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Willow bark extract STW 33-I in the long-term treatment of outpatients with rheumatic pain mainly osteoarthritis or back pain

B. Uehleke[a,b,d,*], J. Müller[e], R. Stange[a], O. Kelber[e], J. Melzer[b,c]

[a] Department of Natural Medicine, Charité University Medicine Berlin, Immanuel Krankenhaus, Königstraße 63, 14109 Berlin, Germany
[b] Institute for Complementary Medicine, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland
[c] Clinic for Psychiatry and Psychotherapy, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland
[d] University of Health and Sports, Vulkanstrasse 1, 10367 Berlin, Germany
[e] Clinical Research, Steigerwald Arzneimittelwerk GmbH, Havelstrasse 5, 64295 Darmstadt, Germany

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ABSTRACT

Study objective: Efficacy and safety of willow bark extract for pain reduction in patients suffering from musculoskeletal disorders (MSD) has been shown in clinical short term trials. Therefore this observational study over 6 months should evaluate patterns of treatments like mono- or combinations therapy, dosage and safety during long-term treatment under pragmatic conditions with the aqueous willow bark extract STW 33-I, (Proaktiv®; drug-extract-ratio 16–23:1).
Patients and methods: The patients were treated with STW 33-I; comedication with other NSAIDs and opioids was allowed. An extensive case report form including pain questionnaires and patient diary was used for outcome evaluation.
Results: Four hundred and thirty-six patients with rheumatic pain mainly due to osteoarthritis (56.2%) and back pain (59.9%) were included. During the study the mean reductions from baseline value 58.4 ± 22.6–31.8 ± 22.5 after 24 weeks in the pain intensity scale (VAS 0–100 mm) were significant even after 3 weeks with a reduction by 26 mm (45.6% of the baseline value) at the end of the study. The relative reductions of the weekly means of the daily patient self-rated scores of the pain (6-point Likert-scales) were between 33% and 44% of the baseline values during the course of the study. We present results of subgroups according their analgetic/antiphlogistic comedication.

The distribution and specification of the main adverse events and the ratings of the treatment showed a good tolerability. No relevant drug interactions were reported.
Conclusion: These data suggest that STW 33-I can be used as a basic treatment in the long-term therapy of painful musculoskeletal disorders and that it can be combined with NSAIDs and opioids if necessary.

Introduction

Willow bark (WB) has already been mentioned in ancient and medieval writings as an agent against fever and pain. A characteristic constituent of WB is salicin and its derivates (ESCOP 2003). Salicin was discovered in 1831 and was used then as isolated substance to treat fever and pain. Yet, salicin is a prodrug which is metabolized in the gut and liver via salicylic alcohol into salicylic acid – the active drug. Salicin as well as its chemically modified derivative acetylsalicylic acid (ASA) are known to inhibit the cyclooxygenases (COX) 1 and 2, COX-inhibition has been regarded as the main mechanism of the anti-inflammatory activity of WB, which contains a complex composition of various salicin-derivates. WB has been considered a natural form of ASA (Nahrstedt et al. 2007).

However, the daily recommended dosage of WB corresponding to only 120–240 mg total salicin might rise doubts about this assumption (ESCOP 2003; Gagnier et al. 2006; Nahrstedt et al. 2007). Consequently there should be other active constituents in extracts from WB. Meanwhile it was shown that preparations from WB can also inhibit lipoxygenase (LOX-5), modulate relevant pro- and anti-inflammatory cytokines (Interleukin 1, 6, 8, 10) and nuclear factors (TNF-α, NF-κB). All these effects were attributed to a lesser extent to salicin derivates rather than to polyphenols, flavonoids and proanthocyanidins in WB. In addition polyphenols and flavonoids showed anti-oxidative effects, which also have an anti-inflammatory impact. Moreover *in vivo* models for acute and chronic inflammation (e.g. paw edema, adjuvant-induced arthritis in rats), and analgesia (e.g. writhing test in mice), showed a dose-dependent effect for aqueous WB extracts corresponding to the same dose of ASA (Bonaterra et al. 2010; Cameron et al. 2009;

* Corresponding author at: University of Health and Sports, Vulkanstrasse 1, 10367 Berlin, Germany. Tel.: +49 30 5779737601.
E-mail address: bernhard.uehleke@my-campus-berlin.com (B. Uehleke).

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Fiebich et al. 2005; Fiebich and Chrubasik 2004; Khayyal et al. 2005; Nahrstedt et al. 2007; Ulrich-Merzenich et al. 2008).

Upto date efficacy and safety of WB have mostly been investigated for alcoholic extracts in patients suffering from pain in various musculoskeletal disorders. For low back pain moderate efficacy was found in 2 placebo- and 1 NSAID-controlled RCT (Gagnier et al. 2006). For osteoarthritis (OA), however, one placebo- and one 3-armed RCT with placebo and NSAID-control found inconsistent results (Cameron et al. 2009). For rheumatoid arthritis a systematic review found no significant efficacy in a placebo-controlled RCT. However, the treatment periods have only been relatively short ranging from 2 to 6 weeks and daily dosage equivalent to 120–240 mg salicin was administered with 2–4 tablets (Cameron et al. 2009; Gagnier et al. 2006; Wegener 2009). Additional trials, 4 open and 2 RCTs have been summarized elsewhere (Wegener 2009). Meanwhile a further open study with 877 patients treated with a WB extract equivalent to 60–240 mg salicin daily over a period of 6–8 weeks showed a clinically relevant pain reduction (Saller et al. 2008).

An aqueous WB extract has been investigated in a NSAID-controlled 3-armed RCT in 60 patients with osteoarthritis (OA) of the hip or knee over 3 weeks with daily dosage equivalent to 90 mg versus 180 mg salicin versus 150 mg diclofenac and resulted in no significant differences between groups (Lardos et al. 2004).

The aim of this observational study was to evaluate efficacy, tolerability and safety of the aqueous WB extract STW 33-I in a long-term treatment for up to 6 months in outpatients suffering from musculoskeletal disorders. Another important aim was to evaluate the role of comedication patterns of the herbal drug with other analgesics like NSAIDs or opioids in daily medical routine.

Patients and methods

Study design

In this observational study ('Anwendungsbeobachtung' according to German regulations) patients of both genders over 18 years were included suffering from musculoskeletal disorders (MD) like OA or back pain. The multi-center study was placed in regional pain centers and in practices of general practitioners (GPs) familiar with pain therapy. Additionally it was planned that the outpatient clinic of the Department of Natural Medicine, Charité University Medicine Berlin would include about 100 outpatients for comparison. Patients were enrolled from 1/2008 to 12/2009.

Study drug

STW 33-I (Proaktiv®, registered as a herbal OTC drug by German Federal Institute for Drugs and Medical Devices (BfArM), drug-extract-ratio (DER) 16–23:1, 23–26% total salicin) is an aqueous extract of WB which allows the daily administration of the equivalent of 240 mg salicylic alcohol derivates with only 2 tablets. The extract STW 33-I has been characterized by a HPLC-fingerprint analysis with identification of the main salicylalcohol-derivatives and flavonoids. This analysis with the necessary description of the technique (apparat, column, solvent system) has been published in Phytomedicine by Bonaterra et al. (2010) and Freischmidt et al. (2012).

In agreement with the open character of the study no strict drug regime was prescribed by protocol. It was the aim of this study to evaluate long-term treatment with STW 33-I alone or in combination with other analgesics (e.g. NSARs, opioids). The patients ought to be treated over a period of 24 weeks with clinical visits at baseline and after 3, 6, 12, 18 and 24 weeks.

Outcome measure

Patients' and physicians' ratings

During the visits the global pain intensity was rated by the patient on a visual analogue scale VAS (0–100 mm from "no pain" to "strongest pain"). Additionally, the global efficacy of the treatment was rated by the physician on a 5 point Likert-scale: 0 = very good/nearly complete remission, 1 = moderate/partly remission of symptoms, 2 = mild improvement, 3 = no improvement/worsening, 4 = not assessable. Safety and tolerability were measured from the 2nd to the last visit onward in terms of adverse drug reaktion (ADR), adverse events (AE) and dropouts. For assessment of severity of the ADRs a 5-point Likert-scale was used: 0 = none, 1 = non-significant impairment, 2 = significant impairment, 3 = ADRs outweigh the therapeutic efficacy, 4 = not assessable. For AEs, intensity (mild, moderate, severe) and for SAE (severe AE), whether they were expected/unexpected, their mode (once, intermittent continuously, unknown), the relation to the drug (assured, likely, possible, unlikely, not assessable, cannot be determined, no correlation) the action undertaken, and the course of AE had to be documented. For dropouts, the reasons had to be documented (e.g. improvement, intolerability).

Patients' rating

Additionally, patients had to fill out their dairy with daily self-rating of (a) pain at rest, (b) pain during movement, (c) the duration of pain, (d) overall impairment due to pain, (e) impairment of quality of sleep due to pain (f) and changes in their pain therapy and dosage of STW 33-I and other analgesics. The scales for all these measures, except duration of pain and dosage, were 6 point Likert-scales: 0 = none/not at all, 1 = mild, 2 = moderate, 3 = marked, 4 = strong, 5 = very strong. For the assessment of pain duration the 6 point scale was: 0 = none, 1 = $\leq$1 h, 2 = 1–2 h, 3 = 2–6 h, 4 = 6–12 h, 5 = permanently. Dosage of analgesics had to be given by number of tablets or in mg.

Statistics

Data were mainly subjected to descriptive statistical evaluation. Statistical analysis was performed with SAS® Version 9.1 (Cary, North Carolina, USA). The data are presented as means $\pm$ one standard deviation (SD), additionally medians as well as 95% confidence intervals and numbers of patients were calculated. Categorical data are presented using counts and percentages rounded to one decimal place. All p-values are two-tailed, and $p < 0.05$ was considered statistically significant.

In this observational study it was planned to evaluate more than 400 patients within 2 years.

Results

Demographic and anamnestic data

A total of 436 patients ($n = 327$, resp. 75.2% female, $n = 108$, resp. 24.8% male) were included in 74 study centers; 103 of those patients were recruited at the Department of Natural Medicine. Demographic data are shown in Table 1. Regarding occupation 44.3% of the patients were retired and 24.8% were in full-time jobs.

A majority of patients suffered from OA or back pain. Other diagnoses were less than 18% of patients (Table 2). Co-morbidity of both, OA and back pain was observed in about 1 third of patients.

The chronic condition is reflected by more than 5 years history of pain in 58% of the patients (Table 3). The majority of the patients had received a multimodal therapy with pharmacological (80.3%) and non-pharmacological treatment (physiotherapy 62.2%,