CLINICAL STUDY

Efficacy and tolerability of piroxicam-β-cyclodextrin in the outpatient management of chronic back pain

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Abstract

Background: **Piroxicam-beta-cyclodextrin (PBC) is the first nonsteroidal anti-inflammatory drug (NSAID), in which the active substance is complexed with the cyclic oligosaccharide cyclodextrin, which acts as an artificial receptor. This complex allows single molecules of the NSAID to be released adjacent to the gastrointestinal mucosa, instead of crystals. Since the piroxicam is immediately bioavailable in this formulation, the onset of action is similar to that of a parenteral drug. Since the time contact with gastric mucosa is reduced, the risk of direct-contact gastric irritation is also reduced. There is good evidence that PBC is beneficial in managing acute non-specific back pain (BP) but sufficient evidence on chronic BP is lacking.**

Methods: **Thirty-one eligible patients aged 18–85 years, resistant to previous therapy with different NSAIDs, were treated with PBC 20 mg once daily in a 40-day open-label noncomparative study. The patients experienced chronic BP defined as pain between the occipital region and gluteal fold, lasting for at least 6 weeks but not more than 6 months. Efficacy was assessed by changes in pain intensity, paravertebral tonus, functional impairment and morning stiffness using a 4-point numerical rating scale. Patients also self-assessed nocturnal and diurnal pain using the visual analogue scale. Tolerability was assessed by adverse events and routine laboratory evaluations. Global assessment of efficacy and tolerability by physician and patients was performed at the last visit.**

Results: **Using intention-to-treat analysis, all efficacy assessments demonstrated statistically significant improvements over baseline at each follow-up. 90.3 % of the patients evaluated the efficacy of PBC as improved or greatly improved, and investigators rated the treatment as improved or greatly improved in 87.1 % of patients. Remission was achieved in 19.3 % of the patients. Tolerability was also rated highly, with 83.9 % of the patients characterizing PBC treatment as good or very good, and the investigators rated the treatment as good or excellent in 87.1 % of the patients. Drug related adverse events were reported in 9.7 % of patients and prompted discontinuation of the study medication in 3.2 % of patients. No serious adverse events were reported.**

Conclusion: **These results suggest that the newly developed dosage form of piroxicam is effective and well tolerated in the treatment of patients with chronic BP. Thus, PBC, may be an important new treatment option in this condition.** ***(Tab. 3, Fig. 3, Ref. 36.)***

Key words: piroxicam-beta-cyclodextrin, nonsteroidal anti-inflammatory drug, back pain, clinical trial, host-guest chemistry.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medications worldwide and are widely used for the the treatment of back pain (BP). Recent evidence from the systematic review of 51 randomized and double-blind controlled trials confirmed that NSAIDs are effective for short-term symptomatic relief in patients with acute uncomplicated BP (1). However, NSAID treatment of chronic BP is less clear, and current controversy centers on the chronic use of nacrotic analges-

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ics for such patients (2). It has been suggested that certain inherent drawbacks of NSAIDs may contribute to their limited value in chronic musculoskeletal disorders (3).

Gastrointestinal (GI) adverse events (AE) are a major concern if NSAIDs have to be given for a long period of time, especially in elderly patients (4). Although most GI events of NSAID are not serious, such AE nevertheless reduce patient compliance with long-term therapy (5). Clinical trial evidence shows that specific COX-2 inhibitors reduce the risk of serious GI events by 50 % compared with conventional NSAIDs. However, NSAIDs induce GI injury due to a combination of prostanoid inhibition and local/topical toxic effects on GI mucosa (6). Unfortunately, various galenic formulations have failed to reduce local COX-independent mucosal injury (7).

As compliance is a crucial issue mainly in elderly patients, an optimal NSAID should provide rapid onset and long-lasting pain relief. However, NSAIDs with a fast onset of action also have a short elimination half-life, necessitating multiple daily dosages. Such agents are less suitable for use in chronic diseases since compliance may decrease as the number of daily doses increases. Moreover, with an increased exposure to drug, the risk of systemic and local AE also increases. Conversely, NSAIDs with a long half-life, such as piroxicam or slow release formulations have a delayed onset of action. Therefore, they are not optimal for rapid relief of symptoms, which is also required to prevent changes in the central nervous system that contribute to chronic pain (8).

The inherent drawbacks of NSAIDs mentioned above are largely attributable to low water solubility, since they are in a crystal form. In order to improve this solubility, formulations with reduced crystal size (e.g. dispersible formulations) have been developed. An extension of this rationale was the synthesis of piroxicam-beta-cyclodextrin (PBC) (Chiesi Farmaceutici S.p.A. Italy), which was a succesful example of the clinical application of „host-guest" chemistry in medicine (3). This Nobel prize winning technique provides the opportunity for the maximum size reduction of the crystals so as to obtain single molecules of the active drug (9).

In PBC, the piroxicam (guest) is attached to a cyclic oligosacharid beta-cyclodextrin (host), forming a highly soluble molecular complex instead of particles or crystals(10). Consequently, absorption of piroxicam from the GI tract is greatly increased and plasma concentrations of the active drug are reached faster than with conventional formulation (11, 12, 13). Clinically, this results in an earlier onset of analgesia, comparable with IM administration – generally within 30 min vs 2 to 4 hours from standard formulation (14). Thus, PBC has the potent analgesic properties of piroxicam, which were previously masked by its slow rate of absorption. Another potential benefit of PBC is improved GI tolerability attributable to reduced contact time with the gastric mucosa (15).

It is now well documented that PBC has a level of efficacy and of tolerability comparable or higher then traditional NSAIDs, when used both in acute and chronic rheumatic diseases (3, 16). This study was undertaken to provide physicians in the Slovak Republic the opportunity to gain practical experience with PBC and to judge patient and physicain satisfaction with this unique NSAID. We initially performed a pilot study in patients with chronic BP, because sufficient evidence on the effectiveness of NSAIDs in this condition, still is lacking (1).

Patients and methods

Patient population

Thirty-one patients of both sexes without age limitation were included in the study. They were drawn from the outpatient population of the four neurologic departments. The patients experienced back pain between the occipital region and gluteal fold, lasting during most days of the preceding 6 weeks, but not more than 6 months. The presence of at least three of the following symptoms were required: pain at rest, pain on movement, increased paravertebral tonus, pain on pressure, functional limitation, and morning stiffness. The study protocol was approved by the ethics committee at each center, and informed consent was obtained from all patients before they entered the study.

The exclusion criteria comprised: symptoms of intervertebral disk herniation with pressure on the nerve roots; former surgery, fracture or trauma in the area of the lumbar spine; current or past history of gastrointestinal diseases such as peptic ulcer, oesophagitis, inflammatory bowel diseases, or gastrointestinal symptoms such as severe dyspepsia, abdominal pain or haematemesis; severe cardiac, hepatic, renal, hematological or metabolic disease, cancer or mental disturbance; known allergy to piroxicam or other NSAID and any disease that could potentially interfere with the evaluation of safety or efficacy. Pregnant or lactating women and women with child-bearing potential were also excluded. NSAID, hypnotic drugs, and antidepressant agents were discontiuned for a minimum of one week before entry into the trial. No other NSAID or analgetic therapy was allowed with the exception of paracetamol and ASA up to 100 mg in cardiac or stroke prophylaxis.

Treatment plan and study design

An open-label, one group repeated-measures design was employed. One tablet of PBC (20 mg) was administered as a single dose in the morning. In elderly patients with a slower rate of elimination this dose could be reduced to half a tablet. The regular treatment duration was 40 days. In case of complete disappearance of symptoms the treatment could be terminated earlier. Further, the treatment could be interrupted for the following reasons: severe intolerance, clinical failure, non-compliance of the patient, and important medical reasons based on the clinician's judgement.

Measurements of Efficacy

Assessment of efficacy was made at each visit on days 0, 10, 20 and 40 during the treatment. The following parameters were evaluated by the physician using a 4-point numerical rating scale graded from 0 to 3: pain intensity (at rest, on active and passive movement and on pressure), paravertebral tonus, functional impairment and morning stiffness. Patients also self-assessed nocturnal and diurnal pain using the 100 mm non-interval visual

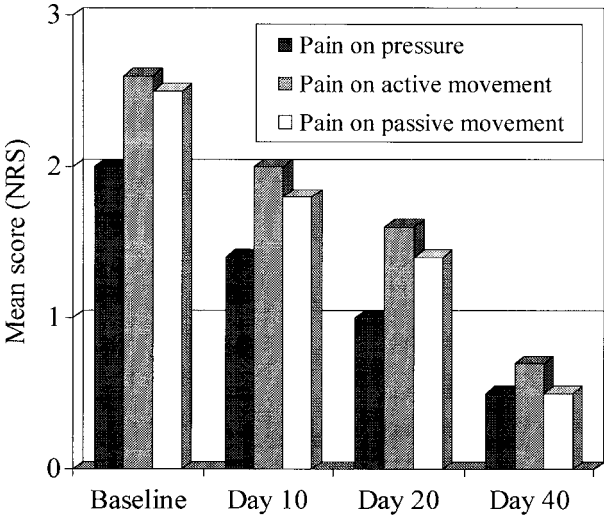

Fig. 1. Mean scores (numerical rating scale) for pain on pressure and pain on active and passive movement (p<0.001, Friedman test).

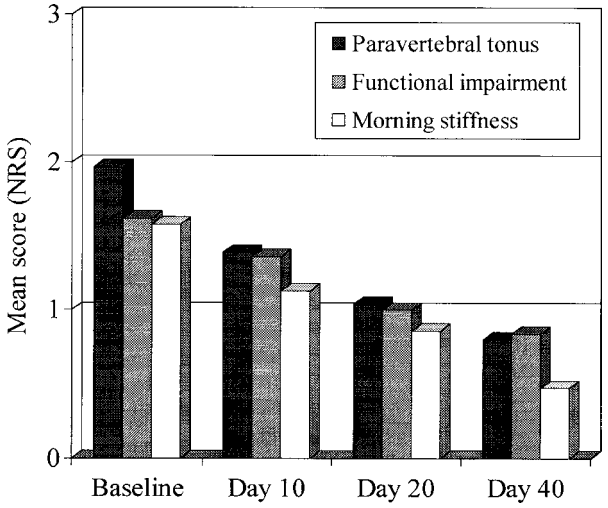

Fig. 2. Mean scores (numerical rating scale) for paravertebral tonus, functional impairment and morning stiffness (p<0.001, Friedman test).

analogue scale (VAS). Global assessment of efficacy by physician and patients was performed at the last visit.

Assessments of adverse events

Physical examinations, hematological and biochemical tests were performed and information about adverse events was collected at each visit during the study. Assessment of adverse events was made with regard to gastrointestinal tolerability (epigastric pain, nausea, vomiting) and general tolerability: development of any other symptom such as increased risk of bleeding, hypersensitivity reactions, oedema, dizzines, headache, sleep disturbances, changes in various liver and kidney function parameters, changes in haematopoesis and metabolic disturbances. Global assessment of tolerability by physician and patients was performed at the last visit.

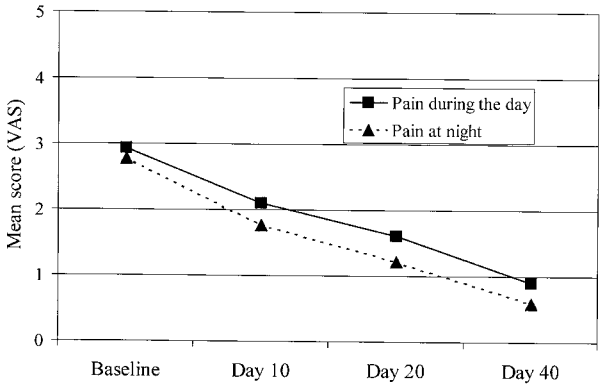

Fig. 3. Mean scores (visual analogue scale) for pain at night and during the day (p<0.001, Friedman test).

Statistical analysis

Data was analysed on an intention-to-treat basis, with the last value carried forward for missing values. Significance was tested with Friedman ANOVA by ranks, a nonparemetric measure for repeated-measures design to compare the overall magnitude of change during the treatment.

Results

Characteristics of the subjects

A total of 31 patients (7 M, 24 F, mean age 52 years) were enrolled in the study (Tab. 1). Premature termination before completing 40 days occured in 10 patients; due to relief of symptoms in 6, adverse events in 1 and poor efficacy in 3 (Tab. 2). Good compliance was maintained over the follow-up visits.

Efficacy

Treatment outcomes evaluated by physician are shown in Figs 1 and 2. Mean scores for pain at night and during the day evalulated by patient are shown in Figure 3. All efficacy assessments demonstrated statistically significant improvements from baseline at each follow-up visit. Remission was achieved in 6 (19.3 %) of patients. Table 3 shows the results of global assessments of efficacy. At the end of treatment, 28 (90.3 %) of the patients evaluated the efficacy of PBC as improved or greatly improved, and investigators rated the treatment as improved or greatly improved in 27 (87.1 %) of patients. The simplicity of PBC therapy – one tablet once a day – was also appreciated by many patients.

Adverse Events

Table 3 shows the results of tolerability assessment, where we see that 26 (83.9 %) of the patients characterized PBC treatment as very good, and investigators rated the treatment as very good in 27 (87.1 %) of all patients. Drug related adverse events were reported in 3 (9.7 %) patients: allergic skin reactions in 2 and epigastric pain in 1 patient. Adverse events prompted discontinuation of the study medication in 1 (3.2 %) patient. No serious adverse events were reported and no significant changes were observed in laboratory tests.

Tab. 1. Patient characteristics.

Number of patients (males/females)	31 (24/7)
Age in years; mean (range)	52.3 (18-85)
Localisation of pain	
Cervical	5
Lumbosacral	20
Combined	6
Median duration of symptoms (weeks)	11

Tab. 2. Summary of patients withdrawing before study completion.

Reason for withdrawal	Number of withdrawals		
	<10 days	<20 days	total
Adverse event	1	-	1
Lack of effect	1	2	3
Relief of symptoms	1	5	6

Tab. 3. Global assessments of efficacy and tolerabilty performed by physicians and patients.

	Physician	Pacient
Efficacy		
None	1	1
Poor	3	2
Improved	10	12
Greatly improved	17	16
Tolerability		
Poor	2	1
Fair	-	2
Good	2	2
Very good	27	26

Discussion

PBC was regarded as an effective analgesic by both patients and physicians in this study. The treatment effects occured by the first assessment (at 10 days) and marked and sustained improvements with a relatively high rate of remissions (19 %) were observed throughout the 40 days of the study. The preference for a single daily treatment is not surprising because many patients were also taking medications for other conditions. For many such patients, simplifying one element of their treatment by using once-daily PBC can be expected to reduce the overall risk of taking the wrong tablets at the wrong time and to facilitate compliance and adherence to therapy.

Although the noncomparative nature of this study and the small sample size reduces the generalisability of the results, such improvements are rarely observed in similar studies with NSAIDs (17). It is important to note, that patients enrolled into the study were typical of patients suffering from chronic BP, which tend to occur more frequently in women than in men. Chronic BP is usually defined as pain that lasts for longer than 7–12 weeks (18). Others classify frequently recurring BP as chronic since it intermittently affects an individual over a long period of time (19). The characteristics of this population are notably different from a population suffering from acute BP. The patients with acute BP tend to be younger, with similar proportions of males and females, and many of these patients have no anatomical abnormalities that clearly explain their symptoms (20).

Most importantly, patients with acute BP respond better to treatment then patients with chronic BP (17). It is therefore not surprising that in patients with acute BP lasting no more than 48 hours, remission was achieved in 50 % of patients during 14 days of treatment with PBC (21). In comparative trials, PBC was more rapidly acting and provided greater pain relief than piroxicam (22) or etodolac (23). Moreover, patients treated with PBC required a shorter treatment period for the pain to disappear in comparison with patients treated with other NSAID, supporting the hypothesis that BP may be self-limiting provided that the initial acute painful phase is rapidly and effectively treated (24).

We assume that in addition to improved pharmacokinetic properties of PBC, its inflammatory site specifity (25) and central analgesic effects (26) may be important in the treatment of chronic BP. In fact, inflammation, as evidenced by leukocyte infiltration and expression of inflammatory mediators, is associated with disc degeneration and serves to alter the neural responses resulting in local and reffered pain (27, 28). The latter assumption is further supported by recent meta-analysis, which demonstrated that a single oral dose of piroxicam (20–40 mg) was of similar efficacy to intramuscular morphine (10 mg) in patients with moderate to severe postoperative pain (29).

It is probable that enhanced GI safety and tolerability of PBC also contributed to the high level of patient and physician satisfaction with PBC observed in this study. The superior GI safety profile of PBC compared with piroxicam and other conventional NSAIDs has been demonstrated in a series of endoscopy studies (15, 30, 31, 32) and outcome trials (33). Interstingly, the most frequently observed AE in this study were allergic skin reactions. There is no explanation for this finding, other then random variation due to small sample size. Although one study in 15 patients has suggested that the incidence of piroxicam-induced photosensitivity reactions in Portugal is higher with PBC than with standard piroxicam (34), there is controversy surrounding the statistical calculations behind this results (35).

In summary, results from this pilot study indicate that patients with chronic BP receiving PBC 20 mg once daily for 40 days showed a clinical improvement that was higher than with other NSAIDs. Consistent with previous observations, PBC showed a generally favorable safety and tolerability profile. The major clinical advantages of PBC over other NSAID include rapid onset of action combined with long duration of acitivity and very favourable risk-benefit ratio. Thus PBC may be an important new treatment option for symptomatic management of chronic BP. Because the amount of clinical evidence is a key factor of drug selection (36), direct comparison against other NSAIDs in randomised clinical trials would better define the role of PBC in this condition.

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