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Sulodexide in the treatment of intermittent claudication

Results of a randomized, double-blind, multicentre, placebo-controlled study

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Aims Patients with peripheral arterial obstructive disease require treatment to prevent major cardiovascular events and to relieve intermittent claudication. The walking performance of peripheral arterial obstructive disease patients was used to evaluate the usefulness of sulodexide, a glycosaminoglycan containing fast moving heparin and dermatan sulphate.

Methods and Results A randomized, multicentre, double-blind, placebo-controlled study was performed in 286 patients with Leriche-Fontaine stage II peripheral arterial obstructive disease. Patients received placebo (n=143) or sulodexide (n=143) for 27 weeks. The primary end-point was the doubling of the pain-free walking distance at the end of treatment, and this was achieved by 23·8% of patients treated with sulodexide and 9·1% of those on placebo (P=0·001). The pain-free walking distance increased on average (± SE) by 83·2 ± 8·6 m (+64·7% from baseline) with sulodexide and 36·7 ± 6·2 m (+29·9% from baseline) with placebo (P=0·001). The maximum walking distance increased by 142·3 ± 15·8 m (+76·0% from baseline) and 54·5 ± 8·4 m (+27·9% from baseline) (P<0·001), respectively. Results for patients with type II diabetes were similar to those for non-diabetic patients. Plasma fibrinogen decreased with sulodexide, but increased with placebo.

Conclusion Sulodexide improved the walking ability of peripheral arterial obstructive disease patients to a significantly greater extent than placebo, with a concurrent significant decrease in fibrinogen. The treatment was well tolerated.

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Introduction

In recent years the prevalence of peripheral arterial obstructive disease in developed countries has increased as the population ages. The prevalence of peripheral arterial obstructive disease assessed as intermittent claudication was evaluated at approximately 2% in subjects over 65 both in the Framingham[1] and in the San Diego Artery studies[2]. In recent assessments, based on more comprehensive diagnostic criteria[3,4], the prevalence of peripheral arterial obstructive disease in elderly subjects was found to be as high as 5 to 6%.

Peripheral arterial obstructive disease is the localization of the multifocal process of atherothrombosis to arteries of the lower limb. The atherothrombotic process is characterized by actual or potential diffusion to

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See Appendix for the list of Centres participating in the study.

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several arterial territories, mainly the coronary and cerebrovascular districts[5]. Indeed, patients with peripheral arterial obstructive disease carry a high risk of coronary and cerebrovascular morbidity and mortality[6]. The risk is present even in asymptomatic patients[7] but increases in patients with advanced stages of the disease. It has been reported that a simple diagnostic parameter, such as the reduced ankle–brachial pressure index, is a reliable predictor of mortality[8].

The specific symptom of peripheral arterial obstructive disease, i.e. intermittent claudication, limits the patient's ability to walk and results in a painful and invalidating condition, significantly affecting the patient's psychological, social and occupational life. Patients with peripheral arterial obstructive disease must therefore be managed for both the prevention of cardiovascular events and the relief of intermittent claudication. Several antiplatelet drugs have been tested for the prevention of cardiovascular risk in this indication[9]. Ticlopidine[10] and its derivative clopidogrel[11] have been shown to be effective in reducing the risk of cardio- and cerebrovascular events in peripheral arterial obstructive disease patients, while evidence for acetyl salicylic acid is provided by meta-analyses[12–14] rather than single studies.

Improvement of intermittent claudication is mainly obtained by surgical and/or interventional measures, when required. Conservative treatment has an important role, and includes not smoking, physical training (walking) and drug therapy. Several drugs have been tested for their ability to improve the walking performance of peripheral arterial obstructive disease patients[15–27] under these conditions.

In the present study we investigated the effect of sulodexide, a standardized extractive glycosaminoglycan containing 80% 'fast moving' heparin and 20% dermatan-sulphate[28,29], on the walking ability of peripheral arterial obstructive disease patients with intermittent claudication. The rationale for selecting sulodexide was its thrombogenesis-inhibiting properties, both through the antithrombin III and the heparin cofactor II pathways, and fibrinolysis stimulating activity through the activation of tPA and inhibition of PAI-1 after parenteral administration[28,29]. Some of these activities, such as tPA increase and PAI-1 reduction, were also demonstrated after oral administration of sulodexide at single[30] and repeated doses[31–33]. The absorption of sulodexide after oral administration has been demonstrated using the radiolabelled compound[34]. Furthermore, reduction of plasma fibrinogen[33,35,36] and other beneficial effects on the microcirculation[37] as well as the promising results achieved in previous clinical studies[38] prompted us to evaluate sulodexide for the treatment of peripheral arterial obstructive disease patients.

Methods

Two hundred and eighty six patients were enrolled into this randomized multicentre, double-blind placebo-controlled study, carried out in 28 centres between August 1998 and November 2000. The study was performed in compliance with the Declaration of Helsinki (Somerset West revision), the Guidelines for Good Clinical Practice and the 'Note for guidance on the clinical investigation of medicinal products in the treatment of chronic peripheral arterial occlusive disease' (CPMP/EWP/233/95 final). Protocol, information and consent procedures were approved by the Ethics Committee at each centre.

Patients

Requirements for eligibility were:

- age 45 to 75 years and presence of chronic obliterative arterial disease diagnosed by echo-colour Doppler ultrasound, with stable, moderate to severe intermittent claudication;
- history of claudication for at least 6 months, no acute deterioration in the last 3 months;
- maximum walking distance 100 to 300 m, measured with a standardized treadmill test (see below);
- repeated treadmill test after a 2-week wash-out and run-in period to check the stability of claudication. Maximal variation of maximum walking distance accepted for inclusion was the previous value $\pm 25\%$;
- an ankle–brachial pressure index at rest, measured by Doppler probe, $\leq 0{\cdot}70$ on the worst leg.

Exclusion criteria were: disorders preventing the correct performance of the treadmill test (e.g. osteoarthrosis, arthritis, cardiopulmonary insufficiency, ischaemic heart disease, arrhythmias, polyneuropathy, low-back pain); aneurysm (>3 cm) of the abdominal aorta; occlusion or severe haemodynamic stenosis of pelvic arteries; any history of gangliotomy or surgical revascularization on the affected limb; presence of serious endocrine disorders; type I diabetes; severe liver or kidney function impairment; severe heart disease; malignant arterial hypertension; any form of cancer; inflammatory vascular diseases (e.g. thromboangioitis, immunoangiopathy, vascular and collagen disorders); history of hypersensitivity to extractive mucopolysaccharides. Patients were not admitted to the study if they needed treatment with oral anticoagulants, ticlopidine or NSAIDs. Pregnant women and nursing mothers were also excluded from the study. Acetyl salicylic acid was not discontinued, if used.

Treatment

Patients were blindly allocated to receive sulodexide (Vessel Due F, Alfa Wassermann, Bologna, Italy) or matching placebo. The study drug was administered at the dose of 60 mg by i.m. injection for the first 20 days, and then at 100 mg orally (two 25 mg capsules b.i.d.) for the following 6 months. Total treatment duration was therefore 27 weeks. One milligram of sulodexide is equivalent to 10 lipoprotein lipase-releasing units.

A progressive walking programme was strongly recommended to all patients, and their compliance with this was checked at each visit.

Investigations

Demographic data, medical history, peripheral pulses, the presence of intermittent claudication and other baseline data were recorded at the screening visit.

A standardized treadmill test (3 km per hour and 10% slope) was used to assess walking ability throughout the study. The pain-free walking distance and the maximum walking distance were recorded at baseline and thereafter at 20 days and 2, 4, and 6 months from the start of treatment. At the same time-points clinical findings, subjective symptoms (see below) and ankle–brachial pressure index were monitored, and blood samples were obtained for plasma fibrinogen testing. Echo-colour Doppler ultrasound of the lower limb arteries was repeated as an auxiliary test at the end of the study.

Study end-points

The primary end-point was doubling of the baseline pain-free walking distance at the end of treatment. Secondary end-points were doubling the maximum walking distance and the time courses of both pain-free and maximum walking distances.

Evaluation of subjective symptoms

Subjective symptoms, such as pain in the extremities, aches, cramps, numbness, cold/burning sensation and sense of fatigue were evaluated according to the following arbitrary score: 0=absent; 1=slight and tolerable, not interfering with normal daily activities; 2=moderate but stressful, limiting normal daily activities; 3=severe and disabling. At each visit patients were also invited to report the segment(s) where the pain causing claudication originated (foot, calf, thigh or gluteus). Patients who quoted a given segment on entry, and did not quote the same segment at conclusion, were classified 'responders' for that segment.

Tolerability and adverse events

To evaluate the systemic tolerability of the drug, the following variables were monitored before and after treatment: standard haematology with platelet and leukocyte count and erythrocyte sedimentation rate, blood glucose, blood urea nitrogen, serum creatinine, bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, total protein and albumin. The onset of adverse events was monitored throughout the trial.

Statistical analysis

The sample size of this study was computed to detect a difference in success rate on the primary end-point higher than 67% (relative) in sulodexide treated patients, based on an expected success rate among controls of approximately 30%, with 90% power and $\alpha=0{\cdot}05$ (two-tailed test).

Statistical analysis was performed blind using SPSS package for PC (version 10). Missing treadmill test values (pain-free walking distance and maximum walking distance) were replaced with the last observation carried forward procedure. The treadmill test values were used to classify patients as a 'success' when the actual or carried forward pain-free (primary end-point) and maximum (secondary end-point) walking distance were at least double the baseline values at the end of the study, or 'failure'. Randomized patients who interrupted the assigned treatment and for whom no measurement of walking distance was recorded were classified as failures. The proportion of successes between the two treatment groups was compared using the chi-square test and relative risk analysis. The influence of the centre effect was monitored with binomial logistic regression; however only data from centres that enrolled at least six patients were included.

The time course of pain-free walking distance and maximum walking distance was analysed, after replacing missing data with the last observation carried forward technique, with the repeated-measures analysis of variance (ANOVA) using observation as a fixed factor within subjects; treatment and gender as fixed factors between subjects, and patients' age and weight as covariates. Furthermore, the total gain in walking distances was directly compared between treatment groups by univariate analysis of variance, using gender as a co-factor, and age, body weight and baseline distance walked as covariates. The same analytical approach was used to test the time course of fibrinogen after replacing the missing values with the last observation carried forward technique, using treatment and gender as fixed factors between treatments and age as a covariate. In addition, the variation over the total treatment period was computed and compared between treatments with the univariate ANOVA. All tests were two-tailed; P values $<0{\cdot}05$ were considered statistically significant. Adverse events were reported as absolute number and proportion; where appropriate a comparison in prevalence by uncorrected chi-square test was also performed.

Results

Baseline data

Two hundred and ninety-three patients were deemed eligible (Fig. 1) but seven among them refused treatment and were not randomized. Therefore, 143 patients were

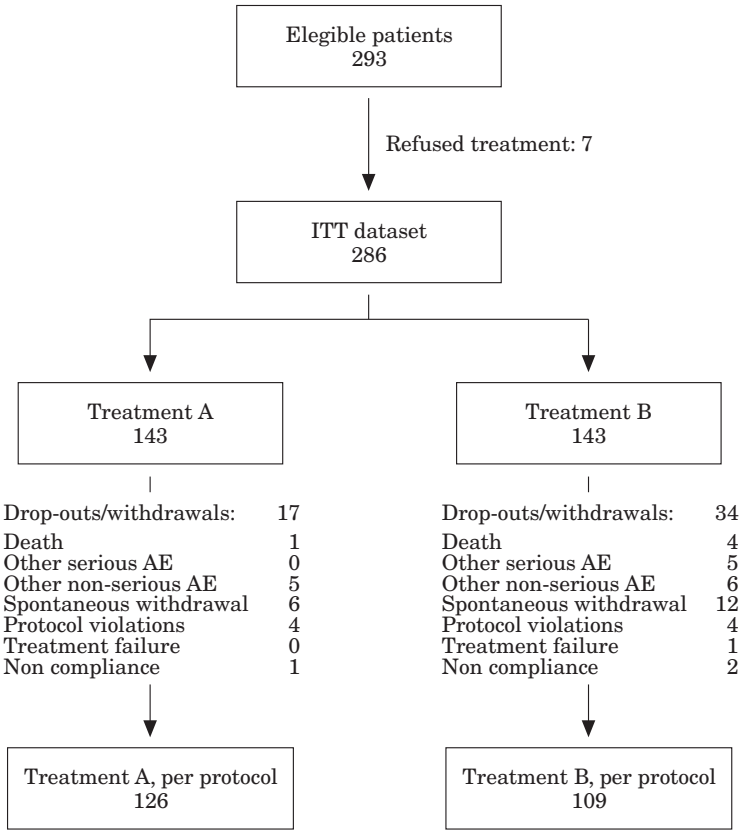

Figure 1 **Trial design. AE=adverse events; ITT=intention-to-treat.**

randomized to sulodexide and 143 to placebo. This set identifies the intention-to-treat population. Table 1 describes the patients' main characteristics; these were comparable between the two groups. Within this population, 17 patients from the sulodexide group and 34 from the placebo group dropped out or were withdrawn from study before completion, due to serious and non-serious adverse events (6 vs 15), protocol violations (5 vs 6), treatment failure (0 vs 1) or spontaneous withdrawal (6 vs 12) leaving 126 and 109 patients to complete the observation period (per-protocol population). The proportion of treatment interruptions was significantly greater in the placebo group ($P=0{\cdot}013$).

Primary end-point

The primary end-point (Fig. 2), i.e. the doubling of pain-free walking distance, was achieved by 23·8% (n=34) of the patients treated with sulodexide and 9·1% (n=13) of those randomized to placebo ($P=0{\cdot}001$). In view of the significant difference in the drop-out rate, the rate of success was also calculated in the per-protocol population and was consistent with that of the intention-to-treat population (26·2% vs 10·2%; $P=0{\cdot}002$). Any appreciable centre effect could be excluded by binomial logistic regression analysis, that yielded 125 and 127 evaluated patients: $P_{centre}=0{\cdot}911$; $P_{treatment}<0{\cdot}001$.

The statistical power was re-computed ex-post facto yielding an actual power of 92%. Thus the sample size actually obtained is consistent with the anticipated power analysis, despite the smaller than foreseen placebo effect.

Secondary end-points

The maximum walking distance doubled in approximately the same proportion of patients as the pain-free walking distance: 25·9% (n=37) vs 6·3% (n=9) ($P<0{\cdot}001$) in the intention-to-treat dataset, and 29·0% vs 6·5% ($P<0{\cdot}001$) in the per protocol population (Fig. 2). Therefore, based on the differences in proportion of primary and secondary outcomes, the number of patients needed to treat in order to have one additional patient doubling the walking distance was seven for the pain-free walking distance and five for the maximum walking distance.

The time course of pain-free walking distance and maximum walking distance progression also after accounting for gender, age, body weight, and the baseline walking distance, was significantly better with sulodexide than with placebo ($P=0{\cdot}002$ and 0·003,

Table 1 Summary of demographic and prognostic profiles

	Sulodexide	Placebo
Gender, males/females (n, %)	120/23 (83·9/16·1%)	110/33 (76·9/23·1%)
Age, years (mean ± SD)	64·7 ± 7·6	66·2 ± 7·5
Weight, kg (mean ± SD)	74·9 ± 11·1	73·2 ± 11·1
Height, cm (mean ± SD)[a]	168·7 ± 6·2	166·4 ± 6·8
Physical activity[b] (n, %) (none/mild/moderate/intense)	11/51/70/10 (7·7/35·9/49·3/7·0%)	11/59/66/7 (7·7/41·3/46·2/4·9%)
Smoking habits non-/ex-/current smokers (n, %)	23/68/52 (16·1/47·6/36·4%)	29/62/52 (20·3/43·4/36·4%)
History of angina[b] (n, %)	9 (6·3%)	7 (4·9%)
History of AMI[b] (n, %)	15 (10·6%)	10 (7·0%)
History of TIA[b] (n, %)	6 (4·2%)	13 (9·1%)
History of stroke[b] (n, %)	5 (3·5%)	2 (1·4%)
Hypertension[b] (n, %)	68 (47·9%)	72 (50·3%)
Type II diabetes[b] (n, %)	36 (25·4%)	34 (23·8%)
Hypercholesterolaemia[b] (n, %)	53 (37·3%)	51 (35·7%)
Hypertriglyceridaemia[b,c] (n, %)	14 (9·9%)	28 (19·6%)
Antiplatelet agents in use at baseline (n, %)	97 (67·8%)	90 (62·9%)
Pain-free walking distance at baseline (m, mean ± SEM)[d]	141·2 ± 3·9	144·0 ± 4·4
Maximum walking distance at baseline (m, mean ± SEM)	201·9 ± 5·8	203·8 ± 6·0
Fibrinogen at baseline, mg . dl^{-1} (mean ± SEM)[e]	370·7 ± 9·4	342·5 ± 7·4

[a] $P=0·003$.
[b] Information missing for one patient in the sulodexide group.
[c] $P=0·032$.
[d] Information missing for three patients in the sulodexide and one patient in the placebo group.
[e] $P=0·018$; information missing for 17 cases in the sulodexide group and for 12 cases in the placebo group.
AMI = acute myocardial infarction; TIA = transient ischaemic attack.

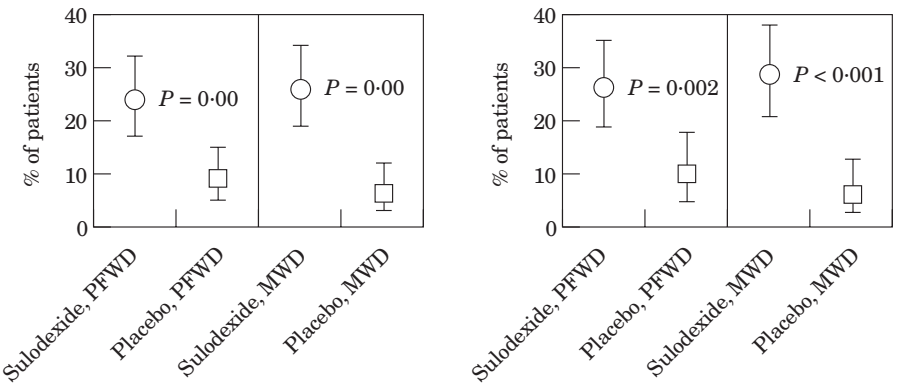

Figure 2 **The proportion (± 95% CI) of patients doubling the pain-free walking distance (PFWD) and the maximum walking distance (MWD) in the intention-to-treat (ITT) population (left panel; n = 143 per group) and in the per-protocol sample (right panel; n = 122 and 124 for pain-free walking distance and maximum walking distance with sulodexide; n = 108 for placebo) after 27 weeks' observation. *P* is from the two-tailed common odds ratio estimate.**

respectively) (Fig. 3). At the end of treatment, the pain-free walking distance increased on average (± SE) by 83·2 ± 8·6 m (+64·7% from baseline) with sulodexide, and 36·7 ± 6·2 m (+29·9% from baseline) with placebo ($P=0·001$). Corresponding values for maximum walking distance were 142·3 ± 15·8 m (+76·0% from baseline) and 54·5 ± 8·4 m (+27·9% from baseline) ($P=0·001$).

Cardiovascular events

This study was not designed to compare the rate of cardiovascular events. However, safety data (Table 2) indicate that a total of 15 patients experienced serious cardiovascular events: four with sulodexide and 11 with placebo. Among these, one patient in the sulodexide

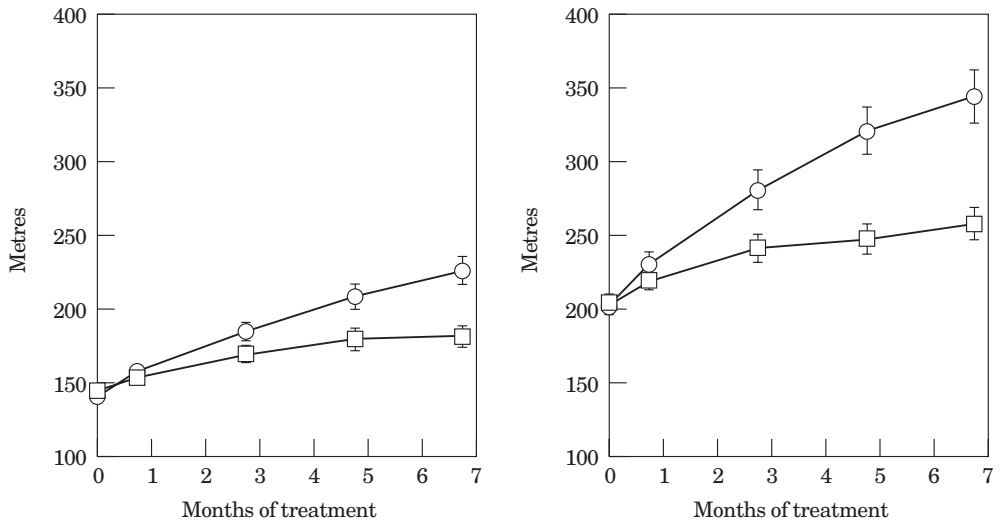

Figure 3 **Mean (± SEM) pain-free (left panel) and maximum walking distance (right panel) during treatment with sulodexide (n=141) or placebo (n=143) in patients with peripheral arterial obstructive disease (P=0·001); last observation carried forward. The time course is significantly different between treatments in both cases (P=0·002 and P=0·003; multivariate test, repeated-measures ANOVA). Considering the total increase (m) a statistically significant difference was reached for both pain-free walking distance (PFWD) and maximum walking distance (MWD) (P=0·001, ANOVA). ○=Sulodexide; □=placebo.**

group and four in the placebo group died during observation, all due to cardio- or cerebrovascular causes: acute myocardial infarction (one and three) and massive stroke (one in the placebo group only).

Other findings

The ankle–brachial pressure index at the end of treatment increased on average from 0·60 to 0·67 in the sulodexide group and from 0·58 to 0·62 with placebo. The difference in the time course of ankle–brachial pressure index changes approached statistical significance in favour of sulodexide (P=0·053) (data not shown). Approximately 25% of the patients enrolled had type II diabetes. The average gain in pain-free walking distance and maximum walking distance associated with sulodexide according to both intention-to-treat and per-protocol analyses was comparable in patients with and without type II diabetes (data not shown).

The time course of plasma fibrinogen indicates a decrease among patients randomized to sulodexide, and an increase among those randomized to placebo, after accounting for gender, age, and baseline fibrinogen value (Fig. 4). At the end of treatment the average (± SE) decrease in fibrinogen with sulodexide treatment was $31{\cdot}9 \pm 8{\cdot}8$ mg . dl^{-1}, while in the placebo group an average increase of $30{\cdot}2 \pm 10{\cdot}0$ mg . dl^{-1} was observed (P=0·001).

Regarding the perception of the anatomical distribution of claudication pain, among patients who indicated the calf (139 sulodexide; 143 placebo), 16 (11·5%) were classified as 'responders' in the treated group vs four (2·8%; P=0·009) in the placebo group.

Subjective symptoms (total number and total score) were reported to be reduced among patients treated with sulodexide (multivariate test from repeated-measures ANOVA using the baseline value as covariate: P=0·045 for total symptom number; P=0·029 for total symptom score) (data not shown).

Table 2 ***Serious adverse events***

Total patients and events	Sulodexide 5	Placebo 14
AMI, non-fatal	0	2
AMI, fatal	1	3
Stroke, non-fatal	1	0
Stroke, fatal	0	1
Other non-fatal vascular events	2[a]	5[b]
Non-vascular events	1[c]	3[d]

[a]Heart failure; hospitalization.
[b]Onset of angina; acute leg ischaemia (two patients); pulmonary embolism with flutter; venous thrombosis.
[c]Metrorrhagia.
[d]Scheduled surgery for hernia with dysarthria; biliary colic; identification of pancreatic cancer.

Tolerability and safety

Overall, 44 patients reported or exhibited a total of 58 adverse events, 19 (13·3%; 24 events) in the sulodexide group, and 25 (17·5%; 31 events) among those randomized to placebo.

Table 2 reports all serious adverse events: five patients (3·5%; 95% CI 1 to 8%) treated with sulodexide,

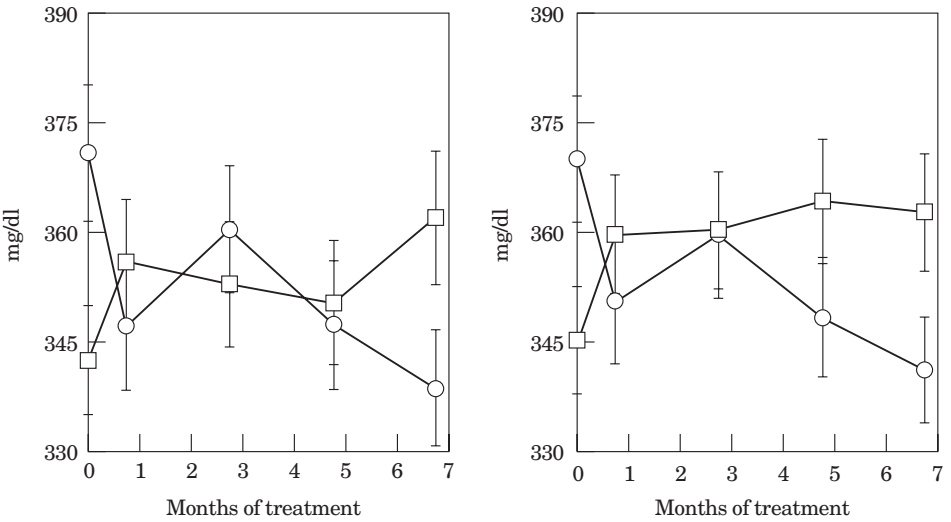

Figure 4 **Mean (± SEM) plasma fibrinogen (mg . dl^{-1}) as an actual value (left panel) and last observation carried forward (right panel). The time course of the parameters is significantly different between treatments in both cases (P=0·011 and P=0·013; multivariate test, repeated-measures ANOVA). ○=Sulodexide; □=placebo.**

including one fatal event, and 14 patients (9·8%; 95% CI 6 to 16%) on placebo, four of whom experienced fatal events.

Among these serious adverse events, four with sulodexide and 11 with placebo, were serious cardiovascular adverse events that were attributed to the underlying disease or to the patient's medical history. The common odds ratio estimate of incurring a serious event is significantly different from one (P=0·040).

In addition to the serious events, another four patients with sulodexide and three with placebo reported or exhibited events causing treatment withdrawal (nine total, 6·3%, and 17 total, 11·9%, respectively; ns).

Six patients (4·2%; for eight events) randomized to sulodexide and five (3·5%; for seven events) in the placebo group reported at least one potentially drug-related adverse events. The events were, for sulodexide: diarrhoea (three), epigastric pain, skin rash with vertigo and feeling faint, haematoma at the site of injection; for placebo: venous thrombosis, pain on injection, erythema, impotence, vertigo with nausea and pain at rest.

Discussion

Sulodexide, a standardized extractive glycosaminoglycan containing 80% 'fast moving' heparin and 20% dermatan sulphate[28,29], was investigated in several trials as a candidate for the treatment of peripheral arterial obstructive disease. A systematic review of these studies led to the inclusion of 19 controlled double-blind trials in a meta-analysis[38] that indicated efficacy of the agent in improving the pain-free walking distance and lowering fibrinogen. However, most of the trials included were under-sized and some of the study criteria, especially in respect to the Leriche-Fontaine stage classification and follow-up duration, were not homogeneous. It was therefore deemed necessary to undertake a new, carefully designed multicentre clinical trial of adequate size and follow-up duration, likely to produce clear and solid evidence.

The study hypothesis was confirmed: the proportion of patients doubling the pain-free walking distance at the end of the study period was higher in the sulodexide than in the placebo group. Similar results were obtained for the maximum walking distance. On the basis of these data it was also possible to define the number of patients needed to treat figures for the doubling of both pain-free and maximum walking distances (seven and five, respectively). The rate of increase of walking distances over time was also significantly greater in the treated patients: after 27 weeks the percent increase from baseline in pain-free walking distance and maximum walking distance on standardized treadmill testing was around 65% and 76% respectively, vs 30% and 28% in the placebo group.

The data of this study for both sulodexide and placebo compare well with those reported in previous papers on effective agents for intermittent claudication[4,15–27]. However, it should be emphasized that the present results were obtained with restrictive inclusion criteria, for instance, maximum walking distance $\geq$100 m and $\leq$300 m, and ankle–brachial pressure index $\leq$0·70.

Among agents successfully investigated for relief of intermittent claudication, pentoxyfylline[15,17] was extensively studied, although with somewhat controversial results. Cilostazol[16,17], defibrotide[18] and l-propionyl carnitine[19] were recently found effective in well-designed clinical trials. Among classic antithrombotic drugs, ticlopidine effectively improved walking

distances[20] and reduced fibrinogen levels[21]. In single studies acetyl salicyclic acid, as well as dipyridamole, failed to influence claudication, and unfractionated, or low molecular weight heparin showed promising but non-conclusive results[23–27]. Thus, sulodexide deserves a place among the few agents capable of inducing significant relief of claudication. In accordance with the meta-analysis mentioned previously[38], this study also suggests that sulodexide is equally effective in non-diabetics and patients with type II diabetes, but this indication should be confirmed in an 'ad hoc' trial.

Although this study was not designed to show a reduction in cardiovascular events, the number of these events was less than half in the sulodexide group with respect to the placebo group. This observation is potentially of remarkable clinical interest and should be tested in properly designed trials. In fact, in a previous investigation[39] sulodexide was able to reduce major cardiovascular events and the onset of new cases of peripheral arterial obstructive disease in post myocardial infarction patients.

The present clinical investigation was not meant to clarify the mechanisms by which sulodexide improves the walking ability of peripheral arterial obstructive disease patients. It can however be surmised that the antithrombotic and pro-fibrinolytic effect of the agent may preserve or improve blood flow in the microcirculation, and that the observed lowering of fibrinogen may in some way be connected with the clinical effect. Indeed, lowering of fibrinogen was also associated with an enhancement of walking ability in studies with other drugs.

Finally, it should be stressed that the absolute gain in walking performance might not be a fully satisfactory outcome, unless there is consistent subjective perception of improvement by the patients. Such perception favours optimal compliance to other important measures such as not smoking, limiting risk factors and the acceptance of a physical exercise programme. The fast onset of the improvement in walking and the favourable effects of the agent on subjective outcomes shown in this study, confirm that the objective improvement observed is also perceived as a subjective benefit.

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Appendix

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