Comparison of Aceclofenac with Piroxicam in the Treatment of Osteoarthritis


Summary
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. The treatment period of two months was preceded by a washout period of one week duration. On completion of the study, patients in both aceclofenac and piroxicam-treated groups exhibited significant improvement in pain intensity and functional capacity of the affected knee, as represented by the Osteoarthritis Severity Index (OSI) (p < 0.0001 and p < 0.001 respectively). This was further substantiated following the patient's assessment of pain intensity using the Visual Analogue Scale (VAS), in which significant improvements were demonstrated at all time points for each treatment group (p < 0.001). Although both treatment groups showed a significant improvement in all investigator’s clinical assessments (functional exploration of the knee, knee flexion and extension (EXT)), there were no significant differences between the groups. There was, however, a more rapid improvement in knee flexion in the aceclofenac group after 15 days of treatment. Both aceclofenac and piroxicam were well tolerated by patients, the most commonly reported adverse events being gastrointestinal, although their incidence was low. Only 24 patients on aceclofenac, as opposed to 33 on piroxicam complained of dyspepsia, epigastralgia and pyrosis. While 7 patients in each group were withdrawn because of adverse events, only one patient with piroxicam was withdrawn because of severe upper gastrointestinal bleeding. Twice as many reports of fecal blood loss were made in the piroxicam group in comparison to the aceclofenac group. In summary, 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.

Key words Aceclofenac, NSAID, Piroxicam, Osteoarthritis, Efficacy, Safety

INTRODUCTION

Osteoarthritis (OA) is a frequent cause of pain and disability in joints (1) and uniformly accompanies ageing. The natural cause of this chronic condition is not well understood (2). Generally, it has an insidious onset and a variable relationship of symptoms and functional impairment with slowly evolving pathologic and radiographic changes. The disease may or may not be associated with inflammation (3).
Nonsteroidal 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, although their use in this condition has sparked controversy (4). In terms of pain relief, a recent study found that 75% of patients ranked the NSAIDs as good or excellent as did 45% of the physicians (5). An indication of the efficacy of these drugs is the high number of prescriptions written annually. In 1986, over 100 million prescriptions (4.5%) for NSAIDs (excluding aspirin) were dispensed in the USA (6), where the most common indication for use comprised arthritic pain syndromes and osteoarthritis. Despite their efficacy, the threat of serious adverse effects poses a major concern for chronic NSAID users. Adverse renal effects (7) and effects on bone and cartilage metabolism (8) are counted among worrisome NSAID-induced side effects, but serious gastro-intestinal complications represent the greatest threat to long-term NSAID therapy (9). Nevertheless numerous clinical trials have demonstrated the efficacy of NSAIDs in pain relief in OA patients (10, 11).

Aceclofenac, a novel NSAID, has recently been described as exhibiting good anti-inflammatory and analgesic efficacy in animal experimental models while maintaining better gastric tolerance as compared to other NSAIDS, such as indomethacin and diclofenac (12). Indeed 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 (13).

Short term clinical studies have demonstrated the efficacy of aceclofenac in pain relief following dental extraction and episiotomy (14,15), and in the chronic treatment of rheumatoid arthritis (16) and osteoarthritis (17, 18). In some comparative studies, there was a tendency for aceclofenac to be better tolerated than diclofenac (17, 19), with fewer patients being withdrawn from treatment due to gastric intolerance.

This paper describes a short term, double-blind, parallel group evaluation of the safety and efficacy of aceclofenac compared to an established NSAID (piroxicam) in patients with OA of the knee.

**PATIENTS AND METHODS**

**Patients and study design**

A double-blind, randomised, comparative, parallel group study was undertaken in 12 centres throughout Spain to investigate the efficacy and safety of aceclofenac (100 mg bd) in comparison with piroxicam (20 mg once daily) in patients with osteoarthritis of the knee joint. The treatment period was preceded by a washout period of a minimum of one week duration. The duration of treatment was 2 months, with control visits at selection, on randomization to treatment, at 15 days, 1 month and 2 months.

Patients of either sex (age 40-80 years) with confirmed radiologic and symptomatic OA of the knee were considered eligible for the study. OA was diagnosed on combined radiological (20) and clinical grounds which fulfilled all criteria established by the World Health Organisation (WHO) for the diagnosis of OA. Based on these diagnoses, active disease was defined by the following criteria: limitation due to pain on movement and/or tenderness at the extremes of knee extension and flexion; narrowing of the medial femurotibial space in standing position; osteophytis and/or subchondral osteocondensation and/or cyst. Eligible patients had to have a pain score of at least 4 cm on the Visual Analogue Scale (scale of 0-10 cm).

The exclusion criteria for the trial included: history of renal, hepatic, cardiovascular or connective tissue disease, diabetes or recent gastrointestinal or haematological disease, clinically significant non-OA arthropathies; a life-expectancy of < 2 years; recent haemorrhage or alcohol or drug abuse; recent febrile viral infection or major surgery; treatment with anti-coagulant or oral hypoglycaemic drugs or other drug which could interfere with the test medication; previous hypersensitivity or other reaction to any NSAID treatment with an investigational drug; intra-articular or parenteral steroids in the previous 2 months; pregnant or nursing females; women of child-bearing age not using adequate contraception.

Individual ethical committee approval was obtained from all participating hospital clinical trials committees and from the Minister of Health in Spain. The study followed the principles of Good Clinical Practice and was conducted in accordance with the declaration of Helsinki and Tokyo Guidelines for Ethics in Research, as well as the Spanish legislation on clinical trials. Written informed consent was obtained from all eligible patients prior to entry.

Based on previous comparative studies of aceclofenac with NSAIDs, a sample size of 111 patients per treatment group was considered sufficient to detect a difference between groups in the Osteoarthritis Severity Index of 21% at the 5% significance level with a power of 90%. Allowing for a 20% drop-out rate during the trial, a sample size of 139 per treatment group was considered appropriate.