word rheumatos ("flowing"). The suffix -oid ("resembling") gives the translation as joint inflammation that resembles rheumatic fever. The first recognized description of rheumatoid arthritis was made in 1800 by Dr Augustin Jacob Landré-Beauvais (1772-1840) of Paris (Landré-Beauvais AJ, 2001).

Rheumatoid arthritis affects women three times more often than men, and it can first develop at any age. The risk of first developing the disease appears to be greatest for women between 40 and 50 years of age, and for men somewhat later (Alamanos Y, Voulgari PV, Drosos AA, 2006).

While rheumatoid arthritis primarily affects joints, problems involving other organs of the body are known to occur. Extra-articular manifestations other than anemia (which is very common) are clinically evident in about 15-25% of individuals with rheumatoid arthritis (Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL, 2003).

1.3.2 Gout:

Gout or metabolic arthritis is a disease created by a buildup of uric acid. Gout occurs when crystals of uric acid, in the form of monosodium urate, precipitate on the articular cartilage of joints, on tendons, and in the surrounding tissues. Uric acid is a normal component of blood serum. Uric acid is more likely to form into crystals when there is hyperuricemia, although hyperuricemia is 10 times more common without clinical gout than with it (Virsaladze DK et al, 2007).Gout can also occur when serum uric acid is normal, and when it is abnormally low. Paradoxically, acute attacks of gout can occur together with a sudden decrease in serum uric acid, such as due to use of drugs, or total parenteral nutrition(Moyer RA, John DS, 2003).

Gout is a form of arthritis that affects mostly men between the ages of 50 and 60 and women following menopause. A seasonal link also may exist, with significantly higher incidence of acute gout attacks occurring in the spring (Schlesinger N et al, 1998)

2. NSAIDs

2.1 Classification of NSAIDs

NSAIDs are drugs which are effective in relieving pain and inflammation (Crofford LJ et al, 2000).

They can be classified by following ways:

1) COX-1 SELECTIVE INHIBITORS

- Acetylsalicylic acid at low dosage

2) NONSELECTIVE COX INHIBITORS

- Acetylsalicylic acid at high dosage
- Diclofenac
- Ibuprofen
- ketoprofen
- Aceclofenac
- Indomethacin
- Piroxicam
- Naproxen

3) MORE COX-2 SELECTIVE INHIBITORS

- Nimesulid
- Meloxicam

4) COX-2 SELECTIVE INHIBITORS

- Celecoxib
- Etorcoxib

2.2 Mechanism of action of pain removing by NSAIDs

NSAIDs remove pain by inhibiting prostaglandin mainly. There is a one type of enzyme known as cyclooxygenase, which is required to convert arachidonic acid to the unstable intermediates PGG_2 and PGH_2. The discovery of cyclooxygenase-2 (COX-2) represented an enormous conceptual advance in prostaglandin biology and provided new therapeutic options (FitzGerald GA, Patrono C, 2001). There are two types of cyclooxygenases called cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (Vane J & Botting R, 1987). COX-1 is a constitutive isoform found in most normal cells and tissues, while COX-2 is induced in setting of inflammation by cytokines and inflammatory mediators (Seibert K et al, 1997). COX-2 is also available in certain areas of Kidney and Brain (Breder et al, 1995).

Nonaspirin NSAIDs inhibit the activity of both COX-1 andCOX-2 by reversibly blocking the access of arachidonic acid to the active site at the apex of a hydrophobic channel within these enzymes. The pharmacodynamic properties of the different NSAIDs with respect to the COX enzymes vary with their chemical structures (FitzGerald GA, Patrono C, 2001).

Since, they inhibit the enzyme COX-1 and COX-2, prostaglandin can not be synthesized and pain is removed.

2.3 Common side effects of NSAIDs:

Studies have shown that NSAIDs are among the most common drugs responsible for adverse drug reactions seen in clinical practice (Doomra R, Gupta SK, 2001). Among these adverse effects gastrointestinal disorders are mainly observed. It is observed that 13 of every 1,000 patients with rheumatoid arthritis who take NSAIDs for one year have a serious gastrointestinal complication (Simon LS, Weaver AL, Graham DY, 1999). The risk in patients with osteoarthritis is somewhat lower (7.3 per1,000 patients per year) (Singh G 1998). Cardiovascular and renal complications have recently assumed importance in the evaluation of their side effects, since the COX enzymes have prominent biologic roles in the vasculature and the kidneys (Catella-Lawson F, Crofford LJ, 2001 & Brater DC, Harris C, Redfern JS, Gertz BJ, 2001). Renal failure is especially a risk if the patient is also concomitantly taking an ACE inhibitor and a diuretic - the so-called "triple whammy" effect (Thomas Mc, 2000).

Here, mechanism of GI ulceration, the most common adverse effect of NSAIDs is given:

Mechanisms of NSAIDs-induced GI ulcerations: What causes ulceration is precisely not known. It is believed to occur as the result of a complex interplay of aggravating factors and protective factors. Prostaglandins (PGs) have long been known to be mucoprotective and ulcer healing agents. Prostaglandins protect GI mucosa by forming a cytoprotective layer and increasing the secretion of bicarbonate ions that neutralise the gastric acidity. All therapeutically useful NSAIDs act by inhibiting the synthesis of PGs (Tamblyn, Robyn et al 1997). Cyclooxygenase has two isoforms, one constitutive (COX-1) and another inducible (COX-2). A third isoform (COX-3) has recently been described as well. NSAIDs are now divided into selective (those inhibiting COX-2) and non-selective (inhibiting both COX-1 and COX-2). Conventional NSAIDs cause non-selective inhibition of cyclooxygenase, which leads to reduction in bicarbonate secretion and reduced mucous production (Raskin JB 1999).Coupled with it is vasoconstriction that occurs due to NSAIDs, which causes hypoxia and consequent formation of ulcer. Most NSAIDs are weak organic acids and have low pKa. Therefore, they remain unionised in stomach and are absorbed appreciably from stomach. However, once they breach the cell membranes of stomach cells and reach within, they encounter a basic pH (e.g., 7.1). This causes so called "trapping" of the drugs inside the cell (Raskin JB 1999).

This topical effect is considered an important mechanism of gastro-duodenal damage associated with their use. Even short-term (< 1 week) use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can precipitate ulcer-related bleeding. Risk of ulcer development is increased in patients with advanced age, positive family history, female sex, prolonged use of high dose of NSAIDs and concomitant use of other gastrotoxic or anticoagulant drugs, alcoholism, heavy coffee consumption, and poor general health (Simon LS et al 1999). Role of H. pylori in the development of NSAID-induced ulcer is not entirely clear. Thus, it can be understood to be the disease of the war between the factors favoring and those opposing the development of ulcers where the former win over the latter. Although NSAID use is primarily associated with upper GI problems, it is also associated with lower gastrointestinal symptoms such as hemorrhage, inflammation, perforation, and stricture formation. ARAMIS data suggested that risk of death from NSAID use is four times more than non-users (Doomra R et al 2001). Over-the-counter (OTC) availability of histamine H2–receptor antagonists for short-term treatment of dyspepsia may lead a patient to delay optimal care for more severe gastrointestinal disease; if the drug is taken on a long-term basis, its use could delay a diagnosis of gastric cancer also (Wilcox, C Mel et al 1994).

2.4 Aceclofenac

Aceclofenac has been shown to exert effects on a variety of mediators of inflammation. The drug inhibits synthesis of the inflammatory cytokines like interleukin (IL)–1β and tumour necrosis factor (TNF), and inhibits prostaglandin E2 (PGE2) production. In vitro data indicate inhibition of COX-1 and COX-2 by aceclofenac in whole blood assays, with selectivity for COX□2 being evident (Gonzalez E, de la Cruz C, de Nicolas R, et al, 1994). It has been suggested that aceclofenac blocks PGE2 production via COX-1 and COX-2 inhibition after intracellular metabolism to 4′-hydroxyaceclofenac and diclofenac in human rheumatoid synovial and other inflammatory cells (Yamazaki R, Kawai S, Matsumoto T, et al, 1999). IC50 values for COX-1 and COX-2, respectively, were > 100 and 0.8 μmol/L for aceclofenac and > 100 and 36 μmol/L for 4′-hydroxyaceclofenac.

The mode of action of aceclofenac has been recently clarified in that the compound was shown to elicit preferential inhibition of COX-2 as a result of limited but sustained biotransformation to diclofenac (Hinz B, Brune K, 2004).

Aceclofenac has also shown stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1β. IL-1β suppresses various growth factors. Inhibition of IL-1β thus stimulates synthesis of cartilage matrix. In vitro data show stimulation by aceclofenac of glycosaminoglycan synthesis in human osteoarthritic cartilage. There is also evidence that aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli (Maneiro E, Lopez-Armada MJ, Fernandez-Sueiro JL, et al, 2001) and that 4'-hydroxyaceclofenac has chondroprotective properties attributable to suppression of IL-1β-mediated promatrix metalloproteinase production and proteoglycan release (Yamazaki R, Kawai S, Mizushima Y, et al, 2000).
Thus aceclofenac may prevent the degradation of articular connective tissue in patients with rheumatoid arthritis and osteoarthritis, and should be classified as a unique NSAID.

3. Aceclofenac and other NSAIDs

3.1 Comparison between Aceclofenac and other NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) have long been the preferred therapy for relief of the pain and stiffness of arthritic diseases, including OA, because of their analgesic and anti-inflammatory properties (Brooks PM, Potter SR, Buchanan WW, 1982). In terms of pain relief, a study found that 75% of patients ranked the NSAIDs as good or excellent as did 45% of the physicians (Haslock I, 1991). Despite their efficacy, the threat of serious adverse effects poses a major concern for chronic NSAID users. Adverse renal effects (Delmas PD, 1995) and effects on bone and cartilage metabolism (Hess EV et al) are counted among worrisome NSAID-induced side effects, but serious gastro-intestinal complications represent the greatest threat to long-term NSAID therapy (Roth SH, Bennet RE, 1987). Since long-term NSAID treatment is indicated for osteoarthritis, the ideal agent should have good efficacy and a low propensity to cause adverse events.

Aceclofenac is an effective analgesic and anti-inflammatory agent with a good tolerability profile. Through its analgesic and anti-inflammatory properties, aceclofenac provides symptomatic relief in a variety of painful conditions including osteoarthritis (Dooley M, Spencer CM, Dunn CJ, 2001). Aceclofenac appears to be particularly well tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects. This good tolerability profile results in a reduced withdrawal rate and greater compliance with treatment (Legrand E, 2004 & Walker G, 1991-2000)

The time of onset of action of Aceclofenac appears similar to that of compititor agents. Significant improvements in symptoms versus baseline were generally apparent by the time of the first assessment at 2 weeks (Perez Busquier M, Calero E, Rodriguez M, et al, 1997).

Here comparison between the aceclofenac and other NSAIDs are given:

3.1.1 Aceclofenac and Diclofenac

Safety and efficacy

The therapeutic index for aceclofenac was reported to be four times greater than that of diclofenac, which has been shown to be well tolerated in clinical use (O'Brien WM, 1886). Aceclofenac is found to act significantly earlier than diclofenac, possibly due to more rapid accumulation in the joint (Ward DE, Veys EM, Bowdler JM, Roma J, 1995).

A study was done on Indian patients at 2006 and found that aceclofenac is better choice of drug than diclofenac in case of osteoarthritis (Pareek A, Chandanwale AS, Oak J, Jain UK and Kapoor S, 2006). In that trial physicians found that Aceclofenac show high efficacy in case of 67% of patients where the number is 31% only in case of Diclofenac (Table 1).

The same thing happened in case of safety. Aceclofenac is highly safe for the 72% of patients where Diclofenac is highly safe for 37% of patients (Table 1).

		Aceclofenac (n=125) n(%)	Diclofenac (n=122) n (%)
Efficacy	High	82 (67%)	36 (31%)
	Moderate	36 (30%)	46 (39%)
	Mild	4 (3%)	36 (31%)
Safety	High	88 (72%)	44 (37%)
	Moderate	34 (28%)	52 (44%)
	Mild	0 (0%)	22 (19%)

Table # 1: Outcome of therapy (safety and efficacy) as assessed by the physician in the two treatment groups after 8 weeks of treatment (Pareek A et al, 2006).

Another study shows that the effectiveness of diclofenac in reducing pain at rest is comparatively less than aceclofenac (Schattenkirchner M, Milachowski KA, 2003). In that study it is observed that Diclofenac reduce pain in lesser amount in same time (Figure 1).

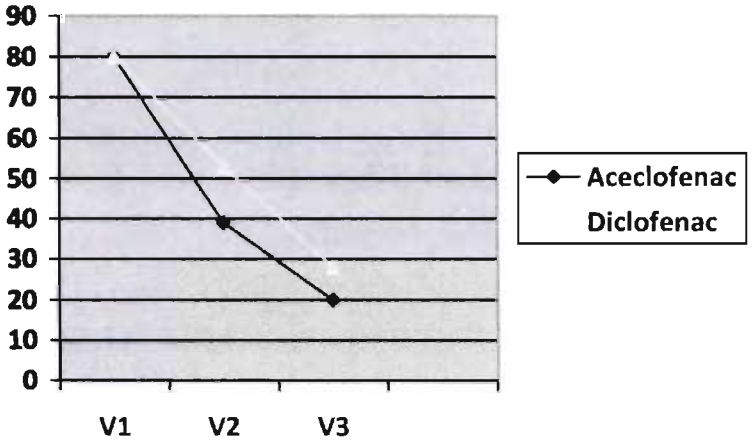


Fig. 1 Visual analogue scale (VAS) pain scores at rest (mean ± SE) at baseline (visit 1, V1) and during treatment (intermediate visit, V2 and final visit, V3) with aceclofenac and diclofenac resinate (perprotocol population) (Schattenkirchner M et al, 2003).

Adverse effects

In some comparative studies, there was a tendency for aceclofenac to be better tolerated than diclofenac with fewer patients being withdrawn from treatment due to gastric intolerance (Diaz C, Rodriguez A, Geli C, Llobet JM, Tapounet R, 1988).

In above mentioned Indian study (Pareek A et al, 2006) it is observed that the frequency of adverse effects is much higher in case of Diclofenac than aceclofenac. As an example the most common adverse effect of NSAIDs, epigastric discomfort, is observed 16 times in case of Diclofenac in first two weeks but the same adverse effect is observed only 8 times in same time for Aceclofenac. More interestingly the frequency of epigastric discomfort is increased with time in case of Diclofenac but it is reduced with time in case of Aceclofenac (figure 2&3).

Other adverse effects including Dyspepsia, Nausea and Flatulence also occurred at a higher rate in Diclofenac than aceclofenac (figure 2&3).

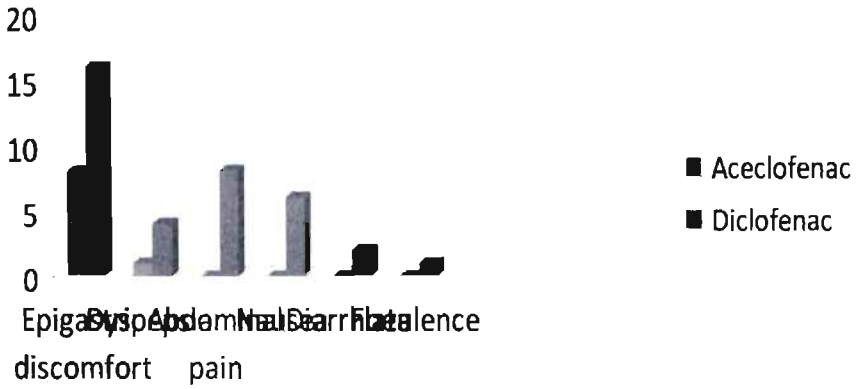


Figure 2: Moderate adverse effects seen after 2 weeks (Pareek A et al, 2006).

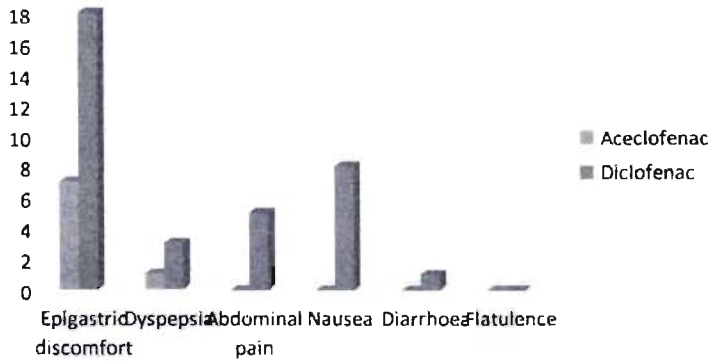


Figure 3. Moderate adverse effects seen after 4 weeks (Pareek A et al, 2006).

3.1.2 Aceclofenac and Piroxicam

Adverse effects: Aceclofenac is well tolerated and shows fewer side effects than piroxicam (Perez Busquier M, Calero E, Rodriguez M, et al, 1997). Less amount of patients withdraw from study due to adverse effects in case of aceclofenac (Table 2).

	Aceclofenac	Piroxicam
Time of withdrawal		
15 days	12	11
1 month	7	13
2 month	5	9
Total	24	33

Table 2: Number of patients with adverse events (Perez Busquier M et al, 1997).

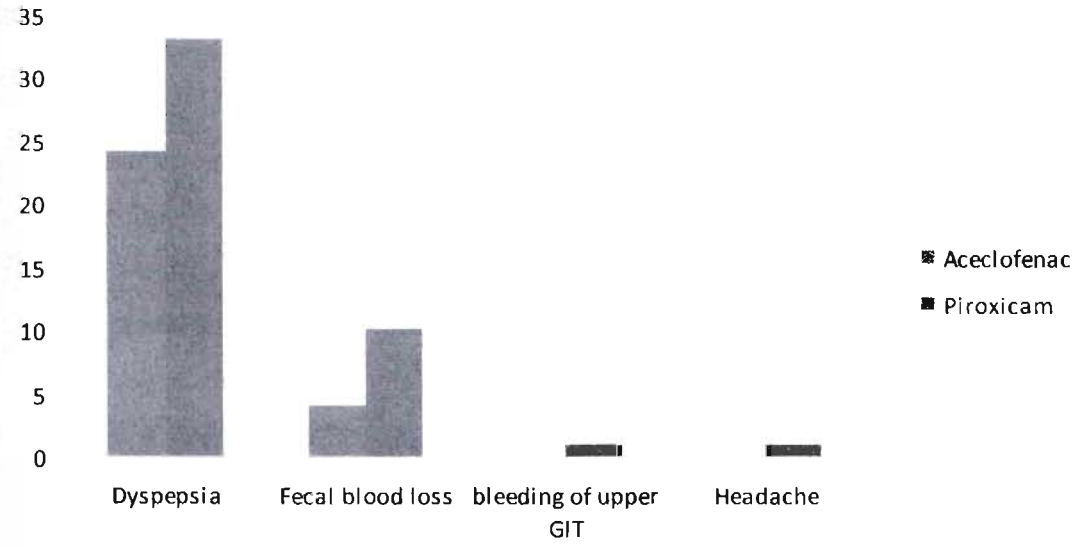


Figure: Adverse effects of Aceclofenac & Piroxicam

Another interesting thing in table 2 is that frequency is reduced drastically between 15 days and 1 month in case of aceclofenac but number is increased in that time in case of piroxicam. That proves that our body system become familiar with aceclofenac in shorter period of time.

Efficacy: The efficacy of aceclofenac is also greater than piroxicam. It is observed that aceclofenac improve the clinical efficacy variable of arthritis in a faster and greater rate than piroxicam (Table 3). In this table we can see that aceclofenac improve OA index, pain, knee function and knee flexibility in a greater rate than piroxicam.

Variables	Aceclofenac (n=109)	Piroxicam n=108
Osteoarthritis Index		
Baseline	12.10 ± 2.91 (109)	12.14 ± 2.94 (108)
15 days	8.92±3.74b (107)	9.15 ± 3.48b (105)
1 month	8.19 ± 3.8% (100)	8.47 ± 4.02b (99)
2months	7.54 ± 3.87b (94)	7,15 ± 3.67b (92)
Pain by VAS (mm)		
Baseline	70.21 ± 15.90 (109)	71.81 ± 14.76 (108)
15 days	48.97±21.48b (107)	52.33 ± 21.99 (105)
1 month	42.24±24.90b (100)	45.46 ± 24.41(99)
2 months	36.39 ± 23.46b (94)	37.01 ± 25.84 (91)
Knee function		
Baseline	7.69 ± 3.05 (108)	6.64 ± 2.94 (108)
1 month	4.42 ± 2.66b (100)	5.01 ± 2.67b (105)
2months	3.96 ± 2.37b (94)	4.25 ± 2.69b (99)
Knee flexion (degrees)		
Baseline	116.44 ± 21.87 (108)	117.93 ± 22.00 (107)
15 days	122.02 ± 23.20 (106)	120.34 ± 24.23 (105)
1 month	124.81 ± 22.11 (100)	122.12 ± 24.35b (99)
2months	128.86 ± 20.84 (94)	125.99 ± 23.41b (92)
Knee extension (degrees)		
Baseline	4.47 ± 6.67 (108)	4.51 _+ 7.66 (106)
15 days	3.23 ±4.87c (106)	3.30 ± 5.87d (105)
1 month	2.66 ± 4.52b (100)	2.98 ± 6.11c (99)
2months	1.99 ± 3.76b (94)	2.84 ± 5.09c (92)

Table 3: The effect of aceclofenac and piroxicam on clinical efficacy variables (Perez Busquier **M** et al, 1997).

3.1.3 Aceclofenac and Naproxen

In experimental studies, aceclofenac was superior in potency than naproxen, but its lower incidence of gastrointestinal side effects resulted in a therapeutic index which was higher than that of naproxen (Grau M et al, 1991).

Study shows that aceclofenac causes fewer side effects than naproxen (Table 4). So aceclofenac can be a good alternate of naproxen (Kornasoff D, Frerick H, Bowdler J, Montull E, 1997).

	Aceclofenac	Naproxen
Number of adverse effects		
Subjects	24 (12.6%)	30 (16.3%)
Events	34	43

Table 4: Adverse events possibly related to study treatment. Number (%) of subjects (Kornasoff D et al, 1997)

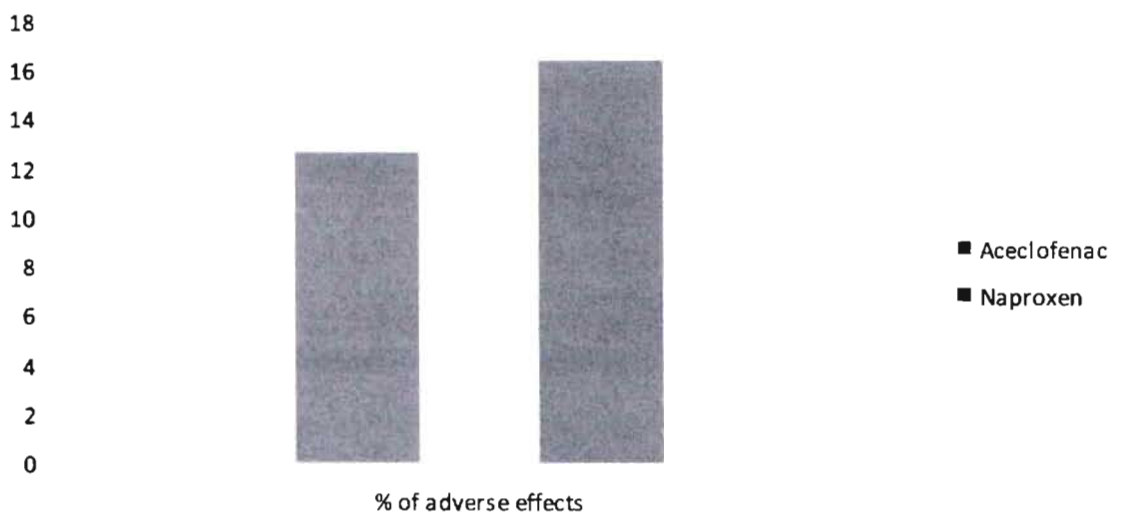
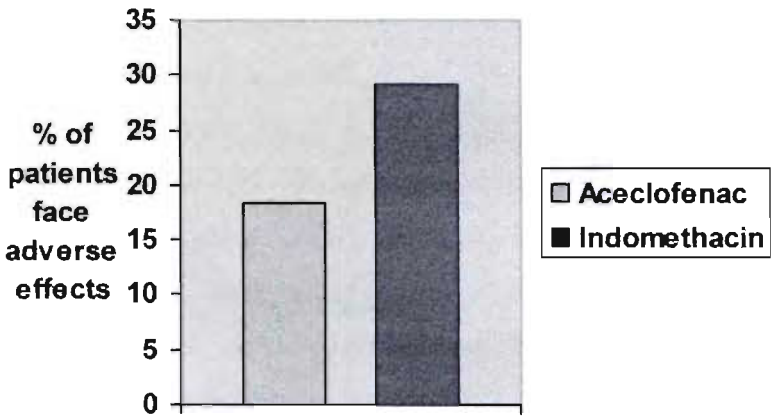


Figure: Percentages of adverse effects of Aceclofenac and Naproxen

3.1.4 Aceclofenac Vs Indomethacin

Among the 109 aceclofenac-treated patients, 26 incidents of adverse effects due to the drug were noted in 20 patients (18.4%). Sixty-four incidents of adverse events were documented in 32 (29.1%) of the 110 patients treated with indomethacin. The most common adverse events reported during treatment with aceclofenac were heartburn (four patients) and vertigo (three patients) which are not very serious (Kornasoff D, Maisenbache J, Bowdler J, Raber A, 1996)



Without this indomethacin inhibited the synthesis of cartilage matrix components, whereas aceclofenac increased matrix synthesis and protected the chondrocytes against apoptosis (Ding C, 2002; Dingle JT, 1999; & Henroitin Y, Reginster JY, 1999).

3.1.5 Aceclofenac Vs Ketoprofen

During a study 11 patients in the ketoprofen group and 2 patients in the aceclofenac group withdrew from the study because of adverse events (Martin-Mola J, Gij6n-Bafios J, Ansoleaga JJ, 1995). Most commonly observed adverse effects were gastric irritation. This proves that aceclofenac is a safer option than Ketoprofen.

4. Result and Conclusion

4.1 Why aceclofenac is superior to other NSAIDs for the pain management of OA.

We have already discussed and done comparison between Aceclofenac and other five NSAIDs, which are most commonly used to manage the pain of osteoarthritis. In OA articular cartilage is lost gradually and which is very difficult to regenerate again. The main advantages of Aceclofenac over other NSAIDs is that it doesn't remove pain only but also increase matrix synthesis and protected the chondrocytes against apoptosis (Ding C, 2002; Dingle JT, 1999; & Henroitin Y, Reginster JY, 1999), where other NSAIDs don't do it , even sometimes decrease it (like indomethacin). Ultimately it not only removes pain (symptomatic relief) but also improve the disease condition. So we can call aceclofenac a unique NSAID for the treatment of OA.

We have already mentioned that Age is the most powerful risk factor for osteoarthritis (Brandt KD et al, 1998). Osteoarthritis rarely occurs before the age of 40, but by the age of 75, at least 85% of the population has either clinical or radiographic evidence of osteoarthritis (Sack KE, 1995). It is estimated that 80% of the population will have radiographic evidence of OA by age 65, although only 60% of those will show symptoms (Green GA, 2001). Its prevalence after the age of 65 is about 60% in men and 70% in women (Sarzi-Puttini P et al, 2005). So we have to consider the elderly patients very carefully before manufacturing and prescribing a drug for osteoarthritis.

Adverse drug reactions (ADRs), including interactions, in older people are a common cause of admission to hospital (Cunningham G et al, 1997; & Mannesse CK et al, 1997), are common in elderly patients in hospital (Mannesse CK et al, 2000), and are an important cause of morbidity and death. So, we have to find out a drug which have very few adverse effects and suitable for the elderly patients.

The most commonly observed an adverse effect of NSAIDs is developing significant injury to the upper gastrointestinal (GI) tract (Macdonald TM et al, 1997).). NSAIDs can increase the risk of peptic ulcer by around four-fold in patients aged ≥ 65 years (Griffin MR et al, 1991). NSAID-related ulcer complications are estimated to lead to 107000 hospitalizations and 16500

deaths yearly (Wolfe MM, Lichtenstein DR, Singh G, 1999). This is a great risk for the health of elderly people.

Aceclofenac reduce this problem since it appears to be particularly well tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects. This good tolerability profile results in a reduced withdrawal rate and greater compliance with treatment (Legrand E,2004 & Walker G,1999). It is seen that Aceclofenac causes less gastric irritation than Diclofenac (Pareek A et al, 2006), Piroxicam (Perez Busquier M et al, 1997), Naproxen (Kornasoff D et al, 1997), Indomethacin (Kornasoff D, Maisenbache J, Bowdler J, Raber A, 1996) and Ketoprofen (Martin-Mola J, Gij6n-Bafios J, Ansoleaga JJ, 1995).

Beside of this Aceclofenac is also is more effective than Diclofenac (Pareek A et al, 2006), Piroxicam (Perez Busquier M et al, 1997), Indomethacin (Kornasoff D, Maisenbache J, Bowdler J. Raber A, 1996) and Ketoprofen (Martin-Mola J, Gij6n-Bafios J, Ansoleaga JJ, 1995) in terms of pain removing.

So, it can be said that Aceclofenac is the best option for the pain management of Osteoarthritis.

4.2 Limitation of the study

There are some limitations of this study which was not possible to overcome due to lack of time. Details study of therapeutic uses of aceclofenac is not done, only its efficacy in OA is studied, though it is very much possible to use it in other painful disease. A market study could be done on aceclofenac and its main competitors to understand its market situation. An attempt to make a suitable marketing strategy for aceclofenac could be taken.

4.3 Recommendation

Aceclofenac is very good NSAIDs and deserves a details study of therapeutic efficacy so that physician can prescribe this drug for various other physical problems. A marketing strategy can be done in future for this drug.

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Aceclofenac

The most tolerable NSAID to treat osteoarthritis

Not only remove pain but also..... **regenerate cartilage**.

Osteoarthritis in Bangladesh

Like all over the world OA is also very common in Bangladesh

About 30.4% male and 32.8% female Bangladeshi of age 55 or above have got OA.[1]

About 50% victims of OA are people like rickshaw puller, domestic servant or labors engaged in earth digging[1], who can not afford the costly treatment likely knee transplantation.

For this kind of people pain management is very much necessary to maintain their normal life

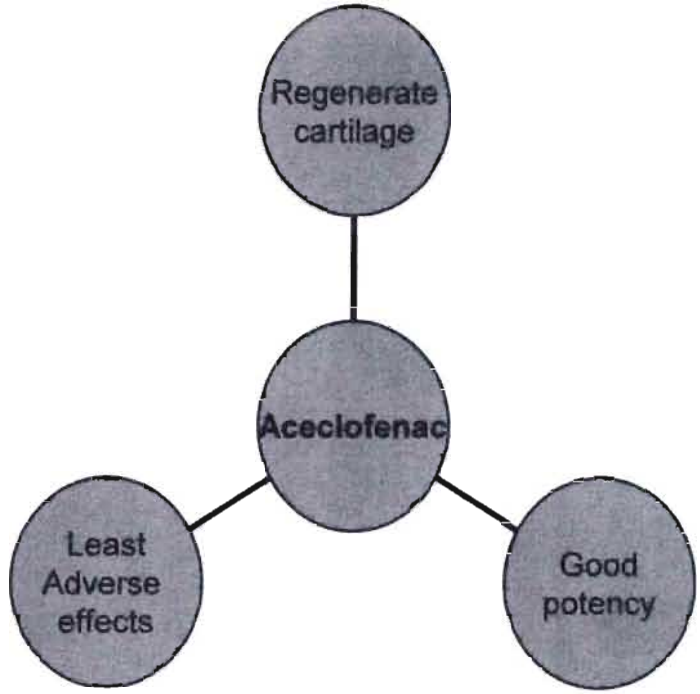
Why Aceclofenac is different.....

No other NSAIDs available in Bangladesh **regenerate cartilage matrix**... except this.[2]

It is useful for the long term use because-

It causes **least adverse effects** among the NSAIDs...

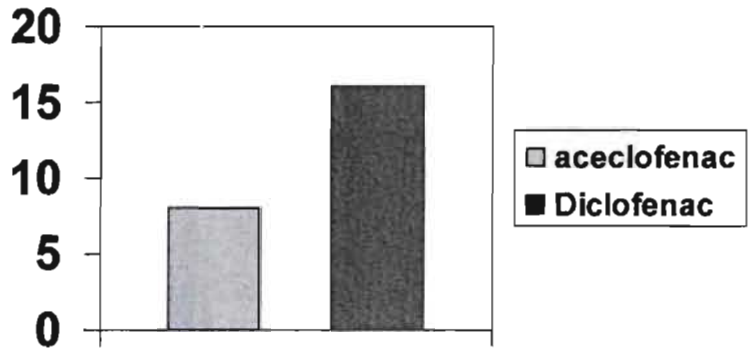
But having **good potency**



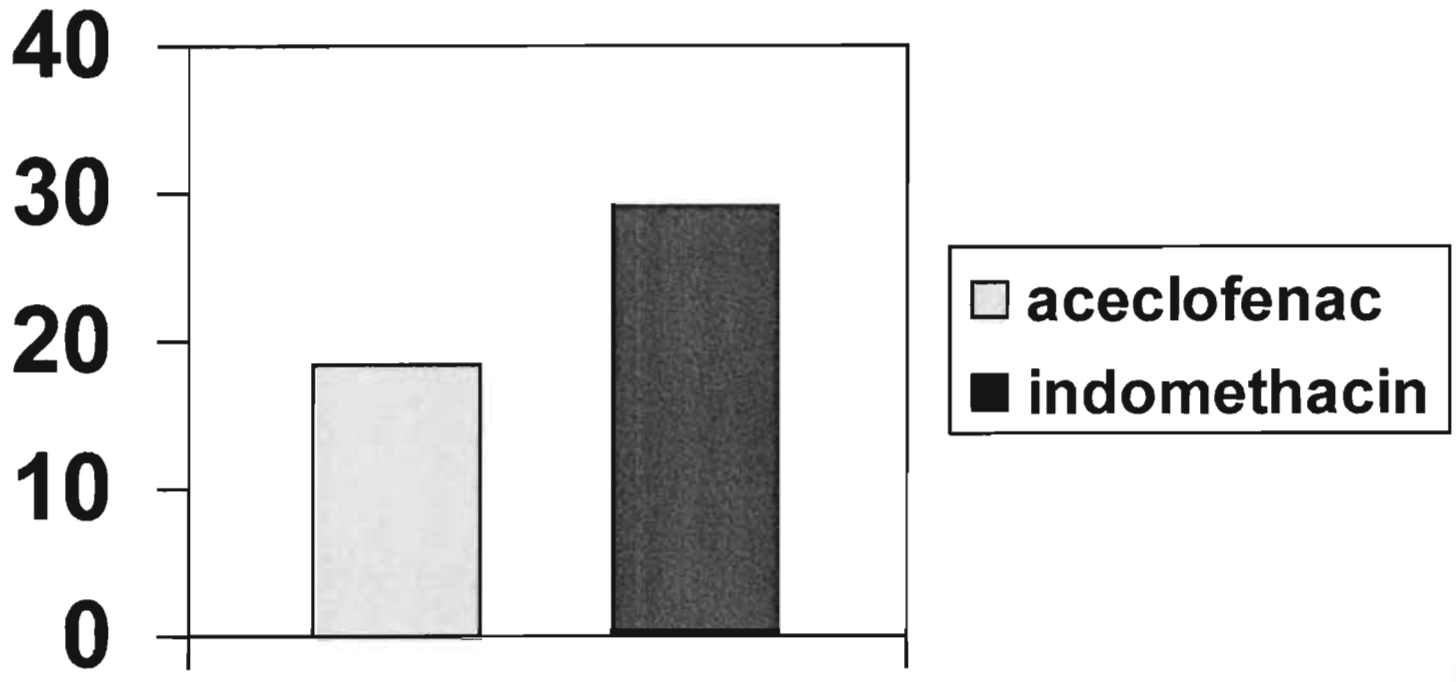
Importance of cartilage generation

- In OA articular cartilage is gradually lost.
- Aceclofenac increases the matrix synthesis.
- It also helps to protect the chondrocytes from apoptosis.
- So cartilage can be regenerate.
- In this way aceclofenac not only remove the pain of OA but also improve the disease condition.

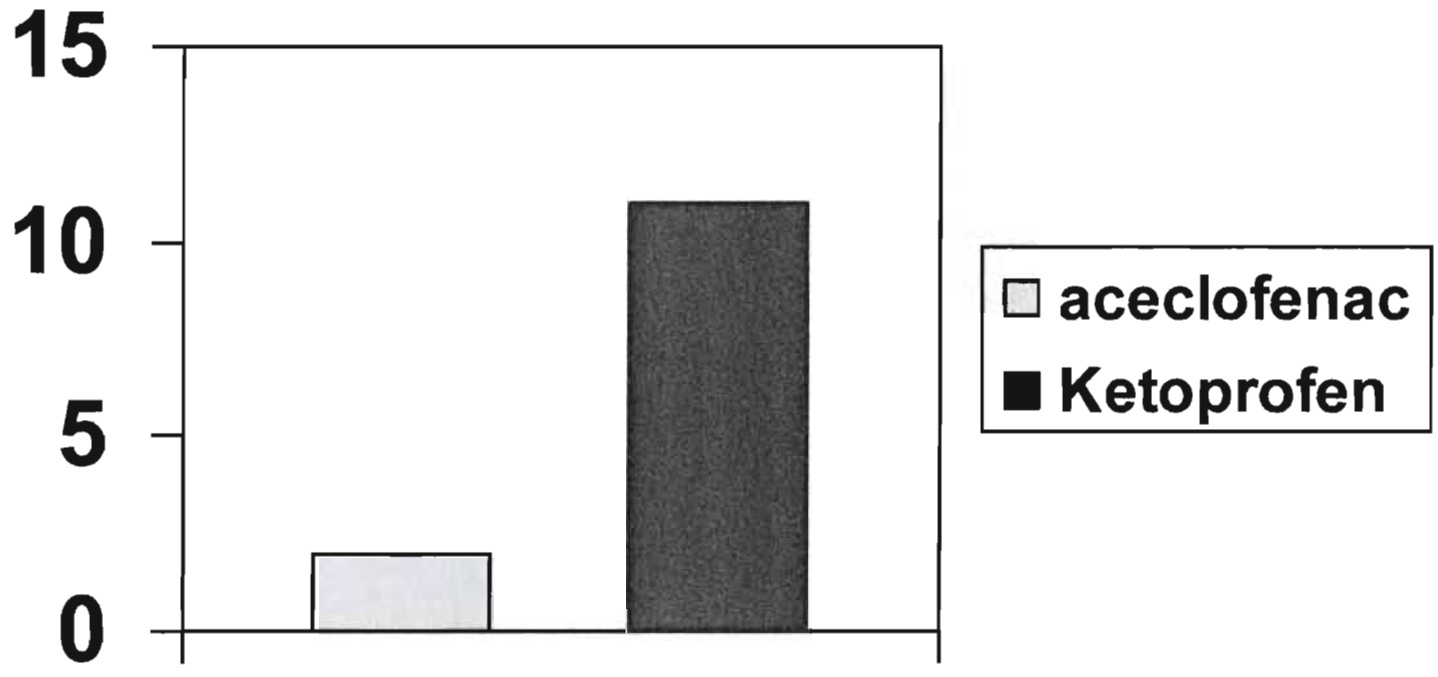
GIT adversre effects observed in Aceclofenac and Diclofenac.[3]



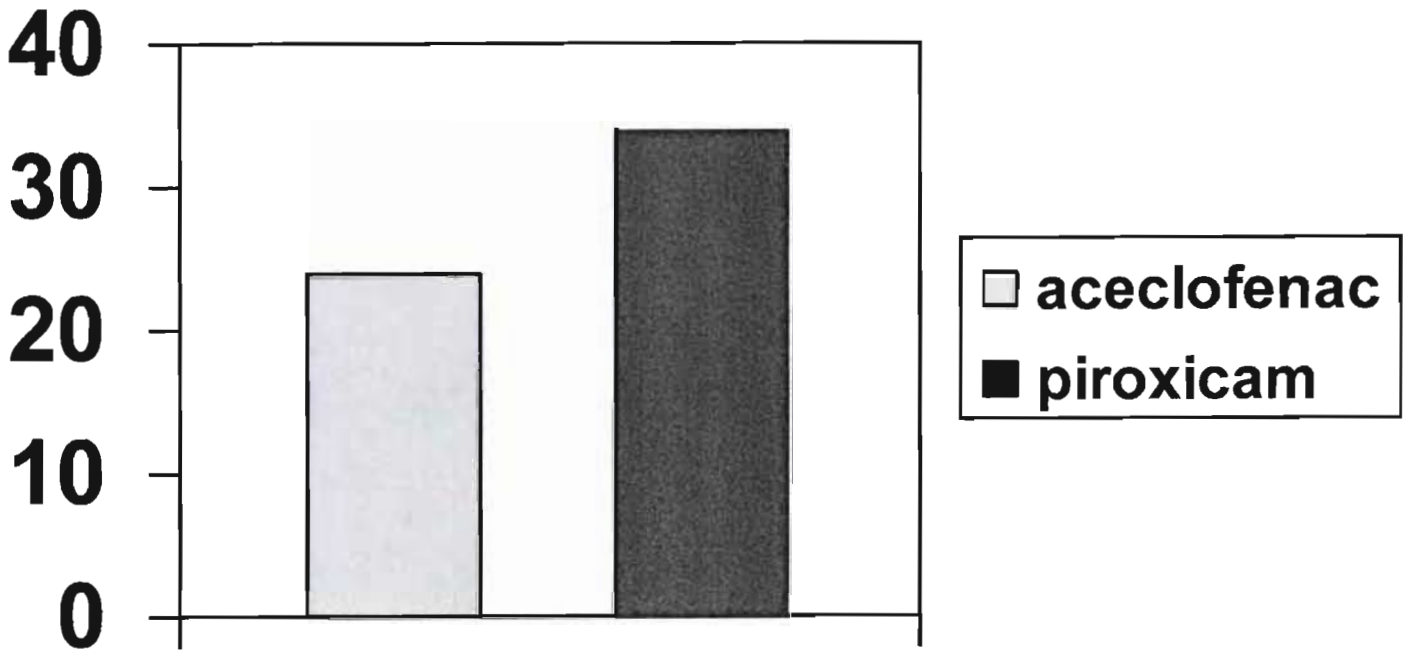
GIT adversre effects observed in Aceclofenac and Indomethacin.[4]



GIT adversre effects observed in Aceclofenac and Ketoprofen.[5]



GIT adversre effects observed in Aceclofenac and Piroxicam.[6]



Main Features

- Regenerate cartilage matrix.[2]
- Reduce the apoptosis of chondrocytes.[2]
- Most tolerable NSAID with least GIT irritation.
- Good efficacy.
- Can be used for long period of time.

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