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SAFETY AND EFFICACY OF A NOVEL PIROXICAM-BETA-CYCLODEXTRIN COMPLEX:

RESULTS OF AN OPEN-LABELED, MULTICENTER, PHASE-IV-STUDY IN PATIENTS WITH INFLAMMATORY AND DEGENERATIVE JOINT OR INFLAMMATORY DISEASES

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SUMMARY

To demonstrate a superior safety profile, the efficacy and tolerability of a novel piroxicam-beta-cyclodextrin complex was assessed in 9,117 outpatients suffering from inflammatory or degenerative joint diseases.
The study was conducted as an open-label, multicenter trial by rheumatologists, orthopedists and general practitioners in private practice. Outpatients eligible for the study received a daily morning dose of 20 mg piroxicam-beta-cyclodextrin for at least 50 days. Visits were performed on day 1, 7-10, and 50. Primary efficacy variables were the overall assessment of pain on a 4-point visual analogue pain scale and the mobility impairment. Safety was assessed by adverse events reporting.
Efficacy data on 9,012 patients showed an overall improvement in 88,7% of the cases.
Safety data of 9,105 patients were evaluable. Adverse events accounted for 13.5%, including 9% gastrointestinal side effects.
Compared to data from the literature, the new NSAID is as active as established preparations but our findings suggest a lower very good safety profile.

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) play a key role to suppress inflammatory conditions and to relieve pain in disorders collectively labeled as rheumatic diseases. Most of these drugs are organic acids with a relatively low pK. This property ensures relatively high concentrations of the active drugs in inflamed tissues, because the pH is lower there. A more recent group of NSAIDs are the oxicams, with piroxicam being in most widespread use because it allows, in many cases, an effective treatment by a single daily dose. Both piroxicam and all other NSAIDs commercially available so far are potent inhibitors of cyclooxygenase 1 and the inducible cyclooxygenase 2, which is expressed mainly in inflamed tissues. This non-specific inhibition leads to an overall suppression of prostaglandins, which participate in the development of the inflammatory response. On the other hand, there is a basic production of prostaglandins to maintain many regulatory processes[6] especially in the kidneys (supporting renal blood flow, water and sodium excretion) and the gastric mucosa, where they suppress gastric acid secretion and maintain the gastric mucosal barrier, thus providing an antiulcerative effect. Because of this mechanism of action, the beneficial effects and the adverse effects of NSAIDs are inevitably linked as long as true specific inhibitors of the inducible cyclooxygenase 2 are not available. Gastrointestinal adverse effects, ranging from hyperemia and diffuse gastritis to erosions and

penetrating ulcers, are a major concern (especially in elderly patients), if NSAIDs have to be given for a long period. Additionally, sparingly soluble NSAIDs like piroxicam may cause local breech of the mucosal barrier, which is due to a local concentration effect resulting in back-diffussion of hydrogen ions, inflammation and bleeding.

Therefore, the development of safer NSAIDs is a crucial issue. New specific blockers of the inducible isoenzyme cyclooxygenase 2, which provides the prostaglandins acting as mediators of inflammation, are certainly a hope not met so far.[16] Another possibility is to improve the solubility and absorption rate of a NSAID, thus preventing local irritation.

Cyclodextrins are cyclic oligosaccacharides which can harbour a second molecule as a host in their internal cavity. As the outer surface is hydrophilic and the internal area hydrophobic an iclusion complex can be formed with suitable host molecules, e.g. piroxicam, which shows a greatly improved solubilty in water and is stable due to van der Waals bonds.[2,5]

Manufacturing of such cyclodextrin complex compounds involves an innovative pharmaceutical technology. Attempts have been made with fenamate-cyclodextrin,[11] flurbiprofen-beta-cyclodextrin[13] and indometacin-beta-cyclodextrin.[12] The only preparation which reached the market so far is piroxicam-beta-cyclodextrin complex (Chiesi SpA, Italy). In the duodenum, the complex will dissociate to form an equilibrium according to its specific dissociation constant. While beta-cyclodextrin undergoes degradation by bacterial amylases (to form glucose in the large intestin[5]), the free piroxicam molecules will be quickly removed from the equilibrium by resorption causing further dissociation. The concentration of free piroxicam as well as mucosal contact remains always low and fewer local gastrointestinal adverse effects should be expected.

The aim of this phase-IV-study was to evaluate the frequency and severity of adverse events as well as the efficacy of piroxicam-beta-cyclodextrin in several thousand rheumatic patients and to verify in clinical practice the theoretical advantages of this new NSAID.

METHODS

One thousand nine hundred and thirteen rheumatologists, orthopedists and general practitioners in private practice recruited a total of 9,117 rheumatic patients requiring antiinflammatory treatment. All patients were treated with one dose of piroxicam-beta-cyclodextrin equivalent to 20 mg piroxicam, for 50 days. Drug intake took place in the morning after breakfast.

All patients eligible for the study had inflammatory, rheumatic or degenerative disease with pain and impaired mobility in their joints or the spinal column. Patients aged 18 to 75 years, of both sexes, were admitted to the study.

Patients with a history of inflammatory bowel diseases, peptic ulcer disease, known allergies to NSAIDs, abnormal blood count, impaired renal, hepatic, respiratory or cardiac functions were excluded. Further exclusion criteria were previous gastrointestinal surgery, malabsorption, treatment with lithium salts, oral anticoagulants or other NSAIDs. Finally, pregnant women, nursing mothers and women without adequate contraception were also excluded.

TABLE - Adverse Events.

Piroxicam-Beta-Cyclodextrin Complex
Total No. of Patients, n=9,105

	n	*100%*
Gi-Tract	818	9
Others	541	5,9
No Side Effects	7894	86,7

After the patient gave their informed written consent, a detailed history was recoded, taking into account the exclusion criteria as well as nicotine and alcohol consumption.
The patients' examination comprised records of height, body weight, blood pressure and pulse rate.
Furthermore, the type of the rheumatic disease, the localization and intensity of pain, and finally, the motion limitation were assessed.
Laboratory test were performed to confirm the diagnosis in case of an inflammatory disease. Visits for (re)examination took place on day 1, between day 7 and 10, and on day 50.
The patient as well as the physician evaluated the efficacy of the treatment by the assessment of the parameters "intensity of pain" and "limitation of motion." The physician employed a 4-point visual analogue score. In the first week of treatment, the patient recorded his complaints, morning stiffness and pain by means of a similar score. Efficacy was defined as a relief of pain and an improvement of limation of motion. Efficacy data of all patients who had taken the study medication up to the second visit were considered evaluable.
The assessment of safety was based on all recorded medical events including laboratory data. As long as no clinically relevant events could be detected, the treatment was considered to be safe. Eligible for safety analysis were all patients who had taken at least one dose of the study medication. The random sample size of 9,117 patients allowed de detection of even infrequent side effects (1:1,000) with a high probability (>99%); in case of highly infrequent adverse events (1:2,500), the probability was 97.4%.
Statistical analysis of the primary variables - pain intensity, limitations of motion and incidence of adverse events - was performed by the χ^2-test. The time required until relief of pain became perceivable was assessed according to the method of Kaplan and Meier.

RESULTS

Nine thousand one hundred and seventeen patients were recruited for this study. Data of 9,105 patients were evaluable for safety while efficacy was assessed on 9,012 patients. The average age of the participants was 56 years. 41.6% were female and 58.4% were male. Overall 22.8% were smokers.
Four thousand nine hundred and ninety-one (56%) patients had degenerative diseases and 1,640 (18,5%) suffered from inflammatory diseases. The main disorders diagnosed were gonarthrosis (18%), polyarthritis (12.1%), coxarthrosis (11.4%), spondyloarthropathy (8.7%).
Five thousand six hundred and four patients (62.6%) had been treated with NSAIDs prior to this study; 1,097 (26.7%) had experienced gastrointestinal adverse effects during their former treatments.
6,688 patients (74.7%) completed the study (treatment course 50 days). Two thousand two hundred and seventy patients were withdrawn because of relief of symptoms (52.9%), adverse events (23.4%) and poor efficacy (15.1%).
Concerning the parameter "pain," 7,036 patients (78.1%) reported a relief at the first visit and further improvement was seen in the second visit (7,994

patients; 88.7%). Improved limitation of motion was seen in 47% of patients at the first and in 66% at the second visit. Safety analysis revealed that 13.5% of the study population developed adverse effects, but only 0.2% were serious. Seven thousand eight hundred and ninety-four (86.7%) of the participants did not complain of side effects. Gastrointestinal adverse effects were most frequently reported (818 patients, 9%), followed by side effects affecting the CNS (3.3%). Allergic reactions (skin eruptions, pruritus) were observed in 99 patients (1.1%). Serious medical events (gastrointestinal bleedings) occurred in 13 patients, additional risk factors could be found in 12 of them: 10 reported elevated consumption of alcohol; two were heavy smokers.

A duodenal ulcer developed in 3 patients and a gastric ulcer was found in two patients.

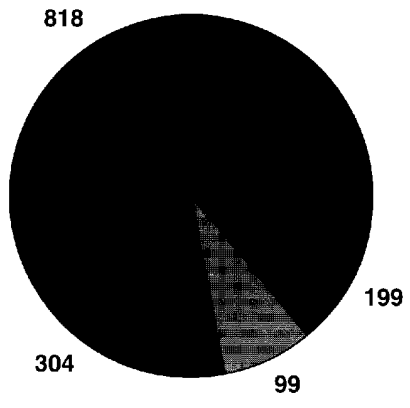
Discussion

All currently available NSAIDs are nonspecific inhibitors of prostaglandin synthesis, this leads to a decrease of prostanglandins and leucotriens in inflamed tissues, where they act as mediators of inflammation. Simultaneously, prostaglandin activity exerting important muliple regulatory and protective functions is also inhibited. Especially the protection of the gastrointestinal mucosa is important: prostaglandin stimulate the secretion of mucus and hydrogencarbonate, regulate perfusion and regeneration of the mucosa. They are key substances in maintaining the mucosal barrier[1,9] and the inhibition of their synthesis in the mucosa triggers unwanted gastrointestinal effects of NSAIDs.

The development of new NSAIDs is aimed on the reduction of gastrointestinal adverse effects, but other aspects of the action of NSAIDs, e.g. the inhibitory effect of leucocyte migration and connective tissue metabolism and their activity as immunemodulators should be considered.[8,17] Furthermore, an optimal NSAID should provide rapid onset and long-lasting pain relief. As compliance is a crucial issue[7] mainly in elderly patients, the pharmacokinetic properties should allow a once-daily administration.

FIGURE - Adverse events

Piroxicam-Beta-Cyclodextrin Complex



Total No. of Patients, n=9.105

■ GI tract ■ CNS ■ Allergies ■ Others

The piroxicam-beta-cyclodextrim complex tested in this study seems to offer these benefits. It is as potent as standard piroxicam preparations[4,14,18] and provides a significantly more rapid onset of pain relief.

This study, on 9,105 patients evaluable for safety, adverse events were reported by 13.5% in total while GI adverse events were experienced by 9% of patients. These findings are in agreement with former results reported by Ambanelli et al.[3] who found a rate of overall side effects of 11% with the

cyclodextrin complex (compared to 23% with an ordinary piroxicam preparation). Further results support the advantageous safety profile of the study medication as the incidence of gastrointestinal side effects is 50% lower than in similar studies[10,14,15] with standard piroxicam.

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