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PHLOGENZYM® *VERSUS* DICLOFENAC IN THE TREATMENT OF ACTIVATED OSTEOARTHRITIS OF THE KNEE. A DOUBLE-BLIND PROSPECTIVE RANDOMIZED STUDY

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Summary: *The aim of this study was to compare the short-term efficacy and tolerability of an oral enzyme therapy (Phlogenzym®) with the nonsteroidal antiinflammatory drug, diclofenac, in patients with active osteoarthritis of the knee. Sixty-three patients with active osteoarthritis of the knee were treated in a randomized, double blind, parallel group trial for 21 days. Thirty-one patients were included in the Phlogenzym® group and 32 patients were included in the diclofenac group. Efficacy was primarily evaluated by the Lequesne index and by using the visual analog scale (VAS) for pain at rest and in motion. In addition, overall assessment of efficacy and tolerability (both by patients and the physician), various laboratory parameters, range of motion without pain (0°), circumference of the affected knee, self-judgment of impairment and therapy outcome were evaluated descriptively. Patients were evaluated at baseline, at weekly intervals throughout the study and at 4 weeks after discontinuing medication intake. All 63 patients were evaluated on an intent-to-treat data set. Statistical evaluation showed that in the main endpoints, the Lequesne index and VAS, the Phlogenzym® group was equivalent to the diclofenac group. The mean value of the Lequesne index decreased from 15.48 to 9.81 after 7 weeks in the Phlogenzym® group and from 15.81 to 10.83 after 7 weeks in the diclofenac group. In the statistical evaluation the lower band of the 95% confidence interval of the Mann-Whitney estimator was above 0.44, the limit for equivalence, at all times. The secondary criteria showed no significant differences. In the majority of patients, overall assessment of efficacy and tolerance were judged in both drug groups as very good or good. In conclusion, short-term evaluation indicates that Phlogenzym® as an oral enzyme formulation can be considered as an effective and safe alternative to nonsteroidal antiinflammatory drugs such as diclofenac in the treatment of active osteoarthritis of the knee.*

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are considered to be the drugs of choice in the treatment of active arthritis. A previous double-blind clinical comparison of Wobenzym® *vs*. diclofenac in patients with active osteoarthritis of the knee showed that after 1 month of therapy both drugs led to a significant improvement in symptoms (1). The positive effect of orally applied hydrolytic enzymes has been reported in numerous case reports and clinical trials. The efficacy of this therapy is similar to that of classic medical treatment for relief of acute pain and improvement in functions. The enzymes have fibrinolytic and hydrolyt-

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ic activity and can activate macrophages. They can eliminate cell debris with phlogogenic potential and reduce inflammation and pain. Fibrin clots are degraded and blood circulation returns to normal.

The aim of this clinical study was to determine whether the efficacy obtained with Wobenzym® in patients suffering from activated osteoarthritis of the knee could also be achieved with the enzyme preparation Phlogenzym® and whether this therapy was equivalent to diclofenac. Enzymes are better tolerated than NSAIDs and produce none of the gastrointestinal effects associated with these drugs. Because a large retrospective cohort study in rheumatic patients demonstrated that the effect of the enzyme started later but lasted longer (2), medication was administered for 3 weeks and comparison between the drugs was made 4 weeks after end of therapy to evaluate the long lasting effects.

Patients and methods

Study drugs. Oral enzyme tablets (Phlogenzym®, Mucos Pharma, Geretsried, Germany) and diclofenac tablets (Duravolten®, Durachemie, Wolfsrathausen, Germany) were used. Each active enteric coated enzyme tablet contained bromelain 90 mg, trypsin 48 mg, rutoside x 3 H_2O 100 mg. Each active diclofenac tablet contained 50 mg of diclofenac sodium.

Inclusion and exclusion criteria. Patients fulfilling the following criteria were included in the study: i) active osteoarthritis of the knee with radiologically verified narrowing of the joint space; ii) a Lequesne index score >10 with typical clinical symptoms; iii) age between 19 and 75 years, and iv) written informed consent according to Good Clinical Practice (GCP)-guidelines.

Exclusion criteria consisted of the following: i) concomitant antirheumatic treatment or treatment of existing osteoarthritis of the knee ending less than 2 weeks before baseline; ii) inflammatory rheumatic disease; iii) other diseases that could be interpreted as a cause of secondary arthrosis of the joint, for example psoriatic arthritis, syphilitic neuropathy, metabolic bone disease, ochronosis and acute injury with or without degenerative joint disease; iv) suspicion of a bacterial inflammation of the joint; v) indication for physical treatment directly at the affected joint; vi) pregnancy or lactation; vii) known intolerance against the active or the inactive ingredients of the study medications (especially lactose); viii) hemorrhagic diathesis; ix) oral anticoagulants; x) systemic or intraarticular corticosteroids within the previous 2 months; xi) clinically relevant cardiovascular, gastrointestinal, hepatic, hematological or renal disease; xii) female patients of child-bearing age not taking contraception; xiii) participation in another clinical trial within the previous 30 days, and xiv) participation in another clinical trial at the time of the present study.

Study design. The aim of this study was to test the efficacy and tolerance of Phlogenzym® for equivalence with diclofenac in monoarticular gonarthritis.

This study was conducted as a prospective, randomized, double-blind phase III clinical trial with two parallel groups. The study drug Phlogenzym® was compared with the NSAID diclofenac for equivalence. The study was conducted in accordance with GCP guidelines. The study was approved by the hospital's institutional review board and informed consent was obtained from all study patients.

Although all patients received standard physiotherapy, a placebo-controlled trial was considered ethically unjustifiable by the investigator and the ethical committee because antiinflammatory medication was required. Therefore, the standard NSAID diclofenac was chosen for comparison.

Dosing schedule and duration of therapy. The dose of diclofenac was chosen to minimize adverse effects and risk to the patients.

To make the drugs compared suitable for the double-blind design, the study material was prepared following the double dummy method: all patients received six tablets per day of the enzyme tablets. They also received three diclofenac tablets per day in the first week, and two diclofenac tablets per day in the second and third weeks. Patients in the enzyme group received active enzyme and placebo diclofenac tablets while the diclofenac group received enzyme placebos and active diclofenac.

Treatment was planned for 3 weeks. Examinations were performed at baseline, after weeks 1, 2 and 3 (end of therapy) and again after week 7 as a follow-up.

Number of patients. Sixty-eight patients (two groups of 34 patients each) were to be included. However, patient numbers 64 to 68 were not included to make earlier evaluation possible. Therefore, according to the randomization, 31 patients received Phlogenzym® and 32 patients received diclofenac.

Assessment of efficacy and tolerance. The main criteria for statistical evaluation were equivalence of Phlogenzym® to diclofenac according to the Lequesne index, and overall pain judgments according to VAS (pain at rest and on movement, restricted movement) 4 weeks after the end of active therapy. Further criteria included the overall descriptive assessment by the physician, patient tolerance to the drug, pain symptoms at each follow-up visit evaluated with a verbal rating scale, and the circumference (cm) and mobility of the affected knee.

Adverse events were recorded at each follow-up visit. To assess the safety of the study drug, laboratory investigations were performed at baseline and at the end of active treatment.

Statistical model. All 63 patients were evaluated in an intent-to-treat data set. The null hypothesis assumed that enzyme therapy was at least equivalent to antirheumatic therapy with diclofenac if 4 weeks after the end of therapy the total score of the Lequesne index in the enzyme group was not more than 10% higher than that in the diclofenac group.

The statistical tests were planned as one-sided equivalence tests. If equivalence was found, a subsequent test for superiority was added. A level of significance of 5% (α-error = 0.05), and a test power of 90% (β-error = 0.01) were defined. Additionally, Mann-Whitney statistics with 95% confidence intervals were calculated and interpreted.

Results

Efficacy. The mean values of the Lequesne index (an index of severity in gonarthritis) in the enzyme and diclofenac group over the treatment period are listed in Table I to III. In the enzyme group, the Lequesne index showed improvement in 29 patients (93.6%) and deterioration in two patients (6.5%) from baseline to the end of therapy. In the diclofenac group, 28 patients (87.5%) showed improvement, one patient (3.1%) showed no change and three

Table I *Sum of the Lesquesne index (average values over the treatment period)*

	Days after baseline				
	Baseline	7	14	21	49
Enzyme group	15.48 (NS)	13.56 (NS)	12.27 (NS)	10.97 (NS)	9.81*
Diclofenac group	15.81	12.61	10.79	10.83	12.77

*p = 0.0165.

Table II *Mean values of different evolution parameters according to VAS (cm)*

	Days after baseline									
	Baseline		7		14		21		49	
1) Pain at rest										
Enzyme group	3.54	NS	2.49	NS	1.96	NS	1.50	NS	1.18	NS
Diclofenac group	3.08	NS	2.07	NS	1.33	NS	1.42	NS	1.90	NS
2) Pain on movement										
Enzyme group	5.99	NS	4.27	NS	3.76	NS	2.66	NS	1.95	*p = 0.011
Diclofenac group	5.42	NS	3.38	NS	2.64	NS	2.74	NS	3.49	*p = 0.011
3) Restricted movement										
Enzyme group	2.84	NS	1.85	NS	1.59	NS	1.35	NS	0.85	NS
Diclofenac group	2.56	NS	1.79	NS	1.24	NS	1.23	NS	1.40	NS
4) Total pain score (1+2+3)										
Enzyme group	12.37	NS	8.62	NS	7.32	NS	5.51	NS	3.97	*p = 0.011
Diclofenac group	11.05	NS	7.28	NS	5.21	NS	5.36	NS	6.78	*p = 0.011

* = Statistically significant at the level of 5% in favor of the enzyme group.

Table III *Comparability of symptoms (Wilcoxon-Mann-Whitney U-test) between the two groups at each follow-up visit*

Variable	Baseline			After 1 week			After 2 weeks			After 3 weeks			After 7 weeks		
	p-value		Mann-Whitney-statistics[1]	*p*-value		Mann-Whitney-statistics[1]	*p*-value		Mann-Whitney-statistics[1]	*p*-value		Mann-Whitney-statistics[1]	*p*-value		Mann-Whitney-statistics[1]
Lesquesne index	0.6443	NS	0.5343	0.3563	NS	0.4320	0.2186	NS	0.4037	0.9178	NS	0.4919	0.0330	*	0.6933
Pain at rest	0.4787	NS	0.4476	0.4406	NS	0.4430	0.2846	NS	0.4165	0.4545	NS	0.4451	0.2367	NS	0.6076
Pain on movement	0.2104	NS	0.4078	0.0164	#	0.3236	0.0922	NS	0.3686	0.8473	NS	0.5146	0.0236	*	0.7049
Restricted movement	0.7155	NS	0.4728	0.8526	NS	0.4859	0.4032	NS	0.4343	0.7151	NS	0.5272	0.4448	NS	0.5706
Total score	0.1507	NS	0.3942	0.0975	NS	0.3780	0.1152	NS	0.3769	0.8527	NS	0.5141	0.0948	NS	0.6528

*Significant at the level of 5% in favor of the enzyme group, # significant at the level of 5% in favor of the diclofenac group.
[1] No difference: 0.50; small difference: >0.56 (<0.44); medium difference: >0.64 (<0.36); big difference: >0.71 (<0.29).

patients (15.6%) showed deterioration from baseline to the end of therapy.

The other criteria (according to VAS) of pain at rest and on movement, restricted movement and total pain score showed no significant differences between groups during the 21-day treatment. At the follow-up visit 4 weeks after the end of therapy there was a statistically significant difference at the level of 5% in favor of the enzyme group in pain on movement and total pain score (Tables II and III). No differences were found between the treatment groups in the patients' pain judgments and the therapeutic results. The difference was statistically significant only at day 49 in favor of the enzyme group (p = 0.0413 and 0.0448). The overall efficacy assessment by the physician and patients showed no differences.

Tolerance. After Phlogenzym® treatment, 18 adverse effects were reported in 15 patients. Of these adverse effects, flatulence, nausea, allergic exanthema and epigastric pain were, or were possibly, related to the treatment. After diclofenac treatment, 20

adverse effects were reported in 16 patients, of which retrosternal pain, pressure and pain over the stomach region, epigastric pain under pressure, nausea and ulcus ventriculi were, or were possibly related to the treatment. In the enzyme group, the physician rated tolerance to therapy as very good in 74.2%, as good in 3.2%, as moderate in 3.2%, and as unsatisfactory in 6.5%. In the diclofenac group, tolerance was rated as very good in 75.0%, as good in 12.5%, as unsatisfactory in 3.1%, and as poor in 3.1%. In the enzyme group, tolerance was rated as very good by 92.3% of the patients, as good by 6.5%, as moderate by 3.2%, and as unsatisfactory by 3.2%. In the diclofenac group, outcome was rated as very good by 71.9% of the patients, as good by 12.5%, and as poor by 3.1%. The study drug was stopped in four patients in the enzyme group (two patients with epigastric pain under pressure, one patient with leg edema unrelated to the drug, and one patient with allergic exanthema). Treatment was stopped in three patients in the diclofenac group (two patients with epigastric pain and pain in the stomach, and one patient with nausea). None of the patients reporting adverse effects developed sequelae.

Discussion

The different types of osteoarthritis show more or less marked progression. Monoarticular active gonarthritis leads to a process similar to the inflammation caused by degeneration or trauma of the knee limited to this joint. Involvement can be restricted to the synovialis or can embrace the cartilage and bone. Thus, osteoarthritis of the knee is characterized by a loss of hyaline cartilage. Hence, pain and increasing loss of function develop after overload and trauma. The aim of treatment is to reduce disease progression, especially activation, which is similar to inflammation and produces involvement of the synovial membrane, release of inflammatory mediators, swelling of the synovia, exudation, an increase in cartilage-metabolism and ensuing degradation.

NSAIDs are the drugs of choice in the treatment of inflammatory reactions in different types of arthritis (1). These drugs have high antiinflammatory potency. The most commonly applied drug is diclofenac, which was used for standard comparison in this study. However, the main problem of all NSAIDs is their risk of adverse effects (3-6). Because these drugs inhibit cyclooxygenase, the protection of the gastric mucosa is missing. This can result in the development of ulcers and microbleeding: gastrointestinal tract complications associated with NSAIDs are the most common serious adverse drug reactions. NSAIDs cause both minor gastrointestinal adverse effects such as abdominal pain and vomiting and serious gastrointestinal events such as ulcers, bleeding and perforation. A multicenter study with 2,000 patients suffering from osteoarthritis of the knee treated with the NSAID ibuprofen reported that treatment was discontinued in 4.7% of the enrolled patients, mostly because of gastrointestinal disorders; the hemoccult tests were positive in 2%, even though patients with a history of gastrointestinal disorders were excluded from the study (7). After NSAID treatment there is a risk that the development of the gastrointestinal syndrome will be clinically silent, *i.e.*, clinical signs of ulcers or bleedings may be absent and patients may be unaware of symptoms. Prophylactic treatment with antacids and H_2 receptor antagonists is of no value and may increase the risk of subsequent serious gastrointestinal complications (6). This is because most patients with serious gastrointestinal complications do not have preceding mild adverse effects.

Because of the adverse effects of NSAIDs, alternative drug therapy should be sought. Enzyme treatment might provide this alternative. The enzyme preparation Phlogenzym® has a marked antiinflammatory effect demonstrated in many preclinical and clinical studies (8, 9). In addition, Phlogenzym® possesses immune modulating properties. Adhesion molecules are very

important for an inflammatory reaction: they are involved in inflammation and in the focusing of the systemic immune response into the target tissue and are upregulated through the action of cytokines. Tumor necrosis factor-α appears to be of primary importance. Circulating adhesion molecules probably reflect acute inflammatory episodes, but may also modulate ongoing inflammatory responses. Cytokines are rendered resistant and immigrant macrophages are activated to synthesize and release increased amounts of inflammatory mediators, such as oxygen radicals and components of the complement system.

Systemic enzyme therapy intervenes in four different processes: the release of inflammatory mediators, the modulation of adhesion molecules, the dissolution of detritus and the activation of fibrinolysis with consequent improved healing. Additionally, enzymes reduce immune complexes, which play a role in the pathogenesis of inflammatory rheumatic diseases. Thus, healing is accelerated. The antioxidative compound in Phlogenzym®, rutoside, eliminates radicals. Therefore, successful treatment of the symptoms typical of these diseases could be achieved by therapeutically influencing this pathological mechanism.

A previous study compared the clinical efficacy (antiinflammatory potency) and tolerability of Wobenzym® with those of diclofenac in 80 patients with osteoarthritis of the knee in acute phase. Standardized pain evaluation and restricted movement are suitable for judging the acute efficacy of drugs in patients with active osteoarthritis of the knee. The Lequesne index has been used in such assessments. After a 4-week course of therapy, this index decreased by 50%, and 80% of the patients showed a clinically relevant improvement. After the treatment period the clinical parameters of pain at rest, in motion, on walking, at night and tenderness showed a significant improvement. No significant differences between the two treatment groups (Wobenzym® and diclofenac) were found (1, 8, 9).

A retrospective epidemiological cohort study with Phlogenzym® in rheumatic diseases showed that the onset of the effect of NSAIDs is faster, while the effect of enzyme preparations lasts longer (2). Because of these results, the time point for evaluation was set at 4 weeks after end of therapy to assess the long-term effect. To avoid gastrointestinal complications as far as possible, the dose of diclofenac in the present study was chosen as 50 mg b.i.d., as it is known that short-term treatment with this dose preserves efficacy but limits adverse effects. When higher doses or longer diclofenac therapy are required, adverse effects rapidly increase.

The data confirm that with enzyme therapy, the onset of antiinflammatory effects is slower compared with the rapid onset of diclofenac but that enzyme therapy produces a longer lasting antiinflammatory effect, which persists after the end of therapy. The greatest improvement in the Lequesne index for Phlogenzym® was achieved 4 weeks after the end of therapy (36.6% improvement); the observed effect at this time point was even better than the maximum effect after diclofenac treatment (31.8% improvement after 2 weeks and 31.5% after 3 weeks), and the decreased value after 7 weeks (19.2% improvement). Because the antiinflammatory effect is long-lasting, the outcome of long-term therapy with an enzyme preparation is clearly advantageous.

Mild adverse effects were observed in both groups. In addition to adverse effects unrelated to the administered drugs, the main adverse effects were gastrointestinal disorders with a clear pathologic difference: adverse effects produced by Phlogenzym® were due to protein digestion, while those produced by diclofenac were due to cyclooxygenase inhibition as a result of insufficient protection by the gastric mucosa.

The advantage of the therapy with Phlogenzym® can be seen in the marked long-lasting antiinflammatory effect and in the high tolerability. Thus, long-term treatment with Phlogenzym® in patients with osteoarthritis can be recommended.

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