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A clinical surrogate model for proof of efficacy of external phytomedicines for muscle pain. Results of a randomized, placebo-controlled clinical study in volunteers with muscle pain due to physical training

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Abstract

Purpose: Surrogate models have been postulated for (re-)registration of external remedies for pain, whose active substances are in accordance to monographs. In a new human model, we investigated an ointment consisting of high dosed herbal ingredients.

Methods: We conducted a clinical study in 32 healthy volunteers. Four muscle regions were treated with the ointments (verum on the one side and placebo on the other) in a randomized and doubleblinded manner immediately after a standardized physical exercise with individual intensity, as well as after 1, 2 and 24 h. Acute muscle pain and muscle tension for each region was documented repeatedly during the following two days by visual analogue scale (VAS). Primary outcome parameter was the difference of pain during the follow up given as area under the curve (AUC) of VAS for corresponding right and left regions, treated with verum or placebo. Also the difference of muscle tension was documented and evaluated in an analogous way.

Results: 30 out of 32 included patients finished the study, but developed only moderate muscle pain, with highest pain scores for extension muscles of the arm. There was less pain in the course for the verum in 3 of the 4 regions, the mean difference of individual AUCs was at highest for the extension (triceps) muscles of the arm, but between-group differences failed significance. Feeling of muscle tension was higher than that of pain, with smaller mean AUCs of verum in all 4 regions; the differences were significant in total ($p < 0.02$) and in 2 of 4 single regions.

Conclusions: Physical exercise was not intensive enough to exert clear symptoms. Our volunteers with sportive background seem not to show severe symptoms of muscle pain and muscle tension even after an intensive training. Despite low levels of symptoms, verum showed better courses of muscle tension and muscle pain. For future studies it seems better not to use volunteers with sportive background but totally untrained persons in order to achieve pronounced symptoms. The model is feasible, sensitive, inexpensive and is much more clinically relevant than those, focusing on perfusion parameters of skin.

Keywords: Clinical surrogate model; Muscle pain; Rheumatic pain; Essential oils; External therapy

Introduction

In order to avoid repeated clinical studies in patients with rheumatic complaints for each single product, the

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German drug licensing agency (Bundesinstitut für Arzneimttel und Medizinprodukte BfArM) requested only proof in surrogate models for external drugs (topica) with their active ingredients in accordance to monographs. For externa with assumed induction of hyperemia like essential oils, proof of skin hyperemia was thought to be appropriate surrogate. But later it became evident, that it is not so easy to show a hyperemia even with high concentrations of essential oils (Knorr et al. 1987; Hübner 1991). Therefore we developed a new surrogate model with an artificially induced muscle pain through an intensive physical exercise (Uehleke et al. 2005). Sour muscles are connected with rhabdomyolysis of muscle cells (Allison and Bedsole 2003). Also mechano-receptors might be involved in the feeling of muscle kater (Weerakkody et al. 2001).

Materials and methods

This was a phase I, randomized, double-blinded clinical study in healthy volunteers in hemilateral comparison. The tested ointment[1] was already on the market as a registered drug. All three active substances (campher 10%, eucalyptus oil 10%, terpentine oil 25%) and also their combination are in accordance to monographs by the commission E with indications rheumatic pain and muscle pain. Placebo ointment did not contain any active ingredient and was very similar in handling and color, but not in aroma. Blinding was improved by spraying a mixture of the active substances in the room, where the application of the tested ointments took place. The study was approved by the ethics-comitee of the Charité – University medicine Berlin, Campus Benjamin Franklin according the German drug law and the guidelines for good clinical practice according International Conference on Harmonization (ICH). The volunteers had an insurance according German drug law for Phase I studies.

Patients/evaluation criteria

32 male volunteers were included after physical examination and exclusion of diseases by routine venous blood parameters. Volunteers with relevant diseases, esp. skin diseases, allergies against the ingredients, use of topical drugs were excluded. Volunteers were to show symmetrical muscles and should not use sports with unilateral activity e.g. tennis. They were informed about the study and gave their written consent to attend all visits, not to use any body care product and to avoid further training or physical activity during the study.

[1]Rheumasalbe Triplex®.

Course of study

After the first visit for inclusion, there were visits on day 1 (training and treatment), day 2 (treatment) and day 3 (follow up). At day 1, after documentation of the initial values and questionnaires, there was a short warming and stretching, followed by a training with apparatus in defined manner and supervised by sport therapists. The training was so intensive in order to induce a muscle pain and muscle tension for the following 4 muscle groups: M. triceps brachii, M pectoralis, M quadriceps femoralis, ischiocrural muscles. In detail 90% of the maximum weight or tension was moved slowly (2–4 s) repeatedly until complete exhaustion, trice.

10 min after exercise there were hemilateral treatments of the muscle regions by a neutral and blinded person using two individual tubes of substance for each volunteer, signed with patient number and "right" or "left". In order to avoid unblinding by the strong aroma of the verum, the mixture of these essential oils was sprayed around the whole room. The resulting aroma was so strong, that it was not possible for the volunteers nor for the applicating person to smell any difference between the hemilateral treatments. There was also neither a difference of acute sensoric feeling between verum and placebo at the skin, nor any apparent hyperemia. The procedure of treatment was repeated 1 and 2 h after the training as well as after 24 h at day 2.

Outcome parameters

Main parameter was the difference between the corresponding hemilateral muscle regions treated with verum and placebo of the courses as given by the area under the curve (AUC) of repeated values of visual analogous scales (VAS, length 100 mm) for acute muscle pain and muscle tension. Secondary parameters were the single muscle regions in hemilateral comparison and the tolerability.

Statistics

A confirmatoric analysis was planned with the main parameter for hemilateral differences of AUCs with verum versus placebo. There were only those muscle regions taken into consideration, where at least one value was higher than zero. The differences of AUCs were to be tested by the paired, two-tailed t-Test at the 0.05 level. In a descriptive manner, the differences of the single muscle regions are described.

An exact estimation of a patient number was not possible, since there were no clinical data on the drug and thereby no idea about the effect nor the variance. Since we regarded the muscle regions as independent, a number of 30 volunteers would lead to $4 \times 30 = 120$