GLOBAL ANALYSIS OF GASTROINTESTINAL SAFETY OF A NEW NSAID, MELOXICAM

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ABSTRACT


Meloxicam is a new preferential cyclo-oxygenase-2 inhibitor. This paper presents a global safety analysis of data from meloxicam clinical studies, focusing on gastrointestinal (GI) adverse events. Meloxicam 7.5 mg and 15 mg (n=893 and 3282) were compared with piroxicam 20 mg (n=906), diclofenac 100 mg slow release (n=324) and naproxen 750-1000 mg (n=243). With respect to all GI adverse events, meloxicam 7.5 mg and 15 mg were significantly superior to all comparators in a pooled analysis of double-blind studies in rheumatoid arthritis and osteoarthritis. When examining non-serious GI events, severe GI events, discontinuations due to GI events, dyspepsia, abdominal pain and upper GI events, both meloxicam doses were significantly superior to comparator NSAIDs in most cases. Where statistical significance was not demonstrated, there was generally a clear trend in favour of meloxicam. With respect to upper GI perforations, ulcerations and bleedings, the most serious of NSAID-associated side-effects, meloxicam was better tolerated than the comparators, reaching statistical significance for piroxicam and naproxen. Meloxicam's improved GI safety profile is likely to be due to its preferential inhibition of inducible cyclo-oxygenase-2 relative to constitutive cyclo-oxygenase-1.

Keywords: cyclooxygenase, gastrointestinal, meloxicam, NSAID, safety

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common pharmacological treatment for rheumatic disease; their use, however, is limited by the associated incidence of side-effects. Gastrointestinal (GI) toxicity represents the most serious health hazard of NSAIDs [1].

It has been estimated that 34-46% of patients receiving NSAIDs will experience some GI side-effect [2]. Upper abdominal pain or indigestion are the main complaints [3,4]. Twenty-nine percent of the patients on NSAIDs had experienced heartburn, indigestion or sour stomach at least once within the previous week [5]. These gastrointestinal symptomatic complaints are important as they interfere with compliance and continuing use of NSAIDs.

The most feared adverse effects of therapy with NSAID are gastrointestinal ulceration [6,7] and associated serious complications, i.e. haemorrhage [8-10], perforation [10], and death [11]. Large case-control studies have examined the risk of GI
performation and bleeding with different NSAIDs and in different patient groups [8,10]. The studies showed that there are differences in GI toxicity between NSAIDs, and the risk increases with higher doses. The risk is greatest in the elderly, patients with a previous history of such events and those treated with concomitant corticosteroids [10,12,13].

It is well established that the inhibition of prostaglandin (PG) synthesis, mediated by the cyclo-oxygenase (COX) enzyme, is responsible for both the anti-inflammatory actions and ulcerogenic potential of NSAIDs [14]. However, it has not been clear why there are differences between agents in terms of their potential to cause GI side-effects, whilst displaying similar anti-inflammatory potency. The discovery of two isoforms of the COX enzyme, COX-1 and COX-2 [15] has gone some way towards explaining this [16].

Recent findings have suggested that the anti-inflammatory actions of NSAIDs are primarily mediated through the inhibition of the inducible enzyme COX-2, whereas unwanted adverse effects, such as gastric and renal toxicity, are due to inhibition of the constitutive enzyme, COX-1 [16].

Meloxicam is a new NSAID which preferentially inhibits COX-2 relative to COX-1, as consistently demonstrated in a number of models [17–19]. In animal studies, this mode of action appears to be reflected in a favourable GI tolerability profile [20].

PATIENTS AND METHODS

Clinical studies with meloxicam 7.5 mg and 15 mg once daily have been conducted in healthy volunteers, patients with rheumatoid arthritis (RA), osteoarthritis (OA) and other rheumatoid diseases. In order to make an overall assessment of the safety of meloxicam, data from individual clinical studies have been pooled. In addition, data from double-blind studies in RA and OA with active comparators have been analysed separately. Table 1 gives the number of subjects who received meloxicam 7.5 mg, 15 mg or the active comparators, piroxicam 20 mg, diclofenac 100 mg SR and naproxen 750 mg or 1000 mg; duration of patient exposure to the study drugs and the type of study are also shown. Table 2 details patient characteristics and disease suffered. For the purposes of the analysis, data from patients receiving naproxen 750 mg or 1000 mg were combined. Comparator agents were chosen to reflect current practice in the treatment of arthritic disease with NSAIDs and were considered to be of equivalent therapeutic potency to meloxicam 7.5 mg and 15 mg.

In phase I studies 168 healthy volunteers received single or multiple oral, rectal, intravenous or intramuscular formulations of meloxicam 7.5 mg or 15 mg. The clinical trials programme included 34 phase II/III studies in 4007 patients. Early dose-ranging studies conducted in patients with various rheumatoid diseases were open-label, non-controlled pilot studies.

The safety and efficacy of meloxicam 7.5 mg and 15 mg oral formulations (tablets or capsules) were evaluated in seven clinical trials in 1820 patients with OA and in 6 studies in 1889 patients with RA. The safety data from the active comparators used in these studies are included in this overall safety analysis.