Available online at www.sciencedirect.com
ScienceDirect
Phytomedicine 14 (2007) 371–376
Phytomedicine
www.elsevier.de/phymed

Patient-perceived benefit during one year of treatment with Doloteffin®

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Abstract

We recruited 114 patients (56 with chronic nonspecific low back pain, 37 with osteoarthritic knee and 21 with osteoarthritic hip pain) into a surveillance of the effects of taking Doloteffin® at a dose providing 60 mg harpagoside per day for up to 54 weeks. Their symptoms and well-being were monitored at 4–6 week intervals by disease-specific and generic outcome measures, and the patients also kept a diary of their pain and requirement for rescue medication.

The principal analyses were on the basis of Intention to Treat (ITT) with Last Value Carried Forward (LOCF). A Multivariate Analysis of Variance (MANOVA) indicated an appreciable overall improvement during the surveillance, similar in the Back, Knee and Hip groups. In separate ANOVAs, most of the individual outcome scores decreased significantly over time. Multiple regression analyses indicated that changes from baseline were independent of patients' characteristics. Additional analgesic requirements (which were very modest) declined during the year of surveillance. ''Response during treatment'', assessed according to criteria adapted from joint proposals of the Outcome Measures in Rheumatoid Arthritis Clinical Trials group and the Osteoarthritis Research Society International group, was achieved in 75% of patients, and was reflected in the percentages who rated the treatment as ''good'' or ''very good''. Adverse events were few and none were serious.

Keywords: Osteoarthritic pain; Hip; Knee; Lower back; stand. *Harpagophytum* extract; Survey

Introduction

In its guideline for the management of osteoarthritis of the hip and knee, the American College of Rheumatology suggests 4 goals: (i) control of pain; (ii) improvement in function; (iii) improvement in health-related quality of life; (iv) avoidance of toxicity (www.rheumatology.org/publications/guidelines/oa-mgmt/oa-mgmt.asp?aud=mem). The overall management should include non-pharmacological modes of treatment as much as possible, to reduce reliance on drugs and their attendant side effects. Adequate doses of some preparations derived from *Harpagophytum procumbens* may be sufficiently effective and safe to be useful for treating low back (Gagnier et al., 2006) or osteoarthritic pain (Chrubasik et al., 2003a). We undertook this surveillance partly to see how closely our Back group might replicate our results in a similar year-long survey in another group of patients with chronic back pain (Chrubasik et al., 2005) and partly to see how success or failure might be reported dichotomously according to criteria recently proposed jointly by the Outcome

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doi:10.1016/j.phymed.2007.04.011

Measures in Rheumatoid Arthritis Clinical Trials group and the – Osteoarthritis Research Society International group (the OMERACT–OARSI) (Pham et al., 2004).

Methods

In 2002, we reported the results of an 8-week, 3-centre surveillance of treatment of back, knee or hip pain with the aqueous standardized *Harpagophytum* extract, Doloteffin® (Chrubasik et al., 2002). (www.uniklinik-freiburg.de/rechtsmedizin/live/forschung/phytomedicine/originalartikel.html). We used a bank of disease-specific and generic outcome measures in the surveillance, which required statutory notification to the Bundesinstitut für Arzneimittel/Bonn and the Bundeskassenärztliche Vereinigung/Köln. Towards the end of the 8 weeks, many patients from the Freiburg centre asked to continue. We therefore offered all 91 of the Freiburg patients who completed 8 weeks of surveillance the option of extending it for a year. Seventy-nine agreed and we recruited an additional 35 patients to give a total of 114. All met the prospectively set criterion that they had experienced pain of at least 50 mm out of 100 mm on a visual analogue scale in the previous 2 weeks. They comprised a Back group (56 patients with chronic non-specific low back pain as defined by the IASP (Fordyce, 1995) and Knee (37) and Hip (21) groups (with chronic osteoarthritis according the criteria of the American College of Rheumatology). After giving written informed consent, all patients received 4-week prescriptions of Doloteffin®, renewable at 4-weekly assessment visits until week 12, and then at 6-weekly intervals for up to 54 weeks. Six 400 mg tablets of Doloteffin® per day contain a total of 2400 mg of aqueous stand. extract of *Harpagophytum procumbens*. This is equivalent to 4.5 g of crude drug per day (drug extract ratio 1.5–2.5:1) as recommended by the German Commission E (Blumenthal, 1998). Each tablet contains 10 mg of the marker substance harpagoside (Sporer and Chrubasik, 1999). The daily dose of 60 mg of harpagoside is about double the dose provided by ethanolic *Harpagophytum* extracts (Sporer and Chrubasik, 1999).

Initially and at each subsequent visit, the assessments consisted of a series of established and unvalidated measures, some of which were location-specific and some generic.[1] Patients were also given a diary to make recordings each morning of the pain they had experienced on the preceding day, using a 5-point verbal rating scale (none, mild, moderate, severe, excruciating). They also recorded any additional pain treatments including the daily doses of any non-steroidal anti-inflammatory drugs (NSAIDs) they may have used, which were later calculated as diclofenac equivalents (see footnote 1). A prospectively designed questionnaire was used for the standardised recording of any adverse events so as to assess their severity and intensity, and to try to assign cause. The patient and one author (S.C.) completed the questionnaire together and the information was subsequently discussed with another physician not otherwise involved in the study.

The data were analysed using the procedures available in the Statistical Analysis System Software package (SAS Institute Inc., Cary, NC). The principal analysis was by Intention-to-Treat (ITT). Results from patients who dropped out of the surveillance were included in the

[1] **Disease-specific instruments**:

The Arhus index was modified as in our other studies by the exclusion of the items relating to analgesic medications, because the analgesic medication was recorded in the patients' diaries and calculated separately. The modifications gave the score a maximum of 120–60 for pain, 30 for disability and 30 for physical impairment. Location-specific Three Item Pain Score (TIPS) which, for the Back patients, was the pain component of the Arhus index ([a] current pain at the time of investigation, [b] worst pain and [c] average pain in the preceding 2 weeks, all assessed on a 0–10 visual analogue scale *directed at the back*) was *directed at the affected joint in* Knee and Hip patients

(*footnote continued*)

and consisted of the same questions.

The location-specific Total Pain Index (TPI) consisted of a sum of 5 visual analogue scale components, with a range from 0 to 10, covering pain *in the affected part* while sitting, standing, lying down, moving and at night.

Generic instruments:

The validated German version of the WOMAC questionnaire consisted of 5 pain-related activities, 2 stiffness categories and 17 functional activities. It was directed at the worse joint or a chosen reference joint if both joints were equally affected.

The HAQ was modified as in another study (Chrubasik et al., 2002) by accrediting each aid/device with an additional point after we demonstrated that this modification correlated well with the original mode of the HAQ calculation ($r = 0.89$–0.98) (www.uniklinik-freiburg.de/rechtsmedizin/live/forschung/phytomedicine/originalartikel.html).

The generic 4-point global patient assessments (PGA) of effectiveness and tolerability of treatment used the terms very good, good, moderate, poor.

The OMERACT-OARSI criterion can be met if there are *large* changes in *either* the assessment of pain *or* function, but it can also be met if there are more moderate changes in any two out of the three assessments – pain, function or patient's global assessment. Because the verbal rating scale for the patients' global assessment of the treatment contained only 4 points, it was too crude to be incorporated into the criterion for this study. The maximum pain in the preceding 2 weeks was used as the assessment of pain and the respective invalidity and disability components of the Arhus and WOMAC indices were used as the indices of function. Responder requirement: Improvement in the maximum pain experienced in the preceding 2 weeks by at least 50% of the value recorded at inclusion and absolute change of 20% of the range of the scale OR improvement in the invalidity/disability score by at least 50% of the value recorded at inclusion and absolute change of 20% of the range of the scale OR Improvement in the maximum pain experienced in the preceding 2 weeks by at least 20% of the value recorded at inclusion and absolute change of 10% of the range of the scale AND improvement the invalidity/disability score by at least 20% of the value recorded at inclusion and absolute change of 10% of the range of the scale.

Diclofenac equivalents were defined as follows: 100 mg of diclofenac was taken as equivalent to 1330 mg metamizol, 1300 mg acetylsalicylic acid, 800 mg of ibuprofen, 550 mg naproxen, 250 mg propyphenazon, 133.3 mg celecoxib, 120 mg acemetacin, 66.6 mg ketoprofen, 50 mg indometacin, 6.66 mg piroxicam and 8.3 mg rofecoxib.