A Modern Homeopathic Medication Works as well as COX 2 Inhibitors for Treating Osteoarthritis of the Knee

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INTRODUCTION

Relieving pain and reducing inflammation are the cornerstones of pharmaceutical therapy for osteoarthritis of the knee. Depending on the patient's symptoms, treatment may be either systemic or topical and may include peripherally active analgesics, anti-inflammatories such as COX 1 or COX 2 inhibitors, topical steroids, hyaluronic acid, and therapeutic injections of local anesthetics.[1] More and more physicians, however, are prescribing alternative therapeutic measures.

In homeopathy, for example, potentized extracts of Rhus toxicodendron, Solanum dulcamara and Sanguinaria canadensis are used to relieve the pain and inflammation of rheumatic conditions. These three ingredients are combined with Arnica montana and Sulfur in the homeopathic medication Zeel® comp. N (tablets).

A previous controlled, double-blind clinical study proved that the clinical efficacy of this combination medication is equivalent to that of COX 1 inhibitors in treating mild to moderate osteoarthritis of the knee.[2, 3] The purpose of the present study is to compare the efficacy of Zeel® comp. N and COX 2 inhibitors.

METHODS

Design of the study

The investigation was conducted as an open, prospective, multicenter, reference-controlled cohort study. To minimize the possibility of treatment bias, the 127 participating physicians (primarily general practitioners) were separated into two groups, one of which prescribed only Zeel® comp. N and the other only COX 2 inhibitors.

Patients

All 592 patients admitted to the study had Stage I or Stage II osteoarthritis of the knee as defined by Richter.[4] Exclusion criteria included Stage III or IV osteoarthritis and concomitant pharmaceutical treatment for osteoarthritis with prescription drugs other than those prescribed for purposes of the study. Non-pharmaceutical therapies and short-term use of OTC pain relievers were permitted.

Target criteria

In each case, both physician and patient evaluated efficacy of treatment. Upon commencement of therapy and over the course of the study, the physicians assessed the degree of severity of four cardinal symptoms (initial pain with movement, pain continuing during movement or weight-bearing exercise, pain when fatigued, and joint stiffness/tension) on a four-point scale (no symptoms, mild, moderate, severe). Physicians also documented the point in time of onset of symptomatic improvement and rated the overall results of therapy on a five-point scale (very good, good, fair, no success, worse) on conclusion of treatment. Patients evaluated their progress during the study with the help of a validated German version of the WOMAC Osteoarthritis Index.[5]

Individual test parameters were documented for each patient at an entry examination, an interim examination after approximately four weeks of treatment and a final examination after at least six but no more than ten weeks.

Test substances

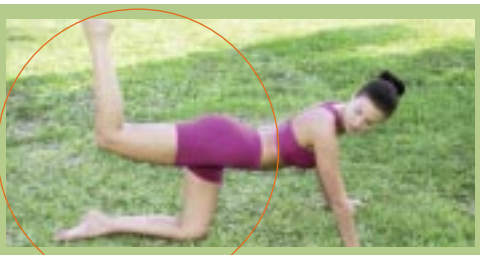
The test medication was Zeel® comp. N (tablets); the reference substances were the COX 2 inhibitors Celebrex® (active ingredient celecoxib, 100 or 200 mg hard capsules) and Vioxx® (active ingredient rofecoxib, 12.5 or 25 mg tablets).[6-10]

Statistics

To compensate for treatment differences among covariates, Rosenbaum's method of logistic regression was applied.[11, 12] This statistical procedure permits calculation of propensity scores, which are then matched to reduce distortion in comparing the nonrandomized treatment groups.[11, 13] Adjusted differences in the size of effects were calculated with 95% confidence intervals. Confidence intervals were calculated through analysis of covariance. The purpose of the statistical analysis was to demonstrate that treatment with Zeel® comp. N is not less effective than treatment with the above-mentioned COX 2 inhibitors at an equivalence limit of 10 percent (one-sided probability of error = 0.025).

Ethics

The study was conducted in accordance with the German recommendations (November 12, 1998) for planning, implementing and evaluating drug monitoring studies.[14]



FINDINGS

Treatment

Of the patients receiving Zeel® comp. N (n = 323), 44% took one tablet three times a day, while 24% took one tablet four times a day and 27% took one tablet five times a day. For 88% of the patients in the test group, the dosage remained unchanged throughout the treatment period. In the reference group (n = 269), 109 patients were treated with celecoxib and 160 with rofecoxib. Participating physicians were left free to decide which COX 2 inhibitor to prescribe for each patient in this group.

Severity of symptoms

Upon commencement of the study, all four cardinal symptoms as assessed by the physicians (initial pain with movement, pain continuing during movement or weight-bearing exercise, pain when fatigued, and joint stiffness or sensation of tension) were moderately severe in both treatment groups, and the groups were comparable in terms of severity of symptoms ($p > 0.05$). After four weeks, significant improvement in all symptoms was observed under both treatment regimens. Improvement was somewhat more pronounced in the group receiving COX 2 inhibitors due to the more rapid onset of efficacy of this type of medication. After six weeks of treatment, scores indicated that the homeopathic medication and the COX 2 inhibitors were equally effective.

The WOMAC Osteoarthritis Index

Upon commencement of therapy, both groups of patients reported pain in the mid-range of the Visual Analog Scale. As with the cardinal symptoms listed above, after four weeks of treatment, the WOMAC Osteoarthritis Index also revealed greater reductions in pain in the group taking COX 2 inhibitors. By the end of the treatment period, however, the difference lay inside the confidence interval, i.e., the efficacy of therapy was equivalent in the two groups.

Onset of efficacy

As expected, improvement in cardinal symptoms occurred significantly earlier in the COX 2 inhibitor group. 48% of these patients (in comparison to 20% in the test group) reported improvement within two weeks. This difference was eliminated, however, within the next two to three weeks.

Results of therapy

Overall ratings of therapeutic efficacy and patient compliance were generally comparable in the two treatment groups. Patient compliance was rated "good" or "very good" for 98% of the test group and 97% of the COX 2 group ($p = 0.129$). 79% and 86%, respectively, rated the overall results of their treatment as "good" or "very good" ($p = 0.160$). 63% of the test group and 59% of the reference group continued treatment after the end of the study.

Tolerability

The test medication scored significantly higher with regards to tolerability ($p < 0.0001$) than the COX 2 inhibitors. 90% of the patients taking the homeopathic medication tolerated it "very well" in comparison to only 74% taking the reference medications.

Adverse drug events

Among the patients taking COX 2 inhibitors, three incidents of undesired effects were reported: edema, diarrhea/vomiting/dizziness and (in the third case) unspecified gastric complaints. The physicians reported that COX 2 inhibitor therapy was "probably" related to the gastric complaints and "possibly" related to the edema, but did not comment on the possibility of a connection between therapy and the case of diarrhea/vomiting/dizziness. No adverse events were reported in the Zeel® comp. N group.

DISCUSSION

This cohort study was conducted according to criteria established by Benson and Concato.[21, 22] After a maximum treatment period of ten weeks, Zeel® comp. N achieved clinical efficacy comparable to that of COX 2 inhibitors as evidenced both by the WOMAC Osteoarthritis Index and by improvement in cardinal symptoms. Furthermore, there were no statistically significant differences between the test and reference groups in ratings of patient compliance and overall success of the therapies. On the other hand, patients gave the homeopathic medication significantly higher scores for tolerability than the COX 2 inhibitors. All three adverse drug events occurred in the COX 2 inhibitor group, and in two of the three cases the physicians reported possible/probable causative connections.

The purpose of pharmaceutical therapy for osteoarthritis is to relieve pain, improve mobility and prevent progression of inflammation. To achieve these ends, analgesic and anti-inflammatory medications such as NSAIDs, unselective COX 1 inhibitors and selective COX 2 inhibitors are commonly prescribed.[1] There are distinct differences, however, in the pharmacological activity of these types of medications. Traditional NSAIDs inhibit both COX 1 and COX 2; their therapeutic effects are due to inhibition of inducible COX 2 [15, 16] while their gastrointestinal, renal and cardiovascular side effects are based on inhibition of constitutive COX 1 activity.[15-18] With fewer side effects of this sort, selective COX 2 inhibitors are considered an advance over COX 1 inhibitors in the treatment of painful rheumatic symptoms.[15-17, 20] (The incidence of cardiovascular and renal disease increases with advancing age and approximately 40% of arthritis patients are treated concurrently for hypertension and/or arteriosclerosis).[17-19] But although COX 2 inhibitors cause fewer side effects, adverse events (primarily cardiovascular) are still known to occur.[17]

Because the COX 2 isozyme plays an important role in healing processes (including ulcer healing) and in maintaining homeostasis (with regards to blood pressure and vasoregulation, kidney function, CNS functions and bone metabolism), inhibiting COX 2 is not completely unproblematic.[17] A more physiologically sound therapeutic approach is to reduce the concentration of proteolytic enzymes (serine proteinases and metalloproteinases) that support inflammation in the extracellular matrix. Suppressing these enzymes also prevents COX 2 overexpression. This is where Zeel® comp. N proves superior: *in vitro* studies have demonstrated that its ingredients effectively inhibit serine proteinases and metalloproteinases.[23, 24]

CONCLUSION

This study proves that **Zeel® comp. N is as effective as the COX 2 inhibitors** celecoxib and rofecoxib and is significantly better tolerated. Therefore, this homeopathic combination medication offers a real alternative to allopathic drugs in treating mild to moderate osteoarthritis of the knee. Due to its lower cost and the fact that it virtually eliminates the need for secondary medication to control adverse effects, Zeel® comp. N should also reduce the cost of long-term arthritis management.

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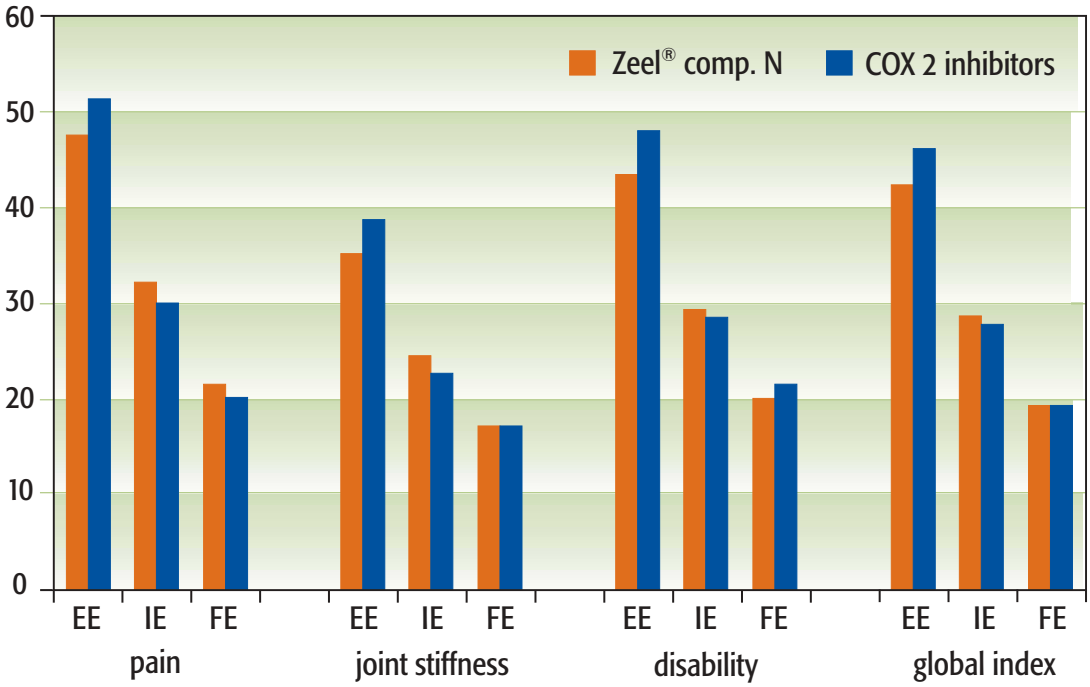

Fig.: Change in scores on the WOMAC Osteoarthritis Index and its subscales over the course of the study. (EE = entry examination, IE = interim examination [after 30-32 days on average], FE = final examination [after 60-64 days on average])

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