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A randomized, placebo-controlled, cross-over study of ginger extracts and Ibuprofen in osteoarthritis

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Summary

Objective: Alternative medicine is used extensively by patients with chronic pain due to e.g., osteoarthritis. Only few of these drugs have be tested in a controlled setting and the present study was undertaken to examine the effect of ginger extract, one of the most popular herbal medications.

Design: Ginger extract was compared to placebo and Ibuprofen in patients with osteoarthritis of the hip or knee in a controlled, double blind, double dummy, cross-over study with a wash-out period of one week followed by three treatment periods in a randomized sequence, each of three weeks duration. Acetaminophen was used as rescue medication throughout the study. The study was conducted in accordance with Good Clinical Practice (European Guideline for GCP).

Results: A ranking of efficacy of the three treatment periods: Ibuprofen>ginger extract>placebo was found for visual analogue scale of pain (Friedman test: 24.65, $P<0.00001$) and the Lequesne-index (Friedman test: 20.76, $P<0.00005$). In the cross-over study, no significant difference between placebo and ginger extract could be demonstrated (Siegel-Castellan test), while explorative tests of differences in the first treatment period showed a better effect of both Ibuprofen and ginger extract than placebo (Chi-square, $P<0.05$). There were no serious adverse events reported during the periods with active medications.

Conclusion: In the present study a statistically significant effect of ginger extract could only be demonstrated by explorative statistical methods in the first period of treatment before cross-over, while a significant difference was not observed in the study as a whole. © 2000 OsteoArthritis Research Society International

Key words: Ginger, Extracts, Osteoarthritis, Pain, Ibuprofen.

Introduction

Patients with chronic, painful diseases often seek alternative therapy,[1] and currently, ginger is one of the most popular herbal medications for rheumatic diseases. Beneficial effects of ginger have been reported casuistically,[2] while no controlled study of the effect has been performed previously. Acetaminophen is generally advocated as a pain killer in osteoarthritis, however, many patients use NSAIDs for prolonged periods with the hazards this may imply due to serious gastric adverse events. The present study was undertaken to test ginger extracts as an alternative to the NSAID as supplementary drug.

With acetaminophen as basal therapy, a three group cross-over study between placebo, ginger extract and Ibuprofen was undertaken to rank ginger extract in comparison to the clinically most relevant alternatives.

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Subjects and methods

SUBJECTS

After approval by the local ethical committee and obtaining signed informed consent, six different investigators included patients in the study from their practices (only out-patients participated). Patients over 18 years of age were eligible for the study. During the study period, very few patients refused to enter the study. Criteria for exclusion were a.o. rheumatoid arthritis, neurological disorders, severe medical diseases, and dementia. Only patients fluent in Danish participated. No injections in joints were accepted within six months before the study.

All patients had complaints of clinical dysfunction and pain due to osteoarthritis and radiologically verified osteoarthritis (Kellgren grade 1–2; $N=16$, grade 3–4; $N=40$) of the hip or knee with pain on movement of more than 30 mm on a 100 mm VAS (mean 52 mm) at the first visit (entry). Mean duration of osteoarthritis was 7.7 years (range 1–30 years) and mean Lequesne index at entry was 11.8 (range 1–21.5).

GINGER EXTRACT

An extract of selected Chinese ginger (Eurovita Extract 33, EV.ext-33) with a standardized content of

hydroxy-methoxy-phenyl compounds (HMP) was used.[3] This extract was formulated in soft gelatine capsules which shields the content of ginger.

DESIGN

The study was conducted in a double-blind, double-dummy, cross-over controlled design. At study entry, treatment with analgesics and non-steroidal anti-inflammatory drugs (NSAID) was discontinued for a one-week wash-out period. The patients were then randomized to three treatment periods of three weeks each, with either 170 mg EV.ext-33 ginger extract, ibuprofen 400 mg or placebo administered t.i.d. No further wash-out periods were used between the three treatment periods. The patients were randomized in blocks of six and furthermore within these blocks there was a randomization according to the six different sequences of the three types of treatment. Each investigator included a minimum of six patients consecutively.

As a rescue drug for pain during wash-out and throughout the rest of the study, acetaminophen was delivered to the patients by the investigators and used in a maximum dosage of 3 grams daily. The study was conducted in accordance with Good Clinical Practice (European Guidelines for GCP).

MASKING

Both the Ibuprofen-tablet placebo and the EV.ext-33-capsule placebo were indistinguishable from the originals, and as long as it was intact, the capsule did not convey any smell or taste of ginger. There was no difference in compliance as judged from tablet and capsule consumption during the three treatment periods.

ASSESSMENT OF EFFICACY (OUTCOME MEASURES)

At study entry and at the end of each period, both wash-out (henceforth, the values obtained at this visit are called baseline-values) and treatment, the following items were noted: a 100 mm VAS for pain assessment (primary outcome variable), Lequesne-index for either hip or knee,[4] and range of motion. The consumption of acetaminophen was counted by patient and investigator at each visit. Furthermore, the investigator's preference of medication in the different treatment periods was noted.

During each treatment period the patients filled in a diary with a 4-point Likert pain scale each week.

Finally, the consumption of all trial medications was counted at each visit by the investigator in the presence of the patients.

ASSESSMENT OF SAFETY

All adverse events, including changes in taste, were noted throughout the study, either in the patients diary and/or in the case record form at each visit. At entry and after each treatment period blood samples were obtained for measurement of haemoglobin.

STATISTICS

The number of patients (60), eligible for calculation, was calculated on the following assumptions: the SD of difference between the patient's VAS pain in two treatment periods was assumed to be 12 mm (Bliddal *et al*. unpublished), and the type 1 and type 2 errors were chosen at 5 and 10% respectively and the minimal relevant difference between placebo and the most effective treatment groups was chosen at 10 mm. Both Ibuprofen and ginger extracts have a very short half-life, and the patient was only evaluated after three weeks of therapy, which should minimize carry-over effects from the previous treatment period. Furthermore, a possible carry-over effect between the three periods was balanced by the randomization of sequences of therapies. In this design with a cross-over of three treatment groups the effect was tested with a Friedman test on the assumption that the ranking of efficiency was Ibuprofen>ginger extract>placebo. The differences of the individual treatments were estimated by Siegel-Castellan test of multiple comparisons.[5] Furthermore, non-parametric tests as Kruskall-Wallis, Mann-Whitney and Page test for trend were applied. Level of statistical significance was chosen at 0.05.

All statistical analyses were performed by P.S. before the breaking of the code.

Results

DEMOGRAPHICS AND COMPLIANCE

A total of 75 patients were evaluated for the study. Eight patients were excluded during the wash-out period: four because of intolerable increase in pain after withdrawal of their regular NSAID and four due to withdrawal of consent. Sixty-seven patients were randomized for the treatment periods, and after secondary exclusion of 11 patients (see 'safety' below) 56 patients were evaluable for the whole study period. All the patients complied with the prescheduled study-visits.

Of the 56 patients, 15 were men and 41 women. Twenty had primarily osteoarthritis of the hip and 36 of the knee. The age of the patients was mean 66 years (range 24–87 years) and the duration of osteoarthritis was mean 7.7 years (range 1–30 years). The weight was mean 78.3 kg (range 53.5–120.0 kg).

Pain level at study entry was not significantly correlated to the severity of the radiological changes. Most of the patients had previously tried NSAID and at entry 31 patients were receiving NSAID treatment.

EFFICACY

During the wash-out period VAS changed from entry value median 51 mm (95% confidence limits 46–54) to the baseline value 54 mm (95% confidence limits 47–63 Willcoxon: $P<0.01$).

The parameters of pain changed during therapy in all periods, however, a highly significant ranking of efficacy of the three treatment periods: Ibuprofen>ginger extract>placebo was found for VAS (Friedman: 24.65, $P<0.0001$), and the same trend was found for acetaminophen consumption (Friedman 11.7, $P<0.01$) as seen in Fig. 1. Also, the Lequesne-index changed positively during treatment with the same ranking (Fig. 2). The Siegel & Castellan test for multiple comparisons showed a significant difference in these tests between Ibuprofen and ginger extract as well as Ibuprofen vs. placebo, but not between ginger extract and placebo.

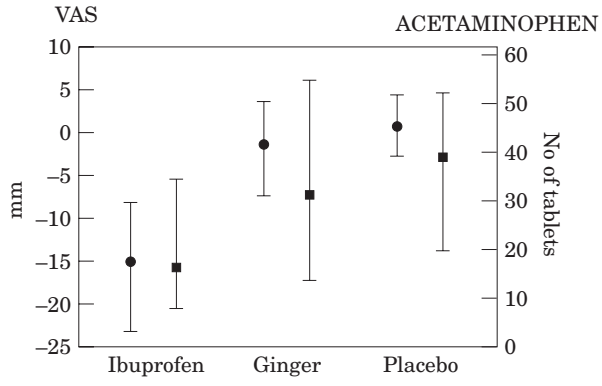

Fig. 1. Changes on a 100-mm visual analogue scale (VAS) and the total consumption of acetaminophen during three weeks treatment with Ibuprofen, EV.ext-33 ginger extract (G) or placebo (P). Median values and 95% confidence limits are shown. The ranking between the three periods were tested by the Friedman test. For VAS: Friedman test $P<0.00001$, Chi-square 24.65 (degree of freedom: 2); for Acetaminophen consumption: Friedman test $P<0.01$, Chi-square 11.7 (degree of freedom: 2). Siegel-Castellan test for multiple comparisons: Ibuprofen vs. EV.ext-33 ginger extract or placebo $P<0.001$, EV.ext-33 ginger extract vs. Placebo n.s.

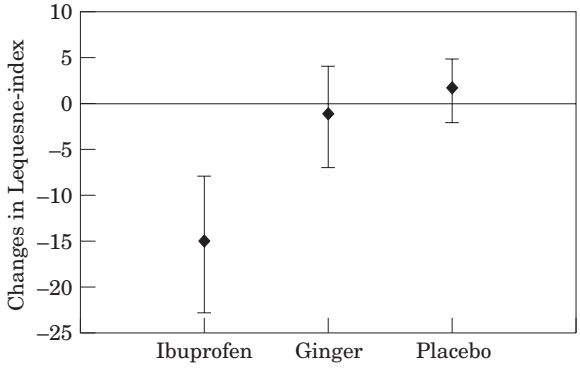

Fig. 2. The changes in Lequesne-index during three weeks treatment with Ibuprofen, EV.ext-33 ginger extract (G) or placebo (P). Median values and 95% confidence limits are shown. The ranking between the three periods were tested by the Friedman test: $P<0.00005$, Chi-square 20.76 (d.f. 2). Siegel-Castellan test for multiple comparisons: Ibuprofen vs. EV.ext-33 ginger extract or placebo $P<0.001$, EV.ext-33 ginger extract vs. Placebo n.s.

The pain scores recorded in the patient diary could not be assessed because the majority of the patients did not fill in this form correctly.

In any of the three periods, no differences in range-of-motion were noted. Investigator preference was in favour of Ibuprofen (66%), while no differences were observed in placebo or ginger extract (14 vs. 11%), and in 9%, all three periods were considered equal.

SAFETY

During the treatment period 11 patients were secondarily excluded. Of these, four withdrew because of adverse events: one patient was operated for intestinal strangulation (placebo period), one had restless legs (placebo period), one bad taste (ginger extract period), and one nausea (Ibuprofen period). The other reasons were unsatisfying therapeutic effect ($N=3$), Lithium treatment ($N=1$), and other, e.g. non-compliance ($N=3$).

In the 67 patients receiving test drugs, a total of 47 adverse events were registered in 34 patients. Two of the adverse events could not be considered as side effects to the trial medications (fall in snowy weather and acute low back pain, both during placebo period). The other adverse events were mainly gastrointestinal complaints (placebo period $N=8$, ginger extract period $N=9$, and ibuprofen period $N=14$). These complaints were characterized as bad taste, which was only reported in ginger extract periods ($N=5$), dyspepsia (placebo $N=1$, ginger extract $N=1$, Ibuprofen $N=7$), changes in stools/intestinal trouble (placebo $N=6$, ginger extract $N=1$, Ibuprofen $N=4$), or nausea (placebo $N=1$, ginger extract $N=1$, Ibuprofen $N=3$). In three patients allergic reactions were noted: skin allergy (placebo period), periorbital oedema (Ibuprofen period), and conjunctivitis (ginger extract period).

The haemoglobin values (pre-period minus end-period value) were not affected to any clinically relevant extent by any of the treatments.

Discussion

This study demonstrates a ranking of efficacy on pain level and function in patients with osteoarthritis of the hip or knee with Ibuprofen being more effective than ginger extract (EV.ext-33) and placebo. The same ranking was seen in the consumption of rescue medication, giving the overall impression of a definite effect of Ibuprofen and a small action of ginger extract. No difference between ginger extract and placebo was demonstrated in a test for multiple comparisons. However, prompted by a comment of a reviewer, explorative statistical testing of the first period of treatment (before cross-over) was performed and this showed a better effect of both Ibuprofen and ginger extract compared to that of placebo (Chi-square test, $P<0.05$). A carry-over effect may blur possible effects of the later treatment periods, and based on the present results, caution should be observed in the interpretation of a cross-over study of ginger extract.

During the three weeks of treatment no significant adverse events were noted which could be ascribed to the active substances.

Although the use of NSAIDs in osteoarthritis is highly controversial[6] the fact is that many doctors and patients do favour these substances for both short and long-term use. In our material two thirds of the patients were regular NSAID users.

Ginger contains chemical substances with an anti-inflammatory potential,[7] and the effect might be attributed to the actions of HMP. These are dual inhibitors of cyclooxygenase and 5-lipoxygenase which makes the substances even more interesting in the field of rheumatology.[8,9] A suppressive effect of constituents of ginger has been reported in arthritic rats.[9] However, a long-term study of the effects would require the development of a dummy substance for the placebo-control, which has not been possible to date.

The three week periods of therapy in this study might not have been sufficient for all effects of ginger extract to be discovered, and only one dose of ginger extract was applied. Future studies might look into dose-response and duration of therapy of EV.ext-33, if possible employing a more potent extract of ginger.

In the present study, the registered adverse events during treatment with neither Ibuprofen nor EV.ext-33 reached statistical significance.

The ginger herb is extensively cultivated in the tropics and, apart from the use as spice in cooking, it has been recommended as medication for various illnesses during several thousand years.[2,11] Of the different constituents of ginger, some seem to be responsible for the distinctive taste,[12] while other, different, compounds have specific pharmacological effect e.g., inhibition of the prostaglandin synthetase. The anti-inflammatory action of ginger has been claimed to be the basis of a positive effect on symptoms in rheumatic disorders.[2]

EV.ext-33 is highly purified with respect to HMP compounds which have a sharp characteristic taste. Thus the EV.ext-33 capsules should be swallowed and definitely not chewed (personal experience). In our study, this effect was described to the patients in detail before entry, and we believe that the participants of the study have been honest in their reports of taste of ginger. The study is as far as possible blinded, but the possibility of bias due to taste cannot be ruled out. However, as observed, the patients reporting ginger taste did not differ from the rest of the group in respect of pain score, Lequesne index or consumption of paracetamol.

Doctors generally believe that 'alternative' medications do not work at all[1,13] and few keep an open mind towards alternative medicine.[14] In contrast, the 'products of nature' seem to be very popular with RA patients, as two thirds of sufferers turn to supplementary unorthodox therapy each year.[15] This inclination may be put to good use if the patients change from NSAID to more harmless substances.

Acknowledgments

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